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Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents – assessment of adverse events in non-randomised studies (Review)

Storebø OJ, Pedersen N, Ramstad E, Kielsholm ML, Nielsen SS, Krogh HB, Moreira-Maia CR, Magnusson FL, Holmskov M, Gerner T, Skoog M, Rosendal S, Groth C, Gillies D, Buch Rasmussen K, Gauci D, Zwi M, Kirubakaran R, Håkonsen SJ, Aagaard L, Simonsen E, Gluud C

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[Intervention Review]

Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents – assessment of adverse events in non-randomised studies

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ABSTRACT

Background

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in childhood. The psychostimulant methylphenidate is the most frequently used medication to treat it. Several studies have investigated the benefits of methylphenidate, showing possible favourable effects on ADHD symptoms, but the true magnitude of the effect is unknown. Concerning adverse events associated with the treatment, our systematic review of randomised clinical trials (RCTs) demonstrated no increase in serious adverse events, but a high proportion of participants suffered a range of non-serious adverse events.

Objectives

To assess the adverse events associated with methylphenidate treatment for children and adolescents with ADHD in non-randomised studies.

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Search methods

In January 2016, we searched CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, 12 other databases and two trials registers. We also checked reference lists and contacted authors and pharmaceutical companies to identify additional studies.

Selection criteria

We included non-randomised study designs. These comprised comparative and non-comparative cohort studies, patient-control studies, patient reports/series and cross-sectional studies of methylphenidate administered at any dosage or formulation. We also included methylphenidate groups from RCTs assessing methylphenidate versus other interventions for ADHD as well as data from follow-up periods in RCTs. Participants had to have an ADHD diagnosis (from the 3rd to the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* or the 9th or 10th edition of the*International Classification of Diseases*, with or without comorbid diagnoses. We required that at least 75% of participants had a normal intellectual capacity (intelligence quotient of more than 70 points) and were aged below 20 years. We excluded studies that used another ADHD drug as a co-intervention.

Data collection and analysis

Fourteen review authors selected studies independently. Two review authors assessed risk of bias independently using the ROBINS-I tool for assessing **r**isk **o**f **b**ias **i**n **n**on-randomised **s**tudies of **i**nterventions. All review authors extracted data. We defined serious adverse events according to the International Committee of Harmonization as any lethal, life-threatening or life-changing event. We considered all other adverse events to be non-serious adverse events and conducted meta-analyses of data from comparative studies. We calculated meta-analytic estimates of prevalence from non-comparative cohorts studies and synthesised data from patient reports/series qualitatively. We investigated heterogeneity by conducting subgroup analyses, and we also conducted sensitivity analyses.

Main results

We included a total of 260 studies: 7 comparative cohort studies, 6 of which compared 968 patients who were exposed to methylphenidate to 166 controls, and 1 which assessed 1224 patients that were exposed or not exposed to methylphenidate during different time periods; 4 patient-control studies (53,192 exposed to methylphenidate and 19,906 controls); 177 non-comparative cohort studies (2,207,751 participants); 2 cross-sectional studies (96 participants) and 70 patient reports/series (206 participants). Participants' ages ranged from 3 years to 20 years. Risk of bias in the included comparative studies ranged from moderate to critical, with most studies showing critical risk of bias. We evaluated all non-comparative studies at critical risk of bias. The GRADE quality rating of the evidence was very low.

Primary outcomes

In the comparative studies, methylphenidate increased the risk ratio (RR) of serious adverse events (RR 1.36, 95% confidence interval (CI) 1.17 to 1.57; 2 studies, 72,005 participants); any psychotic disorder (RR 1.36, 95% CI 1.17 to 1.57; 1 study, 71,771 participants); and arrhythmia (RR 1.61, 95% CI 1.48 to 1.74; 1 study, 1224 participants) compared to no intervention.

In the non-comparative cohort studies, the proportion of participants on methylphenidate experiencing any serious adverse event was 1.20% (95% CI 0.70% to 2.00%; 50 studies, 162,422 participants). Withdrawal from methylphenidate due to any serious adverse events occurred in 1.20% (95% CI 0.60% to 2.30%; 7 studies, 1173 participants) and adverse events of unknown severity led to withdrawal in 7.30% of participants (95% CI 5.30% to 10.0%; 22 studies, 3708 participants).

Secondary outcomes

In the comparative studies, methylphenidate, compared to no intervention, increased the RR of insomnia and sleep problems (RR 2.58, 95% CI 1.24 to 5.34; 3 studies, 425 participants) and decreased appetite (RR 15.06, 95% CI 2.12 to 106.83; 1 study, 335 participants).

With non-comparative cohort studies, the proportion of participants on methylphenidate with any non-serious adverse events was 51.2% (95% CI 41.2% to 61.1%; 49 studies, 13,978 participants). These included difficulty falling asleep, 17.9% (95% CI 14.7% to 21.6%; 82 studies, 11,507 participants); headache, 14.4% (95% CI 11.3% to 18.3%; 90 studies, 13,469 participants); abdominal pain, 10.7% (95% CI 8.60% to 13.3%; 79 studies, 11,750 participants); and decreased appetite, 31.1% (95% CI 26.5% to 36.2%; 84 studies, 11,594 participants). Withdrawal of methylphenidate due to non-serious adverse events occurred in 6.20% (95% CI 4.80% to 7.90%; 37 studies, 7142 participants), and 16.2% were withdrawn for unknown reasons (95% CI 13.0% to 19.9%; 57 studies, 8340 participants).

Authors' conclusions

Our findings suggest that methylphenidate may be associated with a number of serious adverse events as well as a large number of non-serious adverse events in children and adolescents, which often lead to withdrawal of methylphenidate. Our certainty in the evidence is very low, and accordingly, it is not possible to accurately estimate the actual risk of adverse events. It might be higher than reported here.

Given the possible association between methylphenidate and the adverse events identified, it may be important to identify people who are most susceptible to adverse events. To do this we must undertake large-scale, high-quality RCTs, along with studies aimed at identifying responders and non-responders.

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PLAIN LANGUAGE SUMMARY

Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of harmful effects

Review question

Is methylphenidate administration associated with harmful effects in children and adolescents with attention deficit hyperactivity disorder (ADHD)?

Background

ADHD is one of the most common neurodevelopmental disorders in childhood and is associated with impaired functioning and negative outcomes for development. Individuals diagnosed with ADHD are often hyperactive and impulsive. Methylphenidate, a psychostimulant, is the drug most often prescribed for children and adolescents with ADHD.

Study characteristics

We searched for available research up to January 2016 and found 260 studies with different designs. We included a number of non-randomised designs (where investigators did not assign participants to a certain treatment):

– 7 comparative cohort studies (a group of people followed over time; six studies compared 968 patients who were taking methylphenidate to 166 controls who were not taking methylphenidate; and 1 study included 1224 patients that were taking or not taking methylphenidate during different time periods);
– 4 patient-control studies (comparing two groups of people: 53,192 were taking methylphenidate, and 19,906 were not);
– 177 non-comparative cohort studies (2,207,751 participants) with no control group (i.e. who were not taking methylphenidate);
– 2 cross-sectional studies (96 participants were taking methylphenidate at a single time point); and
– 70 patient reports/series (206 participants were taking methylphenidate).

We also included methylphenidate groups from randomised clinical trials (RCTs; experiments in which participants are randomly put into independent groups that compare different treatments). All RCTs assessed methylphenidate versus other interventions for ADHD and follow-up periods from RCTs. We only used the data from the intervention arm with methylphenidate. In all the included non-comparative cohort studies, 2,207,751 participants were taking methylphenidate. Participants' ages ranged from 3 years to 20 years.

Key results

The findings suggest that methylphenidate administration might lead to serious adverse (harmful) events, including death, cardiac problems, and psychotic disorders. About 1 in 100 patients treated with methylphenidate seemed to suffer a serious adverse event. Withdrawal from methylphenidate due to serious adverse events occurred in about 1.2 out of 100 patients treated with methylphenidate. Withdrawal from methylphenidate due to any adverse events occurred in about 7.3 out of 100 patients treated with methylphenidate. We also noted a large proportion of non-serious adverse events. More than half the patients exposed to methylphenidate seemed to suffer one or more adverse events. Withdrawal from methylphenidate due to non-serious adverse events occurred in about 6.2 out of 100 patients exposed to methylphenidate. Withdrawal of methylphenidate for unknown reasons was 16.2 out of 100 patients exposed to methylphenidate.

Quality of the evidence

The quality of the evidence and hence the certainty or reliability of the evidence for the comparative studies is very low. The reliability of the evidence for the non-comparative studies is low due to weaknesses in study design. Accordingly, it is not possible to accurately estimate the risks of adverse events in children and adolescents prescribed methylphenidate.

Conclusions

Methyphenidiate might be associated with a number of serious adverse events. Methylphenidate produces a large number of other non-serious harmful effects in children and adolescents with ADHD. We suggest that clinicians and parents are alert to the importance of monitoring adverse events in a systematic, meticulous manner. If methylphenidate is to continue to have a place in ADHD treatment in the future, we need to identify subgroups of patients in whom the benefits of methylphenidate outweigh the harms. Just as we need to be able to identify who is likely to benefit from treatment, we also need to be able to identify those who are most at risk of experiencing adverse events. In order to do this, we need to undertake large-scale, high-quality RCTs along with other studies aimed at identifying those who respond and those who do not respond to treatment.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Methylphenidate for children and adolescents aged 18 years and under with attention deficit hyperactivity disorder (ADHD): adverse events

Methylphenidate for children and adolescents aged 18 and under with attention deficit hyperactivity disorder (ADHD): adverse events

Patient or population: children and adolescents aged 18 years and under diagnosed with ADHD

Settings: outpatient clinic, inpatient hospital ward and register data

Intervention: methylphenidate

Comparision: control or no control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies) at follow-up	Quality of the evidence (GRADE)
	Risk with control or no control	Risk difference with Methylphenidate			
Comparative studies					
Serious adverse events Measured by: proportion of serious adverse events (total) Average study duration (range): not stated	12 per 1000	4 more per 1000 (2 more to 7 more)	**RR 1.36** (1.17 to 1.57)	72,005 (2 studies)	⊕⊖⊖⊖ **Very low**[a]
Non-comparative studies					
Serious adverse events Measured by: proportion of any serious adverse events Average study duration (range): 4.7 months (14 days to 21 months)	1.20% (0.70% to 2.00%)		—	162,422 (51 studies)	⊕⊖⊖⊖ **Very low**[b]
Withdrawal of methylphenidate due to serious adverse events (non-comparative cohort studies) Measured by: proportion of participants withdrawn from treatment Average study duration (range): 7.9 months (1 month to 37 months)	1.20% (0.60% to 2.30%)		—	1173 (7 studies)	⊕⊖⊖⊖ **Very low**[b]

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Withdrawal of methylphenidate due to adverse events of unknown severity Measured by: proportion of participants withdrawn from treatment Average study duration (range): 4.6 months (21 days to 36 months)	7.30% (5.30% to 10.0%)	—	3708 (22 studies)	⊕⊖⊖⊖ **Very low**[b]
Non-serious adverse events Measured by: proportion of any non-serious adverse events Average study duration (range): 5.99 months (1 day to 41 months)	51.2% (41.2% to 61.1%)	—	13,978 (49 studies)	⊕⊖⊖⊖ **Very low**[b]
Withdrawal of methylphenidate due to non-serious adverse events Measured by: proportion of participants withdrawn from treatment Average study duration (range): 5.60 months (0.6 months to 41 months)	6.20% (4.80% to 7.90%)	—	7142 (37 studies)	⊕⊖⊖⊖ **Very low**[b]
Withdrawal of methylphenidate for unknown reasons Measure by: proportion of participants withdrawn from treatment Average study duration (range): 6.13 months (1 day to 36 months)	16.2% (13.0% to 19.9%)	—	8340 (57 studies)	⊕⊖⊖⊖ **Very low**[b]

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **ROBINS-I:** Risk Of Bias In Non-randomised Studies - of Interventions; **RR**: risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[a]Outcome assessed at critical risk of bias using the ROBINS-I. Consequently, we downgraded the quality of the evidence by 3 levels due to study limitations.

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bOutcome not critically assessed with ROBINS-I due to lack of control group. However, due to the nature of the studies and the risk of confounding, we considered the studies to be at critical risk of bias. Consequently, we downgraded the quality of the evidence by 3 levels due to study limitations.

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BACKGROUND

Description of the condition

Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed and treated childhood neurodevelopmental disorders (Scahill 2000). The estimated prevalence in children and adolescents is between 3% to 8% (Polanczyk 2007a; Thomas 2015; Willcut 2012), depending on the classification system used, with boys two to four times more likely to be diagnosed than girls (Schmidt 2009). Prevalences have remained stable over the past 30 years and do not appear to vary between countries (Polanczyk 2014). Individuals with ADHD may show difficulties in attention and cognitive functions like problem-solving, planning, orienting, flexibility, response inhibition and working memory, as well as impulsivity and hyperactivity (Pasini 2007; Sergeant 2003). Furthermore, children and adolescents have difficulties handling affective components such as motivational delay and mood dysregulation (Castellanos 2006; Nigg 2005; Schmidt 2009). The aetiology of ADHD involves genetic, environmental and social factors but is not yet completely understood. Family and twin studies have shown a high heritability of around 70% to 80% and with a substantial overlap between the two dimensions of hyperactivity/impulsivity and inattention and with no sex differences of heritability (Franke 2012; Neale 2010). Furthermore, genetic factors may be involved in determining the persistence of ADHD into adulthood (Faraone 2000; Franke 2012). Although family studies have shown high heritability, and there are many candidate genes that may be involved in the disorder (Neale 2010), genome-wide studies have yet to find any clear associations.

Several studies have examined environmental risk factors for ADHD; however, researchers have not found any specific predictor for elevated risk. At the population level, poverty (families living under the poverty level) is more likely to be a feature among American children and adolescents diagnosed with ADHD (CDC 2015). In a Swedish cohort of 811,803 individuals, low family income in early childhood was highly associated with ADHD (Larsson 2014). Other potential risk factors for ADHD development include low birthweight (Indredavik 2004; Van Lieshout 2015), prematurity (Bhutta 2002; Burnett 2014; Elgen 2015), maternal exposure to tobacco (Kovess 2015; Obel 2016), and exposure to chemical components like manganese and lead (Hong 2014; Hong 2015).

The diagnosis of ADHD is purely clinical, requiring recognition of excessive inattention, hyperactivity and impulsivity that interfere with or reduce the quality of social, academic, or occupational functioning (APA 2013; WHO 1992). There are 18 core symptoms of ADHD according to the principal diagnostic classification systems: *International Classification of Diseases - 10th Revision* (ICD-10; WHO 1992) and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) - *4th Edition* (DSM-IV; APA 1994), - *4th Edition - Text Revision* (DSM-IV-TR; APA 2000), and- *5th Edition* (DSM-5; APA 2013).

Both the DSM-5 and ICD-10 criteria require excessive inattention, hyperactivity, and impulsivity to be inconsistent with the developmental level and to be pervasive. The symptoms must be present in two or more settings and appear before the age of 6 years according to the ICD-10 (WHO 1992), or 12 years according to the DSM-5 (APA 2013), and they should also persist for at least six months. The DSM-5 modified the criteria for adolescents and adults older than 17 years of age, requiring fewer perceived symptoms and providing further descriptions to better identify typical ADHD symptoms in adolescents. Earlier versions of the DSM and the ICD-10 required that there be clear evidence of clinically significant impairment in social, academic, and occupational functioning (APA 1994; APA 2000; APA 2013; WHO 1992), but the DSM-5 only requires that symptoms interfere with or reduce the quality of these domains (APA 2013). Furthermore the ICD-10 and the DSM-IV differ from the newer DSM-5 in excluding people with autism spectrum disorder; DSM-5 only excludes people during the course of schizophrenia or another psychotic or mental disorder.

The diagnostic criteria describe three different subtypes or 'presentations' in the DSM-5, according to the predominant symptoms: 'predominantly inattentive type', 'predominantly hyperactive-impulsive type', and 'combined type' – a combination of both hyperactive-impulsive and inattentive symptoms. The DSM-5 acknowledges the absence of validity for these subtypes by renaming them predominantly inattentive, predominantly hyperactive-impulsive, and combined presentations (APA 2013; Willcut 2012).

Children, adolescents, and adults with ADHD are at increased risk of a broad spectrum of co-occurring conditions, which frequently result in negative outcomes later in life (Newcorn 2008; Schmidt 2009). The Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) trial identified one or more comorbid disorders in almost 40% of the participants (MTA 1999). These included oppositional defiant disorder, conduct disorder, depression, anxiety, tics, learning disorders, and verbal and cognitive difficulties (Jensen 2001; Kadesjö 2001). ADHD has also been shown to co-occur with bipolar disorder (Perroud 2014). More recently, studies have confirmed such comorbidity (Czamara 2013; Yoshimasu 2012), with some authors noting that excess weight and obesity are found in children with ADHD (Cortese 2016). In a study with 1480 twin pairs from Sweden, researchers found that persistent hyperactivity or impulsivity symptoms of ADHD are associated with both early-onset tobacco and alcohol use (Chang 2012). Similarly, ADHD comorbidity with conduct disorder can lead to adverse outcomes in academic achievement, failure to complete high school, criminality, substance use disorder, and unemployment (Erskine 2016).

In addition, ADHD is associated with several harmful consequences. A cohort of participants with ADHD who were followed up to the age of 40 years demonstrated that these individuals have an elevated risk of criminality and a high risk of death before 40 years of age (Koisaari 2015). Similarly, studies from health insurance plans demonstrated not only elevated risk of injury, but also higher indirect costs of those with an ADHD diagnosis compared to diagnosis of depression (Hodgkins 2011). Recently, ADHD has been linked to increased premature mortality higher than 50%, compared to non-ADHD patients, in a 24.9 million person-years Danish cohort study (Dalsgaard 2015b).

To ensure high standards in assessment, diagnosis and therapeutic practice, professional and national bodies have developed guidelines (AAP 2011; CADDRA 2011; NCCMH 2009; Pliszka 2007a; Scottish Intercollegiate Guidelines Network (SIGN)). Psychosocial interventions are recommended initially for younger children and for mild to moderate symptoms (AAP 2011; NCCMH 2009; Pliszka 2007a). For more severe ADHD symptoms, stimulants, either alone or in combination with psychosocial interventions, may be necessary (AAP 2011; CADDRA 2011; NCCMH 2009).

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Description of the intervention

Stimulant medication, notably methylphenidate and dexamphetamine (or dextroamphetamine), together with the non-stimulants atomoxetine (a non-stimulant selective noradrenaline reuptake inhibitor) and guanfacine (an alpha 2A agonist), are considered the treatments of choice along with psychosocial treatments for children and adolescents with ADHD (Greenhill 2006; NICE 2008; Pliszka 2007a). Globally, methylphenidate is the most commonly used drug prescribed for ADHD; it has been used in practice for more than 50 years (Kadesjö 2002; NCCMH 2009). Methylphenidate is used because it appears to have a favourable effect on reducing the core symptoms of excessive hyperactivity, impulsivity, and inattention in children and adolescents with ADHD. It is licensed for use in children aged six years and older. Rates of prescription of methylphenidate are high and increasing, standing at approximately 8% of children and adolescents under 15 years of age in the USA (Akinbami 2011), and around 3% to 5% in Europe (Bachmann 2017; Hodgkins 2013; Schubert 2010; Trecenõ 2012; Zoëga 2016). ADHD medication appears to be discontinued in 13% to 64% of patients from all age groups (Adler 2010), but information of the continuity of these treatments from childhood or adolescence into adulthood is still lacking. Dexamphetamine is licensed for use in children aged three years and older. It is also available for use as mixed-amphetamine salts (levoamphetamine plus dextroamphetamine) and as a pro-drug of dexamphetamine, lisdexamphetamine. These have a longer duration of action than dextroamphetamine. Clinical choice of preparation by clinicians and families is based on a range of factors, including the presence of co-occurring conditions, adverse events associated with the drug, issues regarding compliance, and the preference of the child and parents.

Methylphenidate dose varies from patient to patient. The dose needs to be titrated individually in order to maximise benefits and minimise potential adverse events (Stevenson 1989). The daily therapeutic range of methylphenidate dosages varies from 5 mg to 60 mg, administered one to three times daily, depending on the release system (immediate, sustained, or extended release) and mode of administration (oral or transdermal) (Pliszka 2007a; Storebø 2015). The British National Formulary suggests that initial doses in children aged four to six years should be 2.5 mg twice daily. Where necessary, it should be increased at weekly intervals by 2.5 mg daily, to a maximum of 1.4 mg/kg daily (divided into two to three doses per day) (BNF 2018). In children aged 6 years to 18 years, the initial dose may be 5 mg once or twice daily, increased, where necessary, at weekly intervals by 5 mg to 10 mg daily in two to three divided doses. Although methylphenidate is licensed to a maximum dose of 60 mg daily, it may be increased by 2.1 mg/kg daily in two to three divided doses (maximum 90 mg daily) under specialist supervision. The bioavailability of oral methylphenidate is 11% to 52%, with an approximate duration of action of 2 to 4 hours for immediate-release methylphenidate, 3 to 8 hours for sustained-release methylphenidate, and 8 to 12 hours for extended-release methylphenidate (Kimko 1999).

How the intervention might work

The pharmacodynamics of methylphenidate are still not entirely clear. Methylphenidate has both dopamine and noradrenaline transporter-binding affinity and binds to and blocks both transporters, leading to increased availability of noradrenaline and dopamine within the synaptic cleft (Heal 2006; Volkow 1998; Volkow 2004; Volkow 2012). This is thought to increase the general firing rate via increased neurotransmission of dopamine and noradrenaline, which, in turn, has an effect on the prefrontal cortex – responsible for executive function – and is linked to sub-performance of dopamine and noradrenaline functions associated with ADHD (Arnsten 2005). As a result, patients can improve function (through symptom control) and experience several benefits such as improved attention and reduced hyperactivity-impulsivity (Barkley 1977; Barkley 1981; Barkley 1989; Connor 2002; Engert 2008; Schulz 2012; Shaw 2012; Solanto 1998), which may improve classroom functioning and academic learning (Biederman 2003; Cox 2004; Evans 2001; Swanson 2004).

Methylphenidate has also been correlated with a reduction of several harmful outcomes. In an extensive cohort of 710,120 individuals, including 4557 individuals diagnosed with ADHD before age 10 years, the use of methylphenidate was found to reduce emergency department visits by 46% and injuries by 44% (Dalsgaard 2015a). However, given the lack of sufficiently powered, well-conducted randomised clinical trials (RCTs), it is not clear if these are genuine benefits or statistical artefacts (Garattini 2016; Storebø 2015). In a Swedish national register composed of 25,656 participants, Lichteinstein 2012 demonstrated a 32% and 41% reduction in criminality among men and woman respectively, when treated with medications for ADHD. In another study, the researchers found that medication was associated with a 58% risk reduction in serious transport accidents, and estimated that 41% to 49% of the accidents could have been avoided if ADHD male patients were in drug treatment (Chang 2014a). There have also been more recent reports of reductions in motor vehicle crashes in patients on methylphenidate (Chang 2017). Similarly, ADHD drugs decreased injuries among 5- to 10-year-old children from 32% to 44%, when compared to ADHD children without treatment (Dalsgaard 2015a). It is also a general concern that ADHD medication treatment can lead to substance abuse. Contrary to this, the prescription of ADHD stimulants was associated with a 31% decrease in substance abuse (Chang 2014b). A similar concern was the association of ADHD treatment and suicide, but again, the treatment was correlated with a protective effect (Chen 2014).

Why it is important to do this review

The most commonly reported adverse events associated with methylphenidate are headache, sleep problems, fatigue, and decreased appetite. Studies have indicated that methylphenidate also impairs both children's height and increases in weight (Schachar 1997; Swanson 2004; Swanson 2009).

Serious adverse events, such as psychosis and mood disorders, are reported to affect approximately 3% of children treated with methylphenidate (Block 1998; Cherland 1999; MTA 1999; NICE 2009; Pliszka 1998). An observational study supports an association between the use of stimulants and sudden unexplained death among children and adolescents (Gould 2009). The study showed an odds ratio (OR) of 7.4 (95% confidence interval (CI) 1.4 to 74.9) for use of stimulants, specifically methylphenidate, in children and adolescents with sudden death compared to aged-matched, motor vehicle accident deaths (Gould 2009). Further research is needed to determine whether these deaths are related to methylphenidate (US FDA 2011).

Reports of sudden death in adults taking methylphenidate are also a concern (Jackson 2016). In an update (US FDA 2011), the

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FDA found no evidence for increased risk of serious cardiovascular events in adults treated with ADHD medications, based on two epidemiological studies (Cooper 2011; Habel 2011).

Recent reviews of methylphenidate treatment have focused on its benefits only, as opposed to its harmful effects (Charach 2013; Faraone 2002; Faraone 2006; Faraone 2010; Hanwella 2011; Maia 2017).

Relatively few randomised clinical trials included in our Cochrane Review assessing methylphenidate versus placebo or no intervention reported adverse events (Storebø 2015). Given the worldwide increase in methylphenidate prescriptions to children and adolescents, the need for an evidence-based risk profile for serious and non-serious adverse events remains (Bushe 2013; Cairns 2014).

To expand our understanding of adverse events, particularly where these are rare or take time to become apparent, it is necessary to bolster the limited data from RCTs by including data from non-randomised studies (Storebø 2015).

Non-randomised studies have a number of advantages; they are often larger (allowing for detection of rare events), have a broader range of participants (reflecting 'real-life'), longer follow-up times, and lower costs than RCTs (Benson 2000; Hannan 2008; Silverman 2009). Non-randomised studies may detect adverse events due to long-term drug exposure, which would not be detected in relatively short RCTs (Storebø 2015). Some adverse events may be too uncommon to be detected in RCTs (Loke 2011), and as a result, cohort studies, patient-control studies, and even patient reports/series may be of value (Reeves 2011). In fact, non-randomised studies can estimate the adverse events of treatment as well as, and maybe even more comprehensively than, RCTs (Vandenbroucke 2006).

RCTs and non-randomised studies investigating adverse events rarely find differences in risk estimates (Golder 2011). In their review, Pitrou 2009 found that some RCTs provided no information on adverse events, and severity was often poorly defined. Only 13% of studies noted the reasons for patient withdrawal due to adverse events. Another study reported that only 18% of all paediatric RCTs published between 2006 and 2009 documented harms adequately according to CONSORT guidelines (De Vries 2010). Our findings were similar (Storebø 2015), with only 17/185 RCTs (9.20%) reporting serious adverse events and approximately 60/185 RCTs (32.0%) reporting non-serious adverse events.

The main disadvantage, however, is that causality cannot be established in observational studies because the observed adverse event may be related to other factors. Nonetheless, in view of the poor reporting of adverse events in RCTs, non-randomised studies may provide important data that would otherwise remain undetected (Loke 2011; Vandenbroucke 2006). Such data from non-randomised studies may help children, adolescents, families, clinicians, and policymakers understand the relative risks and benefits, leading to better informed choices regarding methylphenidate treatment. When we deal with serious adverse events, troublesome non-serious adverse events, and/or prevalent non-serious adverse events, we should remember the recommendations from regulatory authorities stating that P values are of very limited value as substantial differences (expressed as relative risk or risk differences) require careful assessment and will, in addition, raise concern, depending on seriousness, severity or outcome, irrespective of the P value observed (EMA 2017). A non-significant difference between treatments will not allow for a conclusion on the absence of a difference in safety. In other words, in line with general principles, a non-significant test result should not be confused with the demonstration of equivalence (EMA 2017).

OBJECTIVES

To assess the adverse events associated with methylphenidate treatment for children and adolescents with ADHD in non-randomised studies.

METHODS

Criteria for considering studies for this review

Types of studies

We only included the following non-randomised study designs (Higgins 2011).

1. Comparative cohort studies. Here, the experimental group was children or adolescents with ADHD exposed to methylphenidate and the control group was comparable patients not exposed to methylphenidate.
2. Patient-control studies. Here, the patient ('case') group was children or adolescents with ADHD exposed to methylphenidate, and the control group was comparable patients not exposed to methylphenidate.
3. Non-comparative cohort studies. In this study type, children or adolescents with ADHD were exposed to methylphenidate with no control group. We also included the methylphenidate-treated group from randomised clinical trials (RCTs) comparing methylphenidate versus other interventions for ADHD, as these trials were not included in our previous review of RCTs assessing methylphenidate versus placebo or no intervention (Storebø 2015). In this way, we were able to expand our evidence base on adverse events during methylphenidate administration (as such groups are comparable to classic cohort studies), without double-counting from RCTs assessing methylphenidate versus placebo or no intervention (Storebø 2015). For assessment of adverse events in RCTs assessing methylphenidate versus placebo or no intervention, the reader is referred to our systematic review on that topic (Storebø 2015).
4. Patient reports/series. This study type was formerly known and also described in our protocol as 'case-studies' (Storebø 2016).
5. Cross-sectional studies.

For a description of cohort, cross-sectional, and patient-control studies, see Table 1.

See Differences between protocol and review.

Types of participants

Children and adolescents with ADHD, with or without comorbid conditions. At least 75% of study participants were required to be aged 18 years or younger, and the mean age of the trial population had to be 18 years of age or younger. We also required that at least 75% of participants had a normal intellectual quotient (IQ > 70 points). See Differences between protocol and review.

We accepted the following diagnoses of ADHD.

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1. A diagnosis of ADHD made according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) - *3rd Edition* (DSM-III; APA 1980); *3rd Edition - Revised* (DSM-III-R; APA 1987); *4th Edition* (DSM-IV; APA 1994); *4th Edition - Text Revision* (DSM-IV-TR; APA 2000), or*5th Edition* (DSM-5; APA 2013).
2. A diagnosis of hyperkinetic disorders made in accordance with the *International Classification of Diseases - 9th Revision* (ICD-9; WHO 1977) and-*10th Revision* (ICD-10; WHO 1992).

Types of interventions

Methylphenidate administered at any dosage or formulation as part of any medical treatment regimen.

In the comparative cohort studies and patient-control studies, we included studies that compared cointerventions as long as the compared intervention groups received the same cointerventions.

In the non-comparative cohort studies, we allowed some types of comedication but not cointervention with another type of ADHD medication.

See Differences between protocol and review.

Types of outcome measures

We defined the term 'adverse events' as any harm, adverse effect, or adverse drug reaction associated with methylphenidate. We defined 'withdrawals' as any participants withdrawn from methylphenidate medication.

Primary outcomes

1. Serious adverse events. A serious adverse event is defined as any event that is fatal; life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; or results in persistent or significant disability, or any event that requires intervention to prevent any of these outcomes in accordance with the *Guideline for Good Clinical Practice E6(R1)* (ICH 1996).
2. Withdrawal of methylphenidate due to serious adverse events.
3. Withdrawal of methylphenidate due to adverse events of unknown severity.

Secondary outcomes

1. Non-serious adverse events. All other adverse events, including but not confined to, the following common types of adverse events: cardiovascular, neurological, gastrointestinal, difficulty with sleep, and growth retardation in accordance with the *Guideline for Good Clinical Practice E6(R1)* (ICH 1996).
2. Withdrawal of methylphenidate due to non-serious adverse events.
3. Withdrawal of methylphenidate for unknown reasons.

Adverse events were measured during treatment, at the end of treatment and at the longest follow-up, using rating scales, spontaneous reports recorded by the investigators at regular interviews or visits, and physical examinations or para-clinical examinations.

We reported the primary and the secondary outcomes in Summary of findings for the main comparison.

See Differences between protocol and review.

Search methods for identification of studies

Electronic searches

In February 2015, we simultaneously conducted the literature searches for this and another review by including a separate search strategy of adverse events, as described in the previous review (Storebø 2015). We predicted that reports on efficacy as well as adverse events would both describe the adverse events of methylphenidate, which is why it made good sense to combine the two search strategies and thus maximise the retrieval of relevant publications. In order to overcome poor indexing and abstracting, we listed individual brand names in the search strategies. The search strategies, as executed in both reviews, are shown in Appendix 1.

On 8 January 2016, we ran an updated version of the adverse events search strategy that included new brand names and study designs. We also searched a number of additional sources to identify grey literature.

We searched the electronic databases and trial registers listed below, in order to identify relevant studies.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 1), in the Cochrane Library, which includes the Cochrane Developmental, Psychosocial and Learning Problems Specialised Register (searched 8 January 2016).
2. MEDLINE Ovid (1948 to January week 3 2016).
3. Embase Ovid (1980 to January week 3 2016).
4. PsycINFO Ovid (1806 to January week 3 2016).
5. CINAHL EBSCOhost (Cumulative Index to Nursing & Allied Health Literature; 1980 to 8 January 2016).
6. Conference Proceedings Citation Index - Science Web of Science (CPCI-S; 1990 to 14 November 2017).
7. Conference Proceedings Citation Index - Social Science & Humanities Web of Science (CPCI-SS&H; 1990 to 14 November 2017).
8. NDLTD Theses Resources (ndltd.org/resources; all available years; searched 11 January 2016).
9. Trove - National Library of Australia (trove.nla.gov.au; all available years; searched 11 January 2016).
10. British Library E-Theses Online Service (EThOS; ethos.bl.uk; all available years; searched 11 January 2016).
11. Deutsche Nationalbibliothek Dissertations (www.dnb.de/EN/Home/home_node.html; all available years; searched 11 January 2016).
12. Open Access Theses and Dissertations (OATD; oatd.org; all available years; searched 11 January 2016).
13. Theses Collection Wales - The National Library of Wales (www.llgc.org.uk/en/discover/nlw-resources/theses-collection-wales; all available years; searched 11 January 2016).
14. DART-Europe E-Theses Portal (www.dart-europe.eu/basic-search.php; all available years; searched 11 January 2016).
15. Bielefeld Academic Search Engine (BASE; www.base-search.net/about/en; all available years; searched 11 January 2016).
16. Theses France (www.theses.fr/en; all available years; searched 11 January 2016).

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17. ProQuest Open Access Dissertations (PQDT; pqdtopen.proquest.com/search.html; all available years; searched 11 January 2016).
18. ClinicalTrials.gov (clinicaltrials.gov; all available years; searched 11 January 2016).
19. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; who.int/ictrp/en; all available years; searched 11 January 2016).

We did not limit the searches by language, year of publication, or type of publication. We translated relevant sections of non-English language reports when needed.

See Differences between protocol and review.

Searching other resources

In order to find additional relevant studies not identified by the electronic searches listed above, we scrutinised the bibliographic references of identified review articles and meta-analyses. Furthermore, we sent requests for published as well as unpublished data to pharmaceutical companies manufacturing methylphenidate, including Shire (www.shire.com), Medice (represented in Denmark by HB Pharma: www.hbpharma.dk), Janssen-Cilag (www.janssen.com), and Novartis (www.novartis.com) (see supplementary file Letter to pharmaceutical companies). We also requested unpublished studies from several hundred authors (Figure 1).

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Figure 1. Study flow diagram

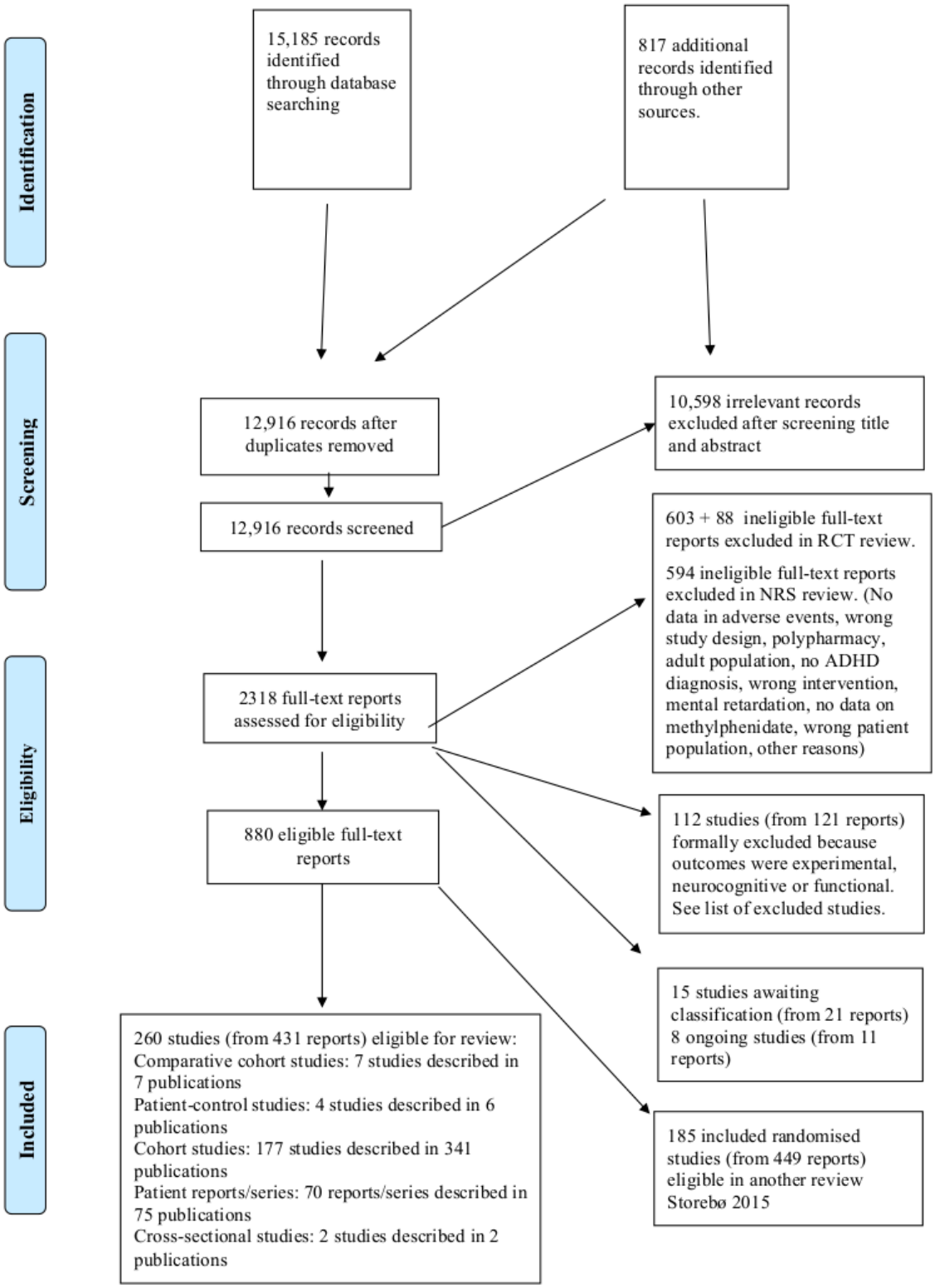

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Figure 1. (Continued)

publications

In addition, we searched the websites of the US Food and Drug Administration (FDA; www.fda.gov) and the European Medicines Agency (EMA; www.ema.europa.eu/ema).

Data collection and analysis

We conducted the review in accordance with guidance in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), the PRISMA guidelines (Liberati 2009; Moher 2015), and the Cochrane ROBINS-I tool for for assessing **r**isk **o**f **b**ias **i**n **n**on-randomised **s**tudies of **i**nterventions (formerly named ACROBAT) (Sterne 2014; Sterne 2016).

We performed the analysis using Cochrane's software, Review Manager 5 (RevMan 5) (Review Manager 2014).

Selection of studies

Fourteen review authors (CRMM, ER, FLM, HBK, KBR, LA, MH, MS, NP, OJS, SJH, SR, TB, and TG) worked together in groups of two and independently screened the titles and abstracts of all records retrieved by the searches; we resolved uncertainty or disagreement by consensus. We obtained the full texts of all potentially relevant reports and assessed each one against our inclusion criteria (Criteria for considering studies for this review). We discussed disagreements and consulted OJS and CG when agreement could not be reached. We have listed relevant non-randomised studies that do not fulfil the inclusion criteria with reasons for exclusion in the Characteristics of excluded studies table. We recorded our selection process in a study flow diagram (Moher 2009).

See Differences between protocol and review.

Data extraction and management

We developed data extraction forms to facilitate standardisation of this process. We extracted data on participants, study design and methods, interventions, adverse events, and relevant data for 'Risk of bias' assessments.

All review authors extracted data. The authors worked together in groups of two, and each pair completed the data collection form independently to ensure accuracy. We resolved disagreements by discussion or used an arbiter if required. Six review authors (CRMM, FLM, HBK, MH, NP, and OJS) entered data into RevMan 5 (Review Manager 2014). In cases of insufficient data, or where data in the published study reports were unclear, we contacted the study authors requesting them to clarify the missing information (see Dealing with missing data).

See Differences between protocol and review.

Assessment of risk of bias in included studies

For each included study, two review authors (LA, SJH) used the ROBINS-I tool and independently assessed the risk of bias of comparative cohort studies and patient-control studies across the following seven domains (Sterne 2014; Sterne 2016).

1. Possible bias due to confounding factors

We assessed risk of bias due to:

- comorbidity;
- age;
- sex;
- subtypes of ADHD;
- socioeconomic factors;
- switch between ADHD medications;
- adjustment of medication; and
- any other confounding factor in the study.

2. Possible bias due to selection of participants

We assessed risk of bias due to:

- inclusion of patients;
- time from diagnosis to inclusion in study; and
- naïve to previous methylphenidate exposure compared to non-naïve patients.

For patient-control studies, we assessed risk of bias due to selection of controls.

3. Possible bias due to measurement of interventions

We assessed risk of bias due to:

- measurement of intervention status at start of follow-up; and
- self-reporting of intervention status.

4. Possible bias due to departures from intended interventions

We assessed risk of bias due to:

- compliance with assigned medication;
- practitioner administration;
- characteristics of the healthcare setting, for instance, public outpatient compared to hospital outpatient;
- adverse events; and
- lack of efficacy of treatment.

5. Possible bias due to missing data

We assessed risk of bias due to loss to follow-up.

For patient-control studies, we assessed risk of bias due to differences in follow-up between exposed and non-exposed patients.

6. Possible bias in measurement of outcomes

We assessed risk of bias due to:

- self-reporting of adverse events; and
- error in instruments measuring adverse events.

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7. Possible bias in selection of reported results

We assessed risk of bias due to:

- type of analysis; and
- selection of results.

Review authors judged each domain to be at low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias, or no information, as follows.

1. Low risk of bias: the study is comparable to a well-performed RCT with regards to this domain.
2. Moderate risk of bias: the study is sound for a non-randomised study with regards to this domain but cannot be considered comparable to a well-performed RCT.
3. Serious risk of bias: the study has some important problems in this domain.
4. Critical risk of bias: the study is too problematic in this domain to provide any useful evidence on the effects of the intervention.
5. No information: there is no information on which to base a judgment about risk of bias for this domain.

We assigned studies an overall rating of low risk of bias when we judged them to be at low risk of bias in all domains; moderate risk of bias when we judged them to be at moderate risk of bias in at least one domain, but not at serious or critical risk of bias in any domain; serious risk of bias when we judged them to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domains; critical risk of bias when we judged them to be at critical risk of bias in at least one domain; and no information when there was no clear indication that the study is at serious or critical risk of bias and there was a lack of information in one or more key domains of bias.

We resolved any disagreements by discussion. It was not possible to assess non-comparative studies for risk of bias using ROBINS-I because it is a prerequisite in this tool that there is a comparative study. The non-comparative studies are at critical risk of bias mostly due to confounding factors, so we considered all these studies to be at critical risk of bias as described in the ROBINS-I manual: "a study is too problematic to provide any useful evidence on the effects of intervention" (Sterne 2014; Sterne 2016).

There is reason to believe that other factors result in an under-reporting of adverse events, such as a general reluctance to report them (Ioannidis 1998; Ioannidis 2009), inadequate monitoring (Loke 2011), and exclusion of patients with risk factors for adverse events (Pagsberg 2017).

Measures of treatment effect

Dichotomous data

We summarised dichotomous data as risk ratios (RR) with 95% confidence intervals (CI). We present pooled proportion data from non-comparative studies using the Comprehensive Meta-Analysis Software (CMA; Comprehensive Meta Analysis). See Differences between protocol and review. For numbers below 10, we gave two decimals. For numbers at 10 or above, we gave one decimal.

Continuous data

For continuous data, we calculated the mean difference (MD) between the two groups and present it with 95% CI. We used the overall MD, where possible, to compare outcome measures from studies. We estimated the standardised MD (SMD) where studies used different measures to assess the same outcome. If studies did not report means and standard deviations (SD) but reported other values, such as t-tests and P values, we calculated the SD using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For numbers below 10, we gave two decimals. For numbers at 10 or above, we gave one decimal.

Unit of analysis issues

We included in this review a number of cross-over trials that met our inclusion criteria (Criteria for considering studies for this review). Cross-over trials are more prone to bias from carry-over effects, period effects, and unit-of analysis issues (Curtin 2002). However, as we only used the data from the methylphenidate groups from the first period of these trials, we believe that these biases do not influence the proportions reported.

Dealing with missing data

We tried to obtain missing data by contacting the authors of the studies. We wrote letters to 174 authors twice and received replies from 108. Many authors supplied us with missing sociodemographic data and missing information about methodology, and some supplied us with missing statistics. If data remained unavailable, we tried to estimate the missing data using the available information (e.g. if the SD was missing, we estimated it from the standard error, if reported).

Assessment of heterogeneity

We assessed the following types of heterogeneity: clinical (variability in participants, interventions, or settings); methodological (variation in study designs); and statistical heterogeneity (variation in intervention effects). We assessed heterogeneity between studies by visual inspection of the forest plot for overlapping CIs; using the Chi^2 test for homogeneity with a significance level of α (alpha) = 0.10, and the I^2 statistic for quantifying inconsistency (estimating the percentage of variation in effect estimates due to heterogeneity rather than sampling error). We judged I^2 values of 0% to 40% to indicate little heterogeneity; 30% to 60%, moderate heterogeneity; 50% to 90%, substantial heterogeneity; and 75% to 100%, considerable heterogeneity (Higgins 2011). We abstained from conducting a meta-analysis if there was a very high level of heterogeneity and the studies seemed to address different questions; Section 9.5.3.2 in the*Cochrane Handbook for Systematic Reviews of Interventions* recommends that if "there is considerable variation in results, and particularly if there is inconsistency in the direction of effect, it may be misleading to quote an average value for the intervention effect" (Higgins 2011). Where it was not possible to undertake a meta-analysis, we provided a narrative description of the prevalence estimate.

Not all studies used the same outcome measures. For example, for height, some studies used centimetres while other studies provided age and sex-adjusted scores, and we could not analyse these studies.

Study characteristics that may have been important to assess included the following.

1. Number of confounders included in the models.

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2. Analysis technique used.

Assessment of reporting biases

Reporting bias and missing studies are more complex issues for non-randomised studies than for RCTs. Registration and publication of protocols for non-randomised studies are not as common as for RCTs (Skoog 2015). We aimed to include a wide range of studies by using a broad search strategy, and we handled different forms of reporting bias, especially publication bias and outcome reporting bias, according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not draw funnel plots (estimated differences in treatment effects against their standard error) due to too few studies, nor did we perform Egger's statistical test for small-study effects (Egger 1997). Asymmetry could be due to publication bias but also to genuine heterogeneity between small and large trials (Higgins 2011).

See Differences between protocol and review.

Data synthesis

We analysed and presented the pooled estimates of the different adverse events according to the following study designs:

1. comparative studies (cohort studies and patient-control studies);
2. non-comparative studies (cohort studies without a control group, including the methylphenidate-treated group from randomised clinical trials (RCTs) comparing methylphenidate versus other interventions for ADHD excluded from our previous review (Storebø 2015), and cross sectional studies); and
3. patient reports/series, which we used to identify less common (rare) adverse events, defined according to the brand leader's Summary of Product Characteristics (SPC; Aagaard 2009).

As prespecified in our protocol (Storebø 2016), we tried to be as pragmatic as possible by further grouping the reported adverse events according to the main body systems affected, namely: central nervous system; cardiovascular and respiratory systems; gastrointestinal system; musculoskeletal system; immune system; urinogenital system; and other body systems. We then conducted meta-analyses of the proportion of different adverse events under each system.

If there were adequate data, we pooled the data from comparative studies and conducted a meta-analysis of the estimates. If there were inadequate data, we reported the results qualitatively.

We synthesised data qualitatively across some cohort studies, cross sectional studies and patient report/series when data could not be used in meta-analyses.

Some studies have combined designs (for example, non-comparative cohort and patient-control study design). In those cases we synthesised the comparative and non-comparative data separately.

Our analyses and conclusions of the results differ between comparative and non-comparative studies. We use data from comparative cohort studies and patient-control studies to evaluate the RR of harms. For the comparative studies, we performed a meta-analysis according to recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

If clinical heterogeneity was not excessive (for example, there was not too much variability in participants' characteristics), we performed a meta-analysis of the results using the inverse-variance method. This method gives more weight to larger studies, reducing imprecision in the pooled estimate of effect. We used the random-effects model in all meta-analyses and the fixed-effect model in sensitivity analyses (see Sensitivity analysis). The random-effects model is best suited to our data due to the relatively high heterogeneity. In most analyses there were no significant differences between the two statistical models. In cases where there was a statistical difference, the fixed-effect model mostly showed a higher proportion of adverse events. The decision to report the random-effects model was therefore a conservative one.

Subgroup analysis and investigation of heterogeneity

Because of high levels of clinical and statistical heterogeneity, we conducted subgroup analyses to identify whether there was an increased risk associated with children who: had received concurrent medication; had a comorbid condition; had received methylphenidate for longer periods; were younger; or had received a higher dose of methylphenidate. Study characteristics that may have been associated with differences in risk included higher quality and independent funding.

We conducted the following subgroup analyses.

1. Studies with concurrent medication versus studies without any concurrent medication (children and adolescents may be more susceptible to adverse events if they are also receiving other medications).
2. Studies with ADHD as the only disease versus studies with ADHD and comorbidity (children and adolescents may be more susceptible to adverse events if they have other behavioural, neurological or psychological comorbidities).
3. Studies with a treatment duration shorter than six months versus studies with a treatment duration of six months or longer (there may be cumulative effects of methylphenidate over time).
4. Studies with participants with a mean age younger than 10 years versus studies with participants with a mean age of 10 years or older (younger children are more susceptible to the adverse events of methylphenidate because of their smaller size and differences in metabolism).
5. Studies with a low dosage of methylphenidate (below 20 mg/day) versus studies with a high dosage of methylphenidate (20 mg/day and above) (adverse events are more likely with high-dose methylphenidate).
6. Cohort studies on methylphenidate originating from RCTs comparing methylphenidate to other ADHD interventions versus studies with a classic cohort design (there may be differences in estimates in higher-quality studies (RCTs) relative to lower-quality studies (cohorts and other observational designs)) (Garattini 2016).
7. Studies funded by industry versus studies not funded by industry (studies sponsored by drug companies have been shown to be less likely to report risks) (Lundh 2017).

See Differences between protocol and review.

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Sensitivity analysis

As we used a random-effects model for all analyses, we conducted a sensitivity analysis to test the robustness of our findings when using the alternative, fixed-effect model for the outcomes of non-serious adverse events (there were inadequate data available to test this for serious adverse events). In addition, we tested the robustness of findings when lower-quality patient-control studies were removed from the analysis.

See Differences between protocol and review.

'Summary of findings' table

We constructed a 'Summary of findings' table for all outcomes, using GRADEpro GDT 2015 software. We assessed the quality of the body of evidence for each outcome using the GRADE approach based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Considerations are due to: within-study risk of bias; the directness of the evidence; heterogeneity of the data; precision of effect estimates; and risk of publication bias (Andrews 2013a; Andrews 2013b; Balshem 2011; Brunetti 2013; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Mustafa 2013). We reported all three primary (serious adverse events, withdrawal of methylphenidate due to serious adverse events, withdrawal of methylphenidate due to adverse events of unknown severity) and secondary outcomes (non-serious adverse events, withdrawal of methylphenidate due to non-serious adverse events, withdrawal of methylphenidate due to unknown reasons) in Summary of findings for the main comparison.

RESULTS

Description of studies

For more information, please see Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification, and Characteristics of ongoing studies.

Results of the search

We carried out the first set of electronic searches in November 2012 (11,329 records), and ran top-up searches in March 2014 (1274 records), February 2015 (1460 records) and January 2016 (1102 records). Conference Proceedings Citation Indexes were not available to us in 2016, but we were able to complete our searches of these two databases in November 2017 (20 records). We included additional sources to the January 2016 search in order to identify new theses but did not find any. Our electronic searches yielded a total of 15,185 records. We also identified an additional 817 publications by reading the reference lists of included articles and reviews, and from correspondence with authors and with pharmaceutical companies and other sources. We contacted the authors of 174 studies and received replies from 109.

After eliminating duplicate records, we screened 12,916 records and excluded 10,598 clearly irrelevant reports on the basis of title and abstract. We retrieved the full texts of the remaining 2318 reports, which we assessed for eligibility. We excluded 691 full-text reports from our systematic review on RCTs assessing methylphenidate versus placebo or no intervention (Storebø 2015). We excluded a further 715 ineligible reports; see Excluded studies and Characteristics of excluded studies tables. We identified 15 studies (from 21 reports) as awaiting classification (see Characteristics of studies awaiting classification) and 8 ongoing studies (from 11 reports, see Characteristics of ongoing studies).

We included 880 reports, of which 449 described 185 RCTs and 431 reports described 260 non-randomised studies (of which 49 originated from 49 head-to head RCTs comparing methylphenidate versus other interventions aimed at treating ADHD). The data from the 185 RCTs in which methylphenidate was compared with placebo or no intervention are published in Storebø 2015. The present review focuses on non-randomised studies only and thus includes 260 studies (Figure 1), which includes methylphenidate groups from the 49 RCTs comparing methylphenidate versus another medication aimed at treating ADHD, excluded in the Storebø 2015 review. Accordingly, we assessed a total of 260 non-randomised studies described in 431 publications. For more information of these studies, please see Characteristics of included studies.

Included studies

Comparative studies

We included 11 comparative studies in this review: seven cohort studies (Cockcroft 2009; Hemmer 2001; Langevin 2012; Shin 2016; Stein 2002; Tzang 2012; Verret 2010), plus four patient-control studies (Ayaz 2014; Dubnov-Raz 2011; Shyu 2015; Zhang 2010). One study had both comparative and non-comparative cohort data (Shin 2016).

Study duration

We were unable to find any information about study duration in two studies (Hemmer 2001; Stein 2002). The other studies ranged in duration from one day in Cockcroft 2009 up to 11 years in Ayaz 2014, Dubnov-Raz 2011, Shin 2016, Shyu 2015, Tzang 2012, Langevin 2012, Verret 2010, and Zhang 2010.

Location

Two studies took place in Canada (Langevin 2012; Verret 2010), two in China (Tzang 2012; Zhang 2010), two in Israel, (Dubnov-Raz 2011; Stein 2002), and one each in South Africa (Cockcroft 2009), South Korea (Shin 2016), Taiwan (Shyu 2015), Turkey (Ayaz 2014), and the USA (Hemmer 2001).

Settings

All were outpatient studies (Ayaz 2014; Cockcroft 2009; Dubnov-Raz 2011; Hemmer 2001; Langevin 2012; Shin 2016; Shyu 2015; Stein 2002; Tzang 2012; Verret 2010; Zhang 2010), two of which were based on register data (Shin 2016; Shyu 2015).

Participants

There was considerable heterogeneity amongst the studies in terms of diagnostic criteria used, presence of comorbidity, numbers exposed to methylphenidate and simultaneous exposure to other medication. The mean age of children varied from 7.4 years in Zhang 2010 to 13.0 years in Stein 2002, with an age range of 3 years to 20 years. All studies involved predominantly male participants ranging from 69% in Cockcroft 2009 to 100% in both Stein 2002 and Verret 2010.

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Six comparative cohort studies involved 1134 participants, 968 of whom received methylphenidate and 166 of whom did not (Cockcroft 2009; Hemmer 2001; Langevin 2012; Stein 2002; Tzang 2012; Verret 2010). A seventh study, Shin 2016, involved 1224 participants, all of whom were exposed to methylphenidate for a specific treatment period. This study only included patients with an adverse cardiovascular event. The four patient-control studies comprised 73,098 participants: 53,192 cases who received methylphenidate and 19,906 controls who did not. All participants were aged 6 years to 19 years. The male-to-female ratio was approximately 80:20.

Three studies made DSM-IV diagnoses (Ayaz 2014; Dubnov-Raz 2011; Zhang 2010); and two made ICD-9 and ICD-10 diagnoses (Shin 2016; Shyu 2015). Ayaz 2014 required that ADHD medication be administered to patients at least 12 months prior to the study. Shin 2016 only included patients with an adverse cardiovascular event.

Interventions

There was considerable variation in dosage and methylphenidate preparation used as well as mean duration of exposure. The control groups not exposed to methylphenidate received atomoxetine in two studies (Ayaz 2014; Dubnov-Raz 2011), while in eight studies the control was no treatment (Cockcroft 2009; Hemmer 2001; Langevin 2012; Shyu 2015; Stein 2002; Tzang 2012; Verret 2010; Zhang 2010). Participants in Shin 2016 received methylphenidate or no treatment at different times.

Non-comparative studies

In the following section, we describe non-comparative studies according to the design of the individual study, namely cohort studies, cross-sectional studies, and patient reports/series.

Cohort studies

We included 177 cohort studies, reported in 341 publications. Of these, 49 cohorts were the methylphenidate group of the RCTs assessing this drug versus other medications for ADHD. Many of the cohort studies included in this review originally had a control group of healthy participants, but these groups did not fulfil our inclusion criteria (Criteria for considering studies for this review); we only included groups with participants diagnosed with ADHD (e.g. Sahin 2014). One study had both comparative and non-comparative cohort data (Shin 2016).

Study duration

The cohort studies lasted from one day in Balázs 2011, Congologlu 2009, Delignieres 2011, Ilgenli 2007, and Lyon 2010 to 9.70 years in Haubold 2010. Nine studies lasted 28 days or less (Dirksen 2002; Döpfner 2011b; Galland 2010; Gau 2008; Kemner 2005 (FOCUS); Lee 2007; Park 2013; Schulz 2010; Sudarmadji 2009). Twenty-five studies were performed over 42 days, and 15 studies over 28 days (Akhondzadeh 2003; Arnold 2010; Ashkenasi 2011; Efron 1997; Gau 2006; Hulvershorn 2012; Jung 2007; Kim 2011; Lamberti 2015; Lee 2012; Maayan 2009; McCracken 2016; Pierce 2010; Wilens 2006; Williams 2008). Sixty-six studies lasted 42 to 180 days. Forty-four studies lasted 180 days or more. Twelve studies did not report any study duration.

Location

Forty-eight studies were carried out in the USA; 18 studies each in Iran, South Korea, and in Germany; 17 studies in Turkey; 7 studies in Taiwan (Chou 2012a; Chou 2012b; Gau 2006; Gau 2008; Shang 2015; Wang 2011; Yang 2004); 6 studies each in Australia (Dupuy 2008; Efron 1997; Hazell 2003; Poulton 2003; Poulton 2012; Williams 2008) and Spain (Durá-Travé 2012; Larrañaga-Fragoso 2015; Montañés-Rada 2012; Tomás Vila 2010a; Valdizán Usón 2004; Valdizán Usón 2013); 5 studies each in Brazil (Chazan 2011; Guerreiro 1996; Maia 2008; Polanczyk 2007; Zeni 2007) and China (Li 2011; Su 2015; Yang 2012; Zheng 2011; Zheng 2015); 4 studies each in Israel (Golubchik 2011; Green 2011; Lahat 2000; Zelnik 2015) and Italy (Atzori 2009; Cortese 2015; Germinario 2013; Lamberti 2015); 3 studies each in Canada (Cherland 1999; Steele 2006; Weiss 2007) and the UK (Abbas 2006; McCarthy 2009; Santosh 2006); 2 studies each in Egypt (El-Fiky 2014; Yang 2012), France (Delignieres 2011; Peyre 2012a), and Indonesia (Sudarmadji 2009; Wiguna 2012); 1 study each in India (Garg 2014), Ireland (Johnson 2013), Japan (Yatsuga 2014), New Zealand (Galland 2010), Serbia (Lakic 2012), Sri Lanka (Perera 2010), Thailand (Moungnoi 2011), the Netherlands (Van der Oord 2007), and Venezuela (Montiel-Nava 2002).

Seven studies (3.9%) were multicentre studies, carried out in more than one country: Altin 2013 (China, Egypt, Lebanon, Russia, Taiwan, and the United Arab Emirates); Goez 2012 (Canada and Israel); Remschmidt 2005 (Germany and the UK); Wang 2007 (China, Korea, and Mexico); and Jensen 1999 (MTA), Klein 2004 and Kratochvil 2002 (Canada and the USA).

The distribution of studies among continents is: 72 studies (40.7%) in Asia, 51 studies (28.8%) in North America, 6 studies (3.40%) in South America (Chazan 2011; Guerreiro 1996; Maia 2008; Polanczyk 2007; Zeni 2007; Montiel-Nava 2002), 38 studies (21.5%) in Europe, 8 studies (4.50%) in Oceania (Dupuy 2008; Efron 1997; Galland 2010; Hazell 2003; Poulton 2003; Poulton 2012; Williams 2008; Montiel-Nava 2002), and 2 studies (1.1%) in Africa (El-Fiky 2014; Yang 2012).

Setting

Most studies took place in outpatient settings, with very few in-hospital settings (Ardic 2014; Kim 2010; Larrañaga-Fragoso 2015; Yalcin 2014).

Participants

The 177 cohort studies included 2,207,751 participants. Not all studies provided information on age and sex. The mean age was 9.71 years; 34,753 participants were male, and 9537 were female. One large study with 2,150,362 participants did not provide information on sex (Kraut 2013).

Fifty-two studies (29.4%) included methylphenidate-naïve participants, 29 (16.4%) included no methylphenidate-naïve participants, and 26 (14.9%) included a combination of naïve and non-naïve participants. The remaining 70 studies (39.5%) did not report any information regarding drug naïvety.

Thirty studies (16.9%) included participants with ADHD diagnoses alone, while 81 studies (45.8%) included patients with one or more comorbid psychiatric conditions. In 66 studies (37.3%), it was not possible to retrieve information regarding comorbidity. Twenty-one studies (11.9%) included participants using concurrent medications, whereas 57 studies (32.2%) excluded participants using non-methylphenidate medication during follow-up. Reported concurrent medication included other ADHD medications, antidepressants, antipsychotics, pain relievers, antiepileptics, anticonvulsants, antiasthmatic drugs,

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allergy medications, and anxiolytics. Ninety-nine studies (55.9%) did not provide data regarding concurrent use of medication.

Interventions

The 177 studies used a range of formulations of methylphenidate. Sixty-three (35.6%) studies did not specify the type of methylphenidate.

Fifty-two studies (29.4%) used extended-release methylphenidate only: 4, dexmethylphenidate (Arnold 2004; Lyon 2010; McCracken 2016; Silva 2004); 7, methylphenidate-spheroidal oral drug absorption system (Haertling 2015; Maayan 2009; Maia 2008; Peyre 2012a; Schulz 2010; Wiguna 2012; Witt 2008); 7, methylphenidate-transdermal patch (Arnold 2010; Ashkenasi 2011; Faraone 2007a; Findling 2009; Findling 2010; Warshaw 2010; Wilens 2008); and 34, methylphenidate-osmotic-release oral system. Thirteen studies did not specify which type of extended-release methylphenidate was used in the study (Buchmann 2007; Chazan 2011; Dirksen 2002; Döpfner 2011a, OBSEER; Döpfner 2011c; Haubold 2010; Hong 2012; Kim 2015a; Mohammadi 2009; Montañés-Rada 2012; Tomás Vila 2010b; Weiss 2007; Wigal 2015).

Twenty-nine studies (16.4%) used immediate-release methylphenidate only. Twenty-two studies (12.4%) used combinations of methylphenidate-immediate release and methylphenidate-extended release, or combinations with placebo (Abbasi 2011; Ghanizadeh 2013). Fifteen studies (8.50%) did not specify dosage.

Sixty-three studies (35.6%) reported methylphenidate dosage in mg/kg/day, ranging from 0.30 mg/kg/day in Efron 1997 to 1.52 mg/kg/day in Wilens 2005. Twelve studies (6.80% of the total sample) used a dosage of 0.60 mg/kg/day or less (Arman 2013; Atzori 2009; Chazan 2011; Congologlu 2009; Dittmann 2014; Efron 1997; Garg 2014; Greenberg 1987; Johnson 2013; Moungnoi 2011; Wang 2007; Zeni 2007).

One hundred and six (59.9%) studies reported methylphenidate dosage in mg/day, 64 studies (36.2%) reported dosage as a range, from 2.50 mg/day in Mayes 1994 and Perera 2010 to 120 mg/day in Döpfner 2011a, OBSEER.

Ninety-seven studies (54.8%) reported mean dosage. The mean daily dose of methylphenidate-immediate release was 0.67 mg/kg/day (13 studies) and 24.7 mg/day (19 studies). Mean daily dose ranged from 0.42 mg/kg/day in Atzori 2009 to 1 mg/kg/day in Schertz 1996 and Spencer 1992), and from 10 mg/day in Lahat 2000 to 36.9 mg/day in Klein 2004. For methylphenidate-extended release, the daily dose was, on average, 0.95 mg/kg/day (18 studies) and 26.8 mg/day (26 studies), ranging from 0.48 mg/kg/day (Chazan 2011) to 1.18 mg/kg/day (Chou 2012a), and from 7.50 mg/day (Lyon 2010) to 60 mg/day (Döpfner 2011a, OBSEER).

Cross-sectional studies

We included two cross-sectional studies described in two publications (Stevens 2010; Thorell 2009).

Location

Thorell 2009 took place in Sweden and Stevens 2010 in the USA.

Setting

Stevens 2010 was carried out in both inpatient and outpatient clinics, whereas Thorell 2009 was an outpatient study.

Participants

The two cross-sectional studies included a total of 96 participants, all of whom were aged between 9 and 20 years. In one study, participants were eligible for inclusion if diagnosed with ADHD and treated with higher than FDA-approved doses of methylphenidate (> 72 mg/d) between December 2006 and August 2007 (Stevens 2010). Seventeen participants were included in the analysis. The most common comorbid disorder with ADHD was mood disorders followed by pervasive development disorders and oppositional disorders. The other study included 79 children between the ages of 9 and 17 years receiving stimulant medication (Thorell 2009). The included participants had the following comorbid diagnoses: Asperger's syndrome (n = 6), Tourette syndrome (n = 11), obsessive-compulsive disorder (n = 2), mild mental retardation (n = 2), and oppositional defiant disorder or conduct disorder (n = 2).

Interventions

In Stevens 2010, all participants were treated with osmotic-release oral-system (OROS) methylphenidate. The mean total daily dose was 169 mg/day (SD 31 mg/day; range 126 mg/day to 270 mg/day) or 2.97 mg/day (SD 0.76 mg/kg/day; range 1.13 mg/kg/day to 4.21 mg/kg/day). All patients received concomitant psychotropic medication during the evaluation period. Bupropion, selective serotonin re-uptake inhibitors, and lithium were the most commonly medications coadministered with OROS methylphenidate.

Nearly all (96.0%) the children in Thorell 2009 took methylphenidate, whereas 4.0% took amphetamine. The authors did not report methylphenidate type or dosage.

Patient reports/series

We included 70 patient reports/series described in 75 publications (Figure 1). Nineteen reports were from the USA; 16 from Turkey; five each from Israel (Artul 2014; Cohen 1992; Confino-Cohen 2005; Gross-Tsur 2004; Halevy 2009) and the UK (Adrian 2001; Corrigall 1996; Hollis 2007; Shibib 2009; Woolley 2003); four each from Iran (Ghanizadeh 2008a; Ghanizadeh 2008b; Ghanizadeh 2008c; Ghanizadeh 2009) and Spain (Aguilera-Albesa 2010; Fernández-Fernández 2010; Fernández-Fernández 2011; Tomás Vila 2010a); three from Italy (Niederhofer 2009; Niederhofer 2011; Porfirio 2011); two each from Germany (Bernhard 2009; Holtkamp 2002), India (Agarwal 2008; Arun 2014), and Norway (Nymark 2008; Tølløfsrud 2006); and one each from Canada (Hechtman 2011), Chile (Saieh 2004), the Czech Republic (Goetz 2011), Denmark (Munk 2015), France (Coignoux 2009), Japan (Mino 1999), Sweden (Strandell 2007), and Taiwan (Tang 2010). The 70 patient reports/series included a total of 206 participants. A single report from a pharmacovigilance programme accounted for 116 of these (Strandell 2007).

All participants were aged between 4 and 20 years, with a mean age of 10 years. Seventy participants were male, 20 were female, and the sex for the remaining 116 patients was not stated. The participants were treated with both immediate-release and extended-release formulations of methylphenidate, and the doses ranged from 10 mg/day to 108 mg/day. The duration of treatment

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ranged from one day in Machado 2010 to 17 years in Ramasamy 2014.

Outcome measures: serious and non-serious adverse events

Adverse events were measured by rating scales, including questionnaires and checklists, by spontaneous reports and/or were recorded by investigators at regular interviews or visits.

Some studies included specific measurements such as physical examinations, para-clinical examinations, or both, including blood testing, electrocardiogram (ECG), blood pressure reading, measurement of heart rate and assessment of weight and height.

Serious adverse events were recorded in accordance with the International Conference of Harmonization (ICH) classification (ICH 1996).

Some studies combined some or all of the above modes of measurement; others used a single measure such as spontaneous reports or rating scales.

Investigators used the Barkley Side Effects Rating Scale most frequently (Barkley 1990). Other scales used included the Safety Monitoring Uniform Report Form (Greenhill 2004), the Pittsburgh Side Effects Rating Scale (Pelham 1993; Pelham 2005), and the Clinical Assessment of Side Effects.

For measuring specific adverse events, some studies used rating scales such as the Children's Depression inventory (Kovacs 1992), the Children's Yale-Brown Obsessive-Compulsive Scale (Scahill 1997), the Revised Children's Manifest Anxiety Scale (Reynolds 1985), the Yale Global Tic Severity Scale (Leckman 1989), the Sleep Disturbances Scale for Children (Bruni 1996), the Children's Sleep Habits Questionnaire (Owens 2000), and the Paediatric Sleep Questionnaire (Chervin 2000).

Comparative cohort studies

In the seven comparative studies that we included, four studies employed a rating scale (Cockcroft 2009; Langevin 2012; Stein 2002; Tzang 2012), two used a specific measurement (Hemmer 2001; Verret 2010), and one used diagnostic assessment (Shin 2016). Cockcroft 2009 also used a subjective pictorial scale designed specifically for the study.

Patient-control studies

In the four included patient-control studies, two used spontaneous reporting (Ayaz 2014; Dubnov-Raz 2011), two used a specific measurement (Dubnov-Raz 2011; Zhang 2010), and one used diagnostic assessment (Shyu 2015). Accordingly, one study used both spontaneous reporting and a specific measurement (Dubnov-Raz 2011).

Cohort studies

Of the 177 included cohort studies, 84 employed a checklist, questionnaire, or rating scale. Sixty-nine studies used a specific physiological measurement, such as heart rate or blood pressure, 26 used spontaneous reporting, and 44 used some other method to assess adverse events. Several studies used more than one mode of measurement.

Cross-sectional studies

Of the two included cross-sectional studies, Stevens 2010 used spontaneous reports, and Thorell 2009 used a questionnaire to measure adverse events.

Patient reports/series

Of the 70 included patient reports/series, 68 had spontaneous reporting of adverse events. One study used both spontaneous reporting and a rating scale (Coşkun 2011), one study used only a rating scale (Rapport 1996), and one study used ophthalmic examination (Lewis 2012).

Funding

Pharmaceutical companies funded 53 out of the 177 non-comparative cohort studies, and 11 out of the 177 had authors with connections to pharmaceutical advisory boards. Forty-five out of the 177 did not report a source of funding, and 68 out of 177 were not funded by or affiliated with pharmaceutical industries.

We performed two subgroup analyses investigating the differences in the proportion of adverse events in studies funded by industry and studies not funded by industry, and we found large differences, with many more adverse events (both serious and non-serious) in the studies not funded by industry (see Subgroup analyses, under Effects of interventions).

Excluded studies

We took an inclusive approach by assessing 2318 full-text reports for eligibility against our inclusion criteria (Criteria for considering studies for this review). We subsequently excluded 1285 reports as ineligible: 691 reported on RCTs (those containing new data will be included in an update of our systematic review; Storebø 2015), and 594 others either did not report data on adverse events; had ineligible study designs; involved polypharmacy; lacked an ADHD diagnosis; had ineligible interventions; had no data; focused on adults, patients with intellectual disability, or other ineligible patient populations; or otherwise failed to meet the inclusion criteria.

In addition, we formally excluded 112 studies (from 121 reports) because they did not report anything about the presence or absence of adverse events. Furthermore, most of these studies had outcomes outside of the focus of this review such as visual attention, reaction time, memory skills, and functional abnormalities. Please see the Characteristics of excluded studies tables. See Differences between protocol and review.

Studies awaiting classification

We included 15 studies awaiting classification (Arnold-Von 2000; Dalsgaard 2011; Flapper 1989; Husár 2006; Ince 2015; Ishizaki 2001; Laezer 2015; Mulas 2014; Ptáček 2008; Radziuk 2015; Socanski 2015; Sugama 2009; TOSCA 2011; Waldon 2016; Yusufoglu 2014). Among these are five patient studies (Arnold-Von 2000; Flapper 1989; Husár 2006; Sugama 2009; Yusufoglu 2014), one parallel-group RCT (TOSCA 2011), one open-label non-controlled trial (Radziuk 2015), one review of parents reports (Mulas 2014), one observational study (Ishizaki 2001), one patient-control study (Ptáček 2008), and two non-comparative cohort studies (Dalsgaard 2011; Socanski 2015). The designs used in Ince 2015 and Waldon 2016 were unclear, and we could not retrieve Laezer 2015.

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Ongoing studies

We included eight ongoing studies (Beau 2009; Bottelier 2014; Dahlgren 2012; Díez-Suárez 2015; Djurkovic-Lazic 2009; Gau 2010; Houmann 2011; Yook 2012).

Among these are one study that examines safety signal profiles in the UK Yellow Card database (Beau 2009), one placebo-controlled trial (Bottelier 2014), one study that retrospectively investigated records of children (Dahlgren 2012), one cohort study (Djurkovic-Lazic 2009), one longitudinal naturalistic follow-up study (Díez-Suárez 2015), one database study (Gau 2010), a multicenter study on CES1 genotype response in ADHD children (Houmann 2011), and one open-label trial (Yook 2012).

Risk of bias in included studies

Risk of bias in comparative studies

Possible bias due to confounding factors

We judged the risk of bias on this domain as moderate in two studies (Stein 2002; Zhang 2010), serious in four studies (Ayaz 2014; Cockcroft 2009; Shin 2016; Tzang 2012), and critical in five studies (Dubnov-Raz 2011; Hemmer 2001; Langevin 2012; Shyu 2015; Verret 2010).

Possible bias due to selection of participants

We judged the risk of bias on this domain as moderate in five studies (Ayaz 2014; Shyu 2015; Stein 2002; Tzang 2012; Zhang 2010), serious in five studies (Cockcroft 2009; Dubnov-Raz 2011; Langevin 2012; Shin 2016; Verret 2010), and critical in one study (Hemmer 2001).

Possible bias due to measurement of interventions

We judged the risk of bias on this domain as moderate in eight studies (Ayaz 2014; Cockcroft 2009; Dubnov-Raz 2011; Langevin 2012; Shyu 2015; Stein 2002; Tzang 2012; Zhang 2010), and serious in three studies (Hemmer 2001; Shin 2016; Verret 2010).

Possible bias due to departures from intended interventions

We judged the risk of bias on this domain as moderate in five studies (Ayaz 2014; Langevin 2012; Tzang 2012; Verret 2010; Zhang 2010), serious in three studies (Cockcroft 2009; Dubnov-Raz 2011; Stein 2002), and critical in three studies (Hemmer 2001; Shyu 2015; Shin 2016).

Possible bias due to missing data

We judged the risk of bias on this domain as moderate in eight studies (Ayaz 2014; Cockcroft 2009; Dubnov-Raz 2011; Langevin 2012; Stein 2002; Tzang 2012; Verret 2010; Zhang 2010), serious in one study (Hemmer 2001), and critical in two studies (Shyu 2015; Shin 2016).

Possible bias in measurement of outcomes

We judged the risk of bias on this domain as low in one study (Ayaz 2014), moderate in five studies (Hemmer 2001; Langevin 2012; Stein 2002; Tzang 2012; Verret 2010), and serious in five studies (Cockcroft 2009; Dubnov-Raz 2011; Shin 2016; Shyu 2015; Zhang 2010).

Possible bias in selection of reported results

We judged the risk of bias on this domain as moderate in seven studies (Ayaz 2014; Dubnov-Raz 2011; Langevin 2012; Stein 2002; Tzang 2012; Verret 2010; Zhang 2010), and critical in one study (Shin 2016). For three studies, no information was available regarding this domain (Cockcroft 2009; Hemmer 2001; Shyu 2015).

Overall risk of bias

Overall, we found five studies to be at serious risk of bias (Ayaz 2014; Cockcroft 2009; Stein 2002; Tzang 2012; Zhang 2010), and six studies to be at critical risk of bias (Dubnov-Raz 2011; Hemmer 2001; Langevin 2012; Shin 2016; Shyu 2015; Verret 2010).

A table depicting the results of our 'Risk of bias' assessment for all individual studies can be seen at at zenodo.org. See supplementary file ROBINS-I Risk of Bias Table.

Risk of bias in non-comparative studies

In our protocol, Storebø 2016, we decided to use the ROBINS-I tool to rate the risk of bias in the included non-randomised studies (Sterne 2014; Sterne 2016). For studies without a control group, we initially set out to use baseline data as control information, comparing them as before-after exposure to methylphenidate. However, a number of time-dependent biases, such as time-lag bias, may limit the validity of this approach (Sterne 2014; Sterne 2016). Therefore, we avoided baseline control information. Realising that the ROBINS-I tool is designed for studies with control groups, we chose not to assess risk of bias for studies without a valid control group. Some of the included non-randomised studies had control groups with healthy participants, but designs with healthy participants were not eligible for inclusion (see Criteria for considering studies for this review). Cochrane does not recommend any tools other than ROBINS-I for rating risk of bias in non-randomised studies. Thus, we deemed all studies without valid or eligible control groups to be at critical risk of bias due to many factors, with the most important being potential confounding factors.

Effects of interventions

See: **Summary of findings for the main comparison** Methylphenidate for children and adolescents aged 18 years and under with attention deficit hyperactivity disorder (ADHD): adverse events

Below, we present our findings for our primary (serious adverse events) and secondary (non-serious adverse events) outcomes, organised by comparative studies, non-comparative studies, and patient reports/series.

A summary of the findings can be found in Summary of findings for the main comparison.

Forest plots for all meta-analyses are available as supplementary files at zenodo.org

1. Comparative studies

1.1 Primary outcomes: serious adverse events

1.1.1 Frequency of any serious adverse events

See Analysis 1.1. Of the 11 comparative studies, only three provided data on serious adverse events. We included two studies of these studies in a meta-analysis (Hemmer 2001; Shyu 2015); we excluded the third because it did not report on total serious adverse events (Shin 2016). Compared to no intervention, methylphenidate

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increased the number of patients with any serious adverse event (RR 1.36, 95% CI 1.17 to 1.57; 72,005 participants). A meta-analysis that included the double-zero event studies did not change this result.

The results of a sensitivity analysis, with the patient-control study removed (Hemmer 2001), gives an RR of 1.36 (95% CI 1.17 to 1.57) and is thus comparable.

1.1.2 Central nervous system

See Analysis 1.2. Two studies reported on different adverse events of the central nervous system (Hemmer 2001; Shyu 2015). Compared to no intervention, methylphenidate did not increase the number of patients with seizures (RR 1.31, 95% CI 0.07 to 23.74; 1 study, 234 participants; Hemmer 2001), but it did increase the number of patients with psychotic disorder (RR 1.36, 95% CI 1.17 to 1.57; 1 study, 71,771 participants; Shyu 2015).

1.1.3 Cardiovascular and respiratory system

See Analysis 1.3. One study with 1224 participants, Shin 2016, reported on cardiovascular and respiratory adverse events. Compared to no intervention, methylphenidate increased the number of patients with arrhythmias (RR 1.61, 95% CI 1.48 to 1.74), but it did not change the number of patients with:

1. hypertension (RR 1.07, 95% CI 0.94 to 1.22);
2. myocardial infarction (RR 1.33, 95% CI 0.90 to 1.98); or
3. ischaemic stroke (RR 0.70, 95% CI 0.49 to 1.01).

Methylphenidate also decreased the number of patients with heart failure (RR 0.54, 95% CI 0.30 to 0.96).

No respiratory outcomes were reported.

No comparative studies reported adverse events related to the gastrointestinal, musculoskeletal, immune, urogenital or other body systems, and no comparative studies reported withdrawal of treatment due to serious adverse events or adverse events of unknown severity.

1.2 Secondary outcomes: non-serious adverse events

Seven studies reported data on this outcome. We included five of these studies in meta-analyses (Cockcroft 2009; Stein 2002; Tzang 2012; Verret 2010; Zhang 2010). We could not use data from two further studies in our meta-analyses because the authors reported other types of outcomes on adverse events with single study results (Dubnov-Raz 2011; Langevin 2012).

1.2.1 Frequency of any non-serious adverse events

None of the seven studies reported data on the frequency of any non-serious adverse events.

1.2.2 Central nervous system

Sleep-related adverse events

See Analysis 2.1. Three studies with 425 participants reported data on sleep disturbance (Cockcroft 2009; Stein 2002; Tzang 2012). We conducted a meta-analysis and found that, compared to no intervention, methylphenidate increased the number of patients with insomnia and sleep problems (RR 2.58, 95% CI 1.24 to 5.34; 3 studies, 425 participants).

One study with 23 participants, Cockcroft 2009, compared methylphenidate to no intervention and found that methylphenidate did not increase the number of patients with:

a. nightmares (RR 1.15, 95% CI 0.41 to 3.21);
b. snoring (RR 4.62, 95% CI 0.25 to 86.7);
c. non-breathing or gasping while sleeping (RR 2.77, 95% CI 0.12 to 61.7);
d. sleepwalking (RR 2.75, 95% CI 0.33 to 22.7);
e. various sleep positions (RR 2.77, 95% CI 0.12 to 61.7);
f. enuresis (RR 4.62, 95% CI 0.25 to 86.7); or
g. talking in sleep (RR 0.46, 95% CI 0.05 to 4.38).

Other specific sleep-related adverse effects

See Analysis 2.2. Langevin 2012 (10 participants) compared methylphenidate to no intervention and found that methylphenidate did not decrease:

1. the number of hours of sleep (MD −0.65 hours, 95% CI −1.32 to 0.02);
2. the number of nocturnal movements (MD −27.84 movements, 95% CI −57.9 to 2.22); or
3. sleep quality (MD −0.20, 95% CI −0.74 to 0.34), as measured on a five-point sleep quality scale (ranging from −2 = very poor to 2 = very good) from “The Morpheus Network Wake and Sleep Calendar.”

Other specific adverse events

See Analysis 2.3. One study with, Tzang 2012, reported on different adverse events of the central nervous system. Compared to no intervention, methylphenidate did not increase the number of patients with:

1. headache (RR 8.13, 95% CI 0.48 to 137.8; 235 participants); or
2. dizziness (RR 4.00, 95% CI 0.23 to 69.3; 335 participants).

1.2.3 Cardiovascular and respiratory system

See analysis Analysis 2.4

Systolic blood pressure

Only one study with 43 participants reported data on this outcome (Verret 2010). Compared to no intervention, methylphenidate did not affect systolic blood pressure (MD 0.10 mmHg, 95% CI −6.27 to 6.47).

Diastolic blood pressure

Only one study with 43 participants reported data on this outcome (Verret 2010). Compared to no intervention, methylphenidate did not affect diastolic blood pressure (MD 3.50 mmHg, 95% CI −1.42 to 8.42).

Pulse rate

Only one study with 43 participants reported data on this outcome (Verret 2010). Compared to no intervention, methylphenidate did not seem to affect pulse rate (MD 0.60 beats per minute, 95% CI −7.95 to 9.15).

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1.2.4 Gastrointestinal system

See Analysis 2.5. One study with 335 participants reported on gastrointestinal adverse events (Tzang 2012). Compared to no intervention, methylphenidate did not increase the number of patients with:

1. nausea (RR 2.64, 95% CI 0.34 to 20.3); or
2. abdominal pain (RR 0.79, 95% CI 0.16 to 3.84).

However, methylphenidate did increase the number with decreased appetite (RR 15.06, 95% CI 2.12 to 106.8).

1.2.5 Musculoskeletal system

See Analysis 2.6.

Height

Two studies reported data on height (Verret 2010; Zhang 2010). We pooled data from both studies (93 participants) in a meta-analysis and found that, compared to no intervention, methylphenidate did not increase the number of patients with reduced height (SMD −0.93, 95% CI −2.61 to 0.75).

Weight

Four studies reported data on weight (Dubnov-Raz 2011; Jensen 1999 (MTA); Verret 2010; Zhang 2010). We pooled data from two studies (93 participants) in a meta-analysis (Verret 2010; Zhang 2010). Compared to no intervention, methylphenidate did not decrease weight (SMD −0.27, 95% CI −1.16 to 0.62).

Body mass index (BMI)

See Analysis 2.7. Compared to no intervention, methylphenidate decreased BMI (MD −1.60 kg/m^2, 95% CI −2.96 to −0.24) in one study with 43 participants (Verret 2010).

Z scores

See Analysis 2.8.

- Height

Compared to no intervention, methylphenidate did not decrease the height z score (MD −0.19, 95% CI −0.43 to 0.05) in one study with 275 participants (Dubnov-Raz 2011).

- Weight

Compared to no intervention, methylphenidate did not decrease the weight z score (MD −0.07, 95% CI −0.30 to 0.16) in one study with 275 participants (Dubnov-Raz 2011).

Dubnov-Raz 2011 also observed no change in weight related to methylphenidate (P = 0.05) when comparing participants receiving methylphenidate (39.7 (SD 17.70) kg; n = 135) to untreated participants (35.30 (SD 13.40) kg; n = 140).

In Jensen 1999 (MTA), weight gain was apparently lower in the methylphenidate group (n = 222) at 14 months (2.36 (SD 3.00) kg) and at 24 months (3.81 (SD 2.84) kg), compared to the untreated group (14 months: 5.14 (SD 3.53) kg; 24 months: 4.83 (SD 3.10) kg; n = 106).

- BMI

One study with 275 participants, Dubnov-Raz 2011, found no difference between those in the methylphenidate group and those in the no intervention group for BMI z score (MD 0.01, 95% CI −0.22 to 0.24).

No comparative studies reported non-serious adverse events related to the immune, urogenital, or other body systems.

1.2.6 Withdrawal of treatment

Due to non-serious adverse events

No comparative studies reported withdrawal of treatment due to non-serious adverse events.

For unknown reasons

See Analysis 3.1. One study with 146 participants, Zhang 2010, compared methylphenidate to no intervention, finding that it increased the proportion of participants withdrawn from methylphenidate for unknown reasons (RR 0.72 95% CI 0.62 to 0.84).

2. Non-comparative studies

2.1 Primary outcomes: serious adverse events

We included a total of 54 studies in meta-analyses on this outcome.

2.1.1. Frequency of any serious adverse events

See Analysis 4.1. We included 50 studies (162,422 participants) that reported data on this outcome in a meta-analysis. The proportion of participants on methylphenidate experiencing one or more serious adverse events was 1.20% (95% CI 0.70% to 2.00%; Figure 2).

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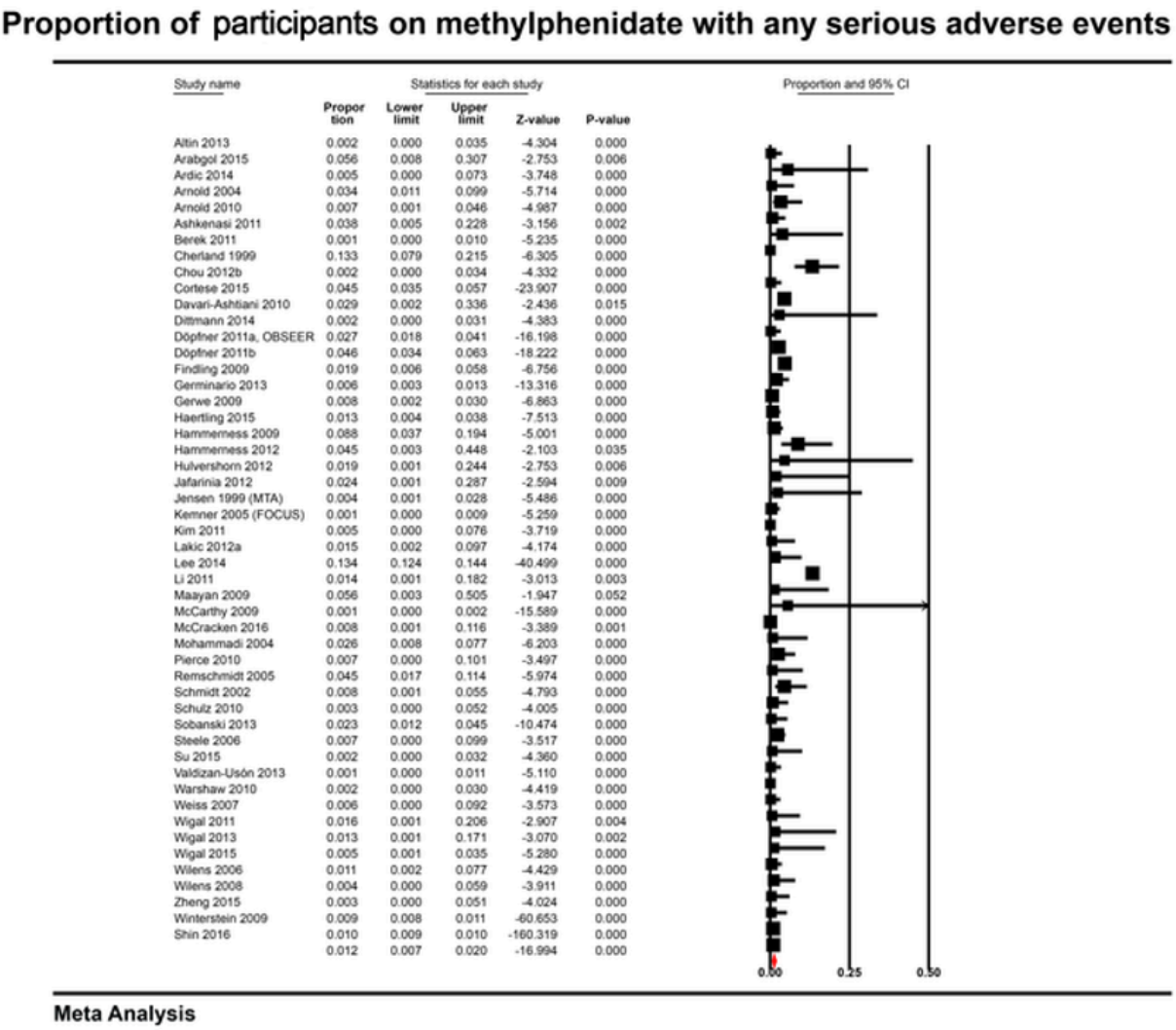
Figure 2. Proportion of participants on methylphenidate with any serious adverse events



2.1.2 Central nervous system

See Analysis 4.2. Twenty-two studies reported data on serious central nervous system adverse events (Arabgol 2015; Arnold 2004; Arnold 2010; Cherland 1999; Cortese 2015; Findling 2009; Germinario 2013; Gerwe 2009; Green 2011; Jensen 1999 (MTA); Kemner 2005 (FOCUS); Lakic 2012; Lee 2014; McCarthy 2009; Mohammadi 2004; Na 2013; Remschmidt 2005; Schmidt 2002; Shyu 2015; Su 2015; Wilens 2005; Wilens 2006).

We included data from 19 of these studies in 10 meta-analyses (Arnold 2004; Arnold 2010; Cherland 1999; Cortese 2015; Findling 2009; Germinario 2013; Gerwe 2009; Jensen 1999 (MTA); Kemner 2005 (FOCUS); Lakic 2012; Lee 2014; McCarthy 2009; Mohammadi 2004; Na 2013; Remschmidt 2005; Schmidt 2002; Shyu 2015; Su 2015; Wilens 2006). The proportion of participants on methylphenidate with:

1. sudden death was 0.20% (95% CI 0.00% to 15.9%; 3 studies, 6301 participants; Kemner 2005 (FOCUS); Lee 2014; McCarthy 2009; see supplementary file S1);
2. suicide was 0.10% (95% CI 0.0% to 0.30%; 2 studies, 5596 participants; Jensen 1999 (MTA); McCarthy 2009; see supplementary file S2);
3. suicide attempt was 2.10% (95% CI 0.40% to 9.00%; 3 studies, 339 participants; Arnold 2010; Lee 2014; Remschmidt 2005; see supplementary file S3);
4. suicidal thoughts was 1.10% (95% CI 0.30% to 4.40%; 2 studies, 176 participants; Remschmidt 2005; Wilens 2006; see supplementary file S4);
5. psychotic symptoms was 1.20% (95% CI 0.50% to 2.70%; 10 studies, 55,110 participants; Cherland 1999; Cortese 2015; Findling 2009; Green 2011; Mohammadi 2004; Na 2013; Remschmidt 2005; Shyu 2015; Su 2015; Wilens 2006; see supplementary file S5);
6. seizure was 0.30% (95% CI 0.10% to 1.10%; 2 studies, 1550 participants; Cortese 2015; Schmidt 2002; see supplementary file S6);

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7. syncope was 0.20% (95% CI 0.00% to 0.70%; 2 studies, 1425 participants; Findling 2009; Germinario 2013; see supplementary file S7);
8. tremor was 0.60% (95% CI 0.20% to 2.40%; 2 studies, 395 participants; Arnold 2004; Gerwe 2009; see supplementary file S8);
9. psychiatric problems was 0.40% (95% CI 0.20% to 0.80%; 3 studies, 2613 participants; Arnold 2004; Cortese 2015; Germinario 2013; see supplementary file S9); and
10. severe depression was 1.20% (95% CI 0.30% to 4.80%; 2 studies, 166 participants; Cherland 1999; Lakic 2012; see supplementary file S10).

Seven studies reported on other adverse events related to the central nervous system.

1. In Lee 2014 (100 participants), the proportion of participants on methylphenidate with overdose was 6.0% (95% CI 3.0% to 12.0%).
2. In Cortese 2015 (1426 participants), the proportion of participants on methylphenidate with:
   a. eating disorder was 0.07% (95% CI 0.01% to 0.40%);
   b. aphasia was 0.07% (95% CI 0.01% to 0.40%);
   c. headache was 0.02% (95% CI 0.01% to 0.06%);
   d. neurological disorder was 0.14% (CI 0.04% to 0.50%);
   e. sleep disorder was 0.07% (95% CI 0.01% to 0.40%); and
   f. mood disorder was 0.07% (95% CI 0.01% to 0.40%).
3. In Gerwe 2009 (306 participants), the proportion of participants on methylphenidate with:
   a. loss of consciousness was 0.33% (95% CI 0.06% to 2.00%); and
   b. family stress was 0.33% (95% CI 0.06% to 2.00%).
4. In Germinario 2013 (1098 participants), the proportion of participants on methylphenidate with impotence was 0.09% (95% CI 0.02% to 0.50%).
5. In Remschmidt 2005 (89 participants), the proportion of participants on methylphenidate with severe aggression was 1.12% (95% CI 0.20% to 6.00%).
6. In Arabgol 2015 (18 participants), the proportion of participants on methylphenidate with severe anorexia was 5.56% (95% CI 0.10% to 25.0%).
7. In Cherland 1999 (98 participants), the proportion of participants on methylphenidate with amphetamine intoxication was 3.06% (95% CI 1.00% to 8.00%).

2.1.3 Cardiovascular and respiratory system

See Analysis 4.3. Five studies reported data on serious cardiovascular and respiratory adverse events (Arman 2013; Cortese 2015; Germinario 2013; Hammerness 2009; Winterstein 2009). We included these five studies across three meta-analyses and found that the proportion of participants on methylphenidate with:

1. respiratory, thoracic and mediastinal disorders was 0.40% (95% CI 0.00% to 6.90%; 2 studies, 1155 participants; Germinario 2013; Hammerness 2009; see supplementary file S11);
2. cardiac problems was 0.70% (95% CI 0.20% to 2.40%; 3 studies, 19,351 participants; Arman 2013; Germinario 2013; Winterstein 2009; see supplementary file S12); and
3. tachycardia was 0.20% (95% CI 0.10% to 0.40%; 2 studies, 2524 participants; Cortese 2015; Germinario 2013; see supplementary file S13).

Two of these studies also reported on other cardiovascular and respiratory adverse events (Cortese 2015; Hammerness 2009).

1. In Cortese 2015 (1426 participants), the proportion of participants on methylphenidate with:
   a. severe hypertension was 0.14% (95% CI 0.00% to 0.05%); and
   b. epistaxis was 0.07% (95% CI 0.00% to 0.40%).
2. In Hammerness 2009 (57 participants), the proportion of participants on methylphenidate with viral illness was 1.75% (95% CI 0.03% to 9.28%).

2.1.4 Gastrointestinal system

See Analysis 4.4. One study with 1426 participants reported data on gastrointestinal adverse events (Cortese 2015). In this study, the proportion of participants on methylphenidate with:

1. gastrointestinal disease was 0.42% (95% CI 0.19% to 0.91%); and
2. liver disease was 0.07% (95% CI 0.00% to 0.40%).

2.1.5 Musculoskeletal system

See Analysis 4.5. We included two studies (384 participants) providing data on musculoskeletal adverse events in a meta-analysis (Findling 2009; Hammerness 2009). The proportion of participants on methylphenidate with fractures was 1.20% (95% CI 0.10% to 11.5%; see supplementary file S14).

2.1.6 Immune system

See Analysis 4.6. Only one study with 1426 participants reported data on adverse events of the immune system (Cortese 2015). In this study, the proportion of participants on methylphenidate with autoimmune disease was 0.07% (95% CI 0.00% to 0.40%).

No comparative studies reported adverse events related to the urogenital or other body systems.

2.1.9 Withdrawal of treatment

Due to serious adverse events

See Analysis 5.1. Seven studies with 1173 participants reported data on the number of participants withdrawn from methylphenidate treatment due to serious adverse events (Arabgol 2015; Arnold 2010; Ashkenasi 2011; Faraone 2007a; Findling 2010; Na 2013; Wilens 2005). We conducted a meta-analysis of data from these seven studies and found that the proportion of participants withdrawn from methylphenidate treatment due to serious adverse events was 1.20% (95% CI 0.60% to 2.30%; Figure 3).

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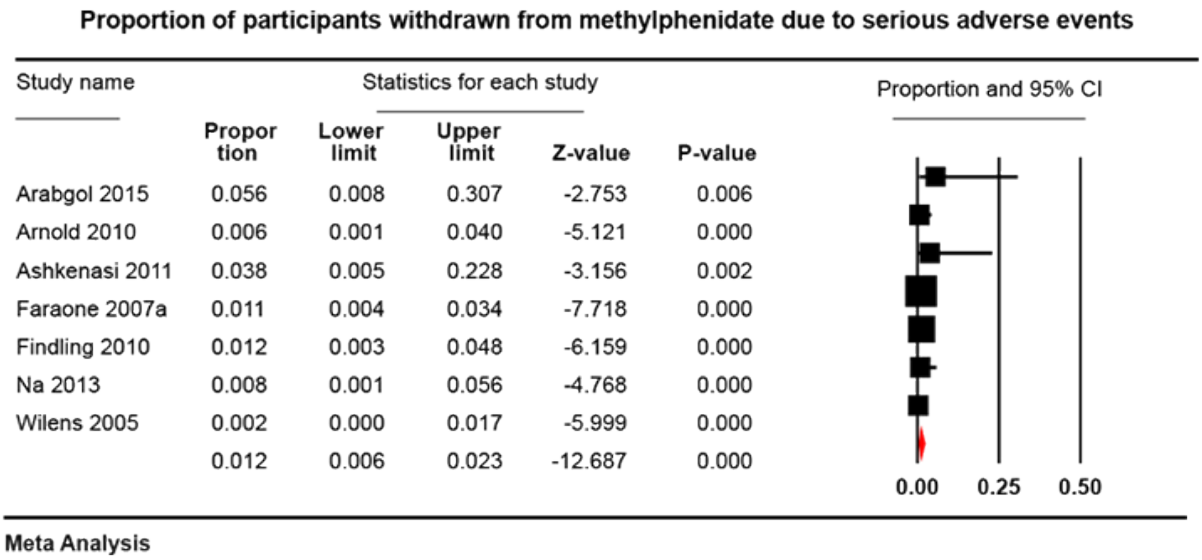
Figure 3. Proportion of participants withdrawn from methylphenidate due to serious adverse events



Three of the studies also reported on the proportion participants withdrawn from methylphenidate treatment due to specific serious adverse events (Arabgol 2015; Arnold 2010; Ashkenasi 2011).

All three studies reported the proportion of participants withdrawn from methylphenidate treatment due to hallucinations (0.90%, 95% CI 0.2% to 4.4%; 554 participants; See supplementary file S15).

Arabgol 2015 (18 participants) also reported the proportion of participants withdrawn from methylphenidate treatment due to severe anorexia as 5.56% (95% CI 1.00% to 25.8%).

Arnold 2010 (171 participants) also reported the proportion of participants withdrawn from methylphenidate treatment due to suicide attempt as 0.58% (95% CI 0.10% to 3.23%).

Due to adverse events of unknown severity

See Analysis 5.2. We conducted a meta-analysis of data from 22 studies (3708 participants) that reported the number of patients withdrawn from methylphenidate treatment due to adverse events of unknown severity. The proportion of participants withdrawn from methylphenidate treatment due to adverse events of unknown severity was 7.3% (95% CI 5.3% to 10.0%; Figure 4).

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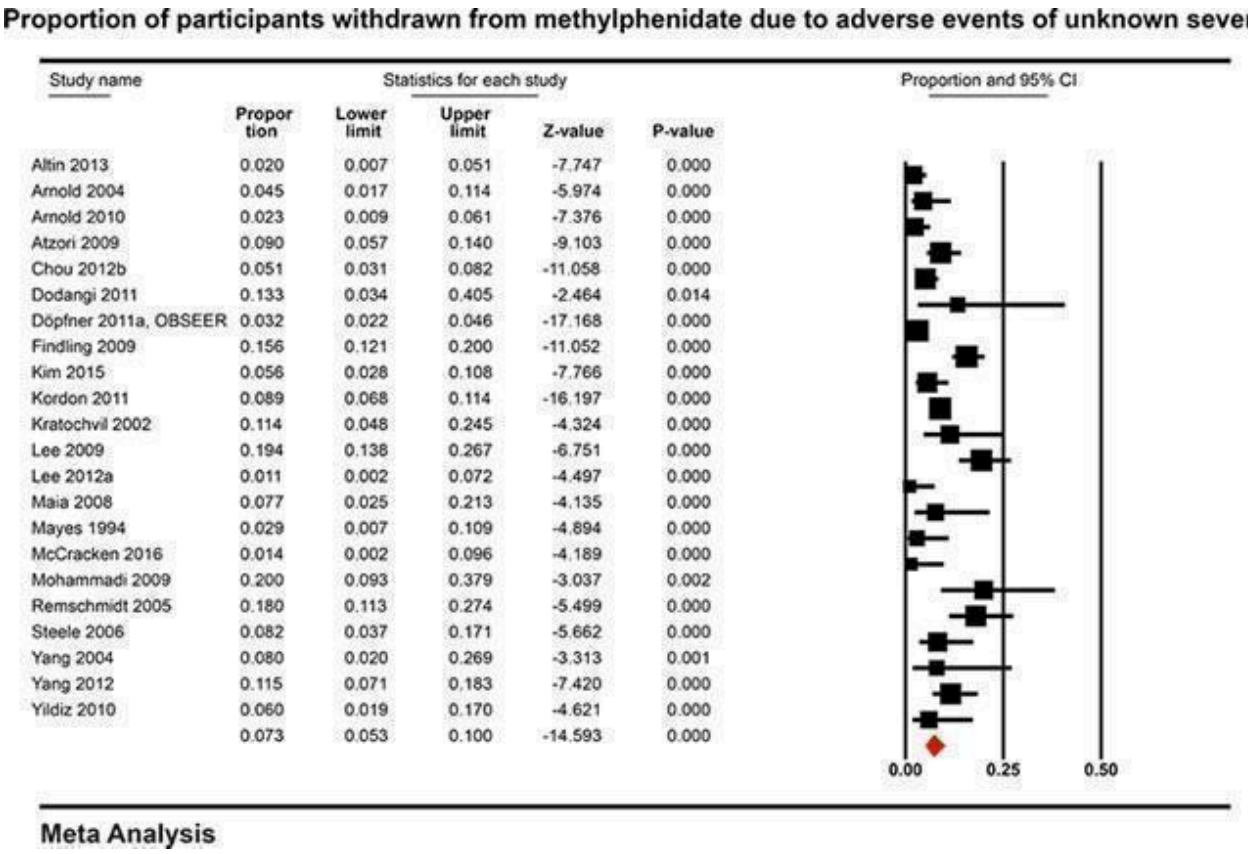
Figure 4. Proportion of participants withdrawn from methylphenidate due to adverse events of unknown severity



2.2 Secondary outcomes: non-serious adverse events

All but 11 studies contributed data to our meta-analyses (see details below). For the 11 studies which contributed data that we could not combine, we reported the results qualitatively (Cho 2012; Dubnov-Raz 2011; Durá-Travé 2012; Ilgenli 2007; Lahat 2000; Lamberti 2015; Özcan 2004; Poulton 2012; Schertz 1996; Spencer 1992; Vincent 1990).

Proportion of participants with adverse events of unknown severity

See Analysis 6.1. One study with 251 participants also reported data on the frequency of adverse events of unknown severity (Barbaresi 2006). In this study, the proportion of participants on methylphenidate with adverse events of unknown severity was 25.1% (95% CI 20.0% to 31.0%).

2.2.1 Frequency of any non-serious adverse events

See Analysis 7.1. The proportion of participants on methylphenidate with non-serious adverse events was 51.2% (41.2% to 61.1%; 49 studies; 13,978 participants; Figure 5).

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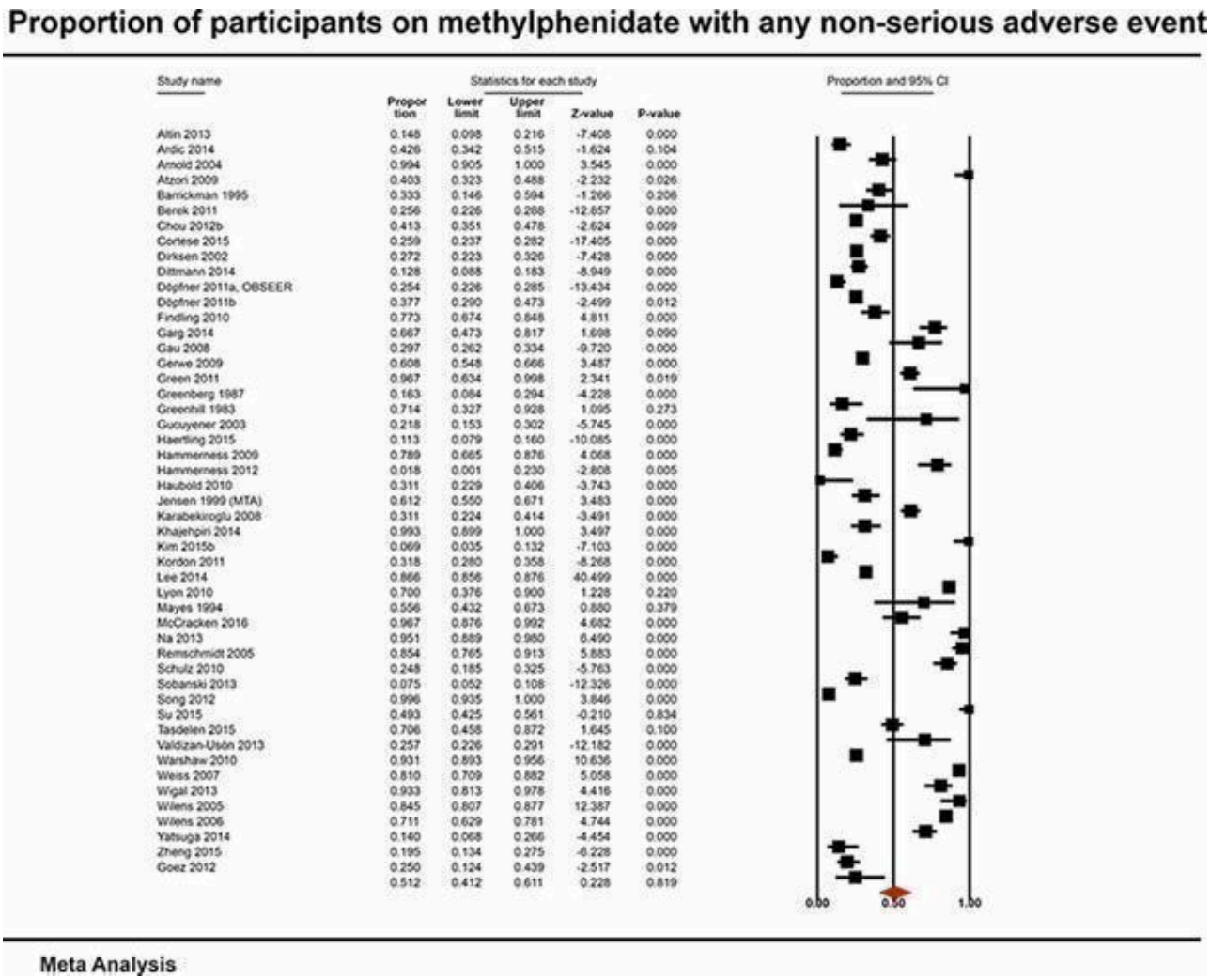
Figure 5. Proportion of participants on methylphenidate with any non-serious adverse event



2.2.2 Central nervous system

See Analysis 7.2. We included 109 studies in 37 meta-analyses.

The proportion of participants on methylphenidate with:

1. affect lability was 29.8% (95% CI 20.5% to 41.2%; 2 studies, 74 participants; Sahin 2014; Wigal 2013; see supplementary file S16);
2. aggression was 2.40% (95% CI 1.60% to 3.60%; 14 studies, 4292 participants; see supplementary file S17);
3. anorexia was 16.5% (95% CI 9.10% to 28.2%; 23 studies, 5739 participants; see supplementary file S18);
4. anxiety was 18.4% (95% CI 11.3% to 28.7%; 22 studies, 1287 participants; see supplementary file S19);
5. fingernail biting was 14.3% (95% CI 6.90% to 27.5%; 9 studies, 402 participants; Blader 2010; Efron 1997; El-Fiky 2014; Gau 2006; Green 2011; Hazell 2003; Maia 2008; Sahin 2014; Shang 2015; see supplementary file S20);
6. daydreams was 35.1% (95% CI 16.2% to 60.1%; 4 studies, 199 participants; Efron 1997; Gau 2006; Green 2011; Sahin 2014; see supplementary S21);
7. difficulty falling asleep was 17.9% (95% CI 14.7% to 21.6%; 82 studies, 11,507 participants; see supplementary file S22);
8. depression was 4.00% (95% CI 2.20% to 7.10%; 13 studies, 2823 participants; see supplementary file S23);
9. disturbed sleep was 13.2% (95% CI 7.70% to 21.8%; 24 studies, 3076 participants; see supplementary file S24);
10. dizziness was 6.00% (95% CI 3.7% to 9.4%; 29 studies, 4521 participants; see supplementary file S25);
11. drowsiness was 9.50% (95% CI 5.20% to 16.6%; 17 studies, 1146 participants; see supplementary file S26);
12. dysthymia was 0.90% (95% CI 0.10% to 5.30%; 2 studies, 255 participants; Haertling 2015; Mohammadi 2004; see supplementary file S27);
13. emotional lability was 7.20% (95% CI 3.80% to 13.3%; 16 studies, 2609 participants; see supplementary file S28);
14. euphoria/hypomania was 7.90% (95% CI 3.90% to 15.4%; 9 studies, 329 participants; Blader 2010; El-Fiky 2014; Gau 2006; Grcevich 2001; Green 2011; Kim 2010; Maia 2008; Mohammadi 2004; Sahin 2014; see supplementary file S29);
15. asthenia and fatigue was 5.30% (95% CI 3.00% to 9.40%; 19 studies, 2497 participants; see supplementary file S30);

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16. headache was 14.4% (95% CI 11.3% to 18.3%; 90 studies, 13,469 participants; see supplementary file S31);
17. increased need to sleep was 11.7% (95% CI 4.40% to 27.5%; 8 studies, 485 participants; Blader 2010; Galland 2010; Mohammadi 2004; Mohammadi 2012a; Na 2013; Pierce 2010; Wang 2007; Zarinara 2010; supplementary file S32);
18. involuntary movements was 6.30% (95% CI 3.20% to 11.8%; 7 studies, 1554 participants; Balázs 2011; Berek 2011; Blader 2010; Galland 2010; Kordon 2011; Kratochvil 2002; Lee 2014; see supplementary file S33);
19. irritability was 17.2% (95% CI 11.5% to 25.0%; 35 studies, 4792 participants; see supplementary file S34);
20. nervousness was 11.7% (95% CI 5.80% to 22.3%; 14 studies, 2142 participants; see supplementary file S35);
21. nightmares was 8.10% (95% CI 5.20% to 12.5%; 11 studies, 553 participants; see supplementary file S36);
22. restlessness and agitation was 7.40% (95% CI 3.60% to 14.5%; 14 studies, 1793 participants; see supplementary file S37);
23. sadness was 16.8% (95% CI 9.40% to 28.3%; 21 studies, 1802 participants; see supplementary file S38);
24. stares was 22.5% (95% CI 8.50% to 47.5%; 4 studies, 137 participants; Blader 2010; El-Fiky 2014; Hazell 2003; Maia 2008; see supplementary file S39);
25. excessive talking was 17.6% (95% CI 6.10% to 41.3%; 3 studies, 146 participants; Blader 2010; Hazell 2003; Khajehpiri 2014; supplementary file S40);
26. taciturnity ('talking too little') was 16.9% (95% CI 5.90% to 39.8%; 4 studies, 141 participants; Blader 2010; El-Fiky 2014; Green 2011; Maia 2008; see supplementary file S41);
27. tics was 6.40% (95% CI 4.50% to 8.90%; 39 studies, 1980 participants; see supplementary file S42);
28. isolation and lack of interest in others was 15.9% (95% CI 9.40% to 25.8%; 10 studies, 524 participants; Blader 2010; Efron 1997; El-Fiky 2014; Green 2011; Hazell 2003; Maia 2008; Sahin 2014; Yildiz 2010; Khajehpiri 2014; Perera 2010 see supplementary file S43);
29. 'zombie-like' demeanor was 5.20% (95% CI 1.20% to 20.6%; 3 studies, 668 participants; Davari-Ashtiani 2010; Jensen 1999 (MTA); Wilens 2005; see supplementary file S44);
30. somnolence was 4.10% (95% CI 2.30% to 7.30%; 9 studies, 1016 participants; Chou 2012b; Khajehpiri 2014; McCracken 2016; Na 2013; Shang 2015; Wang 2007; Weiss 2007; Wilens 2005; Yildiz 2011; see supplementary file S45);
31. obsession was 1.50% (95% CI 0.20% to 8.60%; 3 studies, 1529 participants; Çetin 2015; Cortese 2015; Khajehpiri 2014; see supplementary file S46);
32. mood disorder was 1.50% (95% CI 0.20% to 10.6%; 2 studies, 1665 participants; Cortese 2015; Haertling 2015; see supplementary file S47);
33. confusional state was 2.30% (95% CI 0.10% to 39.4%; 2 studies, 390 participants; Haertling 2015; Zelnik 2015; see supplementary file S48);
34. sleep disorder was 3.50% (95% CI 0.80% to 14.4%; 3 studies, 1211 participants; Dittmann 2014; Döpfner 2011a, OBSEER; Su 2015; see supplementary file S49);
35. propensity to cry was 24.8% (95% CI 7.00% to 59.0%; 2 studies, 61 participants; El-Fiky 2014; Sahin 2014; see supplementary file S50);
36. sedation was 11.8% (95% CI 3.50% to 33.2%; 2 studies, 80 participants; McCracken 2016; Mohammadi 2010; see supplementary file S51);
37. daytime sleepiness was 3.60% (95% CI 0.90% to 14.0%; 2 studies, 141 participants; Galland 2010; Tomás Vila 2010b; see supplementary file S52).

Sixteen studies reported data on different adverse events related to the central nervous system (Atzori 2009; Berek 2011; Garg 2014; Galland 2010; Haertling 2015; Hammerness 2009; Khajehpiri 2014; Kordon 2011; Lee 2014; Mohammadi 2004; Sahin 2014; Schmidt 2002; Thorell 2009; Tomás Vila 2010b; Valdizán Usón 2013; Yildiz 2011).

1. In Atzori 2009, the proportion of participants on methylphenidate with:
   a. dysphoria was 1.49% (95% CI 0.40% to 5.27%, 134 participants); and
   b. logorrhoea (that is, excessive, uncontrollable or incoherent talkativeness) was 0.78% (95% CI 0.14% to 4.27%; 129 participants).
2. In Berek 2011 (822 participants), the proportion of participants on methylphenidate with impaired concentration was 1.70% (95% CI 1.01% to 2.83%).
3. In Galland 2010 (28 participants), the proportion of participants on methylphenidate with difficulty waking up was 25.0% (95% CI 12.7% to 43.4%).
4. In Garg 2014 (32 participants), the proportion of participants on methylphenidate with urinary incontinence was 3.13% (95% CI 0.56% to 15.8%).
5. In Haertling 2015 (239 participants), the proportion of participants on methylphenidate with paralysis was 0.42% (95% CI 0.07% to 2.33%); and affective disorder was 0.42% (95% CI 0.07% to 2.33%).
6. In Hammerness 2009 (154 participants), the proportion of participants on methylphenidate with jumbled thoughts was 0.65% (95% CI 0.03% to 0.90%).
7. In Khajehpiri 2014 (71 participants), the proportion of participants on methylphenidate with:
   a. bulimia was 7.04% (95% CI 3.00% to 15.5%);
   b. sleeping late was 30.9% (95% CI 21.4% to 42.5%);
   c. tooth grinding was 4.23% (95% CI 1.40% to 11.7%);
   d. tremor was 2.82% (95% CI 0.08% to 9.71%);
   e. stuttering was 5.63% (95% CI 2.21% to 13.6%); and
   f. flushing 12.7% (95% CI 6.82% to 22.4%).
8. In Kordon 2011 (541 participants), the proportion of participants on methylphenidate with apathy was 1.10% (95% CI 0.50% to 2.40%).
9. In Lee 2014 (100 participants), the proportion of participants on methylphenidate with abnormal behaviour was 5.00% (95% CI 2.20% to 11.2%).
10. In Mohammadi 2004 (16 participants), the proportion of participants on methylphenidate with stereotypies was 0.00% (95% CI 0.00% to 19.4%).
11. In Sahin 2014 (30 participants), the proportion of participants on methylphenidate with quietness was 20.0% (95% CI 9.50% to 37.3%).

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12. In Schmidt 2002 (124 participants), the proportion of participants on methylphenidate with EEG changes was 20.2% (95% CI 14.0% to 28.0%).
13. In Thorell 2009 (79 participants), the proportion of participants on methylphenidate who did not like themselves was 12.7% (95% CI 6.50% to 21.8%).
14. In Tomás Vila 2010b (114 participants), the proportion of participants on methylphenidate with sleep walking was 1.75% (95% CI 0.50% to 6.20%).
15. In Valdizán Usón 2013 (633 participants), the proportion of participants on methylphenidate with personality and behaviour disorders was 2.20% (95% CI 1.30% to 3.70%).
16. In Yildiz 2011 (11 participants), the proportion of participants on methylphenidate with vertigo was 27.3% (95% CI 9.70% to 56.6%).

2.2.3 Cardiovascular and respiratory system

See Analysis 7.3. Thirty-nine studies reported data on this outcome.

We included 18 studies in seven meta-analyses (Arnold 2004; Arnold 2010; Blader 2010; Cortese 2015; Findling 2009; Findling 2010; Jafarinia 2012; Kratochvil 2002; Maayan 2009; Mohammadi 2004; Na 2013; Pierce 2010; Sangal 2006; Shang 2015; Su 2015; Wang 2007; Wigal 2015; Wiguna 2012). The proportion of participants on methylphenidate with:

1. cough was 7.7% (95% CI 3.80% to 15.2%; 7 studies, 724 participants; Arnold 2004; Arnold 2010; Findling 2009; Kratochvil 2002; Pierce 2010; Sangal 2006; Wang 2007; see supplementary file S53);
2. pharyngolaryngeal pain was 5.10% (95% CI 3.50% to 7.30%; 3 studies, 547 participants; Arnold 2010; Findling 2009; Pierce 2010; see supplementary file S54);
3. upper respiratory tract infection was 10.5% (95% CI 4.40% to 22.9%; 5 studies, 614 participants; Findling 2009; Pierce 2010; Wang 2007; Wigal 2015; Wiguna 2012; see supplementary file S55);
4. tachycardia was 2.50% (95% CI 1.40% to 4.30%; 6 studies, 2101 participants; Blader 2010; Cortese 2015; Findling 2009; Jafarinia 2012; Kratochvil 2002; Su 2015; see supplementary file S56);
5. abnormal ECG was 2.90% (95% CI 0.00% to 66.6%; 2 studies, 503 participants; Findling 2009; Findling 2010; see supplementary file S57);
6. nasal congestion was 11.8% (95% CI 8.30% to 16.4%; 3 studies, 247 participants; Findling 2009; Maayan 2009; Sangal 2006; see supplementary file S58); and
7. palpitation was 8.30% (95% CI 2.10% to 27.5%; 3 studies, 180 participants; Mohammadi 2004; Na 2013; Shang 2015; see supplementary file S59).

Systolic blood pressure

Nineteen studies provided data on this outcome (Cho 2012: Döpfner 2011b; Findling 2009; Gadow 1995; Germinario 2013; Gerwe 2009; Hazell 2003; Kim 2010; Kratochvil 2002; Lamberti 2015; Maayan 2009; McCracken 2016; Na 2013; Song 2012; Wilens 2005; Winsberg 1982; Yildiz 2011; Zheng 2011; Zheng 2015).

Nine studies reported an increase in systolic blood pressure as follows.

1. Cho 2012: marginal increase following methylphenidate treatment, but this difference was not significant.
2. Gadow 1995 (27 participants): increase of 6 mmHg at 24 months.
3. Kratochvil 2002 (44 participants): significant (P = 0.03) increase from 102.2 (SD 9.89) mmHg at baseline to 105.6 (SD 10.7) mmHg at follow-up.
4. Lamberti 2015 (54 participants): short-term increase from 105.4 (SD 10.3) mmHg at baseline to 109.6 (SD 11.5) mmHg two hours postmethylphenidate.
5. McCracken 2016 (61 participants): increase of 7.30 (SD 11.5) mmHg.
6. Na 2013 (121 participants): increase from baseline of 5.26 (SD 18.5) mmHg.
7. Song 2012 (143 participants): increase from 105.3 (SD 12.6) mmHg to 108.4 (SD 70.9) mmHg.
8. Winsberg 1982 (25 participants): increase from 103.1 mmHg to 110.5 mmHg at week five.
9. Wilens 2005 (407 participants) increase from 104.7 (SD 8.10) mmHg to 108.1 (SD 8.70) mmHg at end of treatment.

Six studies reported either no change or no apparent changes in systolic blood pressure: Döpfner 2011b (baseline: 106.0 (SD 1.00) mmHg; follow-up at week three: 106.0 (SD 1.00) mmHg); Gerwe 2009 (mean change in systolic blood pressure between visit one and four: 0.1 (SD 10.8) mmHg); Maayan 2009 (baseline: 96.2 (SD 14.0) mmHg; follow-up at week four: 96.09 (SD 10.1) mmHg); Zheng 2011 (baseline: 96.6 (SD 10.6) mmHg, N = 1247; follow-up at week six: 97.5 (SD 10.3) mmHg, N = 959); Germinario 2013 (baseline: 100.6 (SD 12.3) mmHg; follow-up at month 24: 99.6 (SD 13.0) mmHg); and Zheng 2015 (reporting no changes in blood pressure).

Four studies reported a drop in systolic blood pressure. Hazell 2003 reported a drop in 8/10 participants. There were also apparent decreases in systolic blood pressure in Kim 2010 (baseline: 113.8 (SD 10.2) mmHg; follow-up: 110.0 (SD 10.6) mmHg), and Yildiz 2011 (baseline: 97.0 (SD 10.8) mmHg; week 12: 92.7 (SD 10.1) mmHg). One study, Findling 2009, reported that across dose levels, the proportion of participants with systolic blood pressure above the upper limit of normal (> 123 mmHg) ranged from 1% to 10%, whereas 1.5% had an above-normal systolic blood pressure at baseline.

Diastolic blood pressure

Sixteen studies reported data on this outcome (Cho 2012; Döpfner 2011b; Findling 2009; Germinario 2013; Gerwe 2009; Hazell 2003; Kim 2010; Kratochvil 2002; Lamberti 2015; Maayan 2009; McCracken 2016; Na 2013; Song 2012; Zheng 2011; Yildiz 2011; Zheng 2015).

Six studies reported apparent increases in diastolic blood pressure in participants receiving methylphenidate: Lamberti 2015 (baseline: 59.2 (SD 7.10) mmHg; follow-up after two hours: 63.1 (SD 7.80) mmHg); Döpfner 2011b (baseline: 69.0 (SD 1.00) mmHg; follow-up after three weeks: 86.0 (SD 1.00) mmHg); McCracken 2016 (mean change: 5.80 (SD 10.4) mmHg); Na 2013 (mean change: 4.83 (SD 12.3) mmHg); Kratochvil 2002 (baseline: 63.5 (SD 7.9) mmHg; follow-up: 66.46 (SD 7.41) mmHg, P = 0.04), and Song 2012 (baseline: 66.9 (SD 10.1) mmHg; follow-up: 70.9 (SD 10.5) mm Hg). One study, Cho 2012, reported a marginal increase that was not significant.

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Four studies reported minimal changes in diastolic blood pressure: Gerwe 2009 (mean change: 0.70 (SD 9.70) mmHg), Maayan 2009 (baseline: 61.4 (SD 13.7) mmHg; follow-up at week 4: 60.9 (SD 14.5) mmHg), Zheng 2011 (baseline: 64.6 (SD 7.51) mmHg, N = 1247; follow-up at week six: 65.6 (SD 7.32) mmHg, N = 959), and Yildiz 2011 (baseline: 63.5 (SD 12.0) mmHg; follow-up at week 12: 62.5 (SD 9.70) mmHg). One study, Zheng 2015, reported no changes in blood pressure.

Two studies reported a drop in diastolic blood pressure: Hazell 2003 (diastolic blood pressure decreased in 9/10 participants) and Kim 2010 (baseline: 75.2 (SD 12.0) mmHg; follow-up 72.0: (SD 8.40) mmHg). One study, Germinario 2013, reported an apparent decrease after 24 months of methylphenidate (baseline: 63.2 (SD 10.9) mmHg; follow-up: 59.28 (SD 9.66) mmHg).

One study, Findling 2009, reported that no participants had an above-normal diastolic blood pressure (> 90 mmHg) at baseline; however, one participant in each methylphenidate-dose group had an above-normal diastolic blood pressure at some point in the study.

Pulse rate

Fifteen studies reported data on this outcome (Cho 2012; Döpfner 2011b; Germinario 2013; Ilgenli 2007; Kim 2010; Kim 2015a; Kratochvil 2002; Lamberti 2015; Maayan 2009; McCracken 2016; Na 2013; Özcan 2004; Yildiz 2011; Zheng 2011; Zheng 2015).

Pulse rate was significantly higher in participants receiving methylphenidate in: Cho 2012 (mean increase 3.83 (SD 10.5) beats per min (bpm), P = 0.001) and Kratochvil 2002 (baseline: 80.4 (SD 9.70) bpm; follow-up: 86.1 (SD 12.4) bpm, P = 0.009). There was an apparent increase in Lamberti 2015 after two hours of methylphenidate (baseline: 80.5 (SD 15.5) bpm; follow-up: 87.7 (SD 18.4) bpm), and at week 12 in Kim 2015a (baseline: 86.4 (SD 11.2) bpm; follow-up: 93.5 (SD 15.6) bpm). Yildiz 2011 reported increased pulse rate (baseline: 80.8 (SD 9.80) bpm; follow-up: 84.5 (SD 13.5) bpm). Na 2013 also reported an increase from baseline of 9.65 (SD 14.6) bpm and McCracken 2016 an increase of 3.60 (SD 15.7) bpm.

There was no apparent difference in pulse rate in participants after two hours of methylphenidate in Ilgenli 2007 (baseline: 88.0 (SD 13.8) bpm; two hours: 88.4 (SD 9.70) bpm), after three weeks in Döpfner 2011b (baseline: 79 (SD 1) bpm; week three: 80 (SD 1) bpm), six weeks in Kim 2010 (baseline: 87.5 (SD 6.10) bpm; week six: 87.8 (SD 6.00) bpm), or 12 weeks in Zheng 2011 (baseline: 82.5 (SD 7.8) bpm, N = 1254; 12 weeks: 82.8 (SD 7.40) bpm, N = 942). Zheng 2015 reported no changes in pulse rate.

Two studies indicated a decrease in pulse rate: Maayan 2009 observed a decrease after four weeks (baseline: 95.5 (SD 16.0) bpm; follow-up: 91.8 (12.2) bpm), and Germinario 2013 after 24 months (baseline: 79.9 (SD 12.9) bpm; follow-up: 76.1 (SD 11.2) bpm). In one study, Özcan 2004, mean heart rate also seemed to decrease (baseline: 148.2 (SD 29.7) bpm, N = 42; follow-up: 139.9 (SD 34.0) bpm, N = 42).

ECG-QT

Four studies reported data on different ECG-QT adverse events.

1. Cho 2012 (101 participants) reported no significant change in QT and QRS scores after treatment.
2. Germinario 2013 (840 participants) reported that 8 out of 77 (10.4%) participants receiving methylphenidate had an altered ECG at 24 months, and that out of 38 participants, 11 (29.0%) reported sinus bradycardia, 12 (31.6%) reported sinus tachycardia, and 6 (15.8%) reported lengthened corrected QT interval (QTc).
3. Ilgenli 2007 (25 participants) reported a minimum QT of 317.00 (SD 23.3) at baseline and 322.3 (SD 21.6) after two hours, and a maximum QT of 373.7 (SD 21.8) at baseline and 361.8 (SD 29.0) after two hours.
4. Lamberti 2015 (54 participants) reported at baseline a corrected QT (QTc) of 407.6 (SD 12.4) ms, which was 409.8 (SD 12.0) ms at two hours postmethylphenidate.

Other specific adverse events

Four studies reported on other adverse events.

1. In Khajehpiri 2014 (71 participants), the proportion of participants on methylphenidate with:
   a. cold fingers was 18.3% (95% CI 11.0% to 28.9%); and
   b. sweating was 8.45% (95% CI 3.93% to 17.2%).
2. In Cortese 2015 (1426 participants), the proportion of participants on methylphenidate with:
   a. hypertension was 0.56% (95% CI 0.28% to 1.10%); and
   b. hypotension was 0.21% (95% CI 0.05% to 0.62%).
3. In Haertling 2015 (239 participants), the proportion of participants on methylphenidate with respiratory, thoracic, and mediastinal disorders was 0.42% (95% 0.01% to 2.33%).
4. Walitza 2009 (26 participants) assessed the proportion of participants on methylphenidate with micro-nucleated (Mn) peripheral lymphocytes and found no alteration in the number of Mn cells in the group of chronically treated (> 12 months) children compared to the ADHD group before treatment initiation. They also reported no elevation after initiation of methylphenidate treatment at three and six months after treatment initiation.

2.2.4 Gastrointestinal system

See Analysis 7.4. We were able to use data from 102 studies in 12 meta-analyses. The proportion of participants on methylphenidate with:

1. abdominal pain was 10.7% (95% CI 8.60% to 13.3%; 79 studies, 11,750 participants; see supplementary file S60);
2. constipation was 7.60% (95% CI 3.70% to 15.1%; 4 studies, 249 participants; Ardic 2014; Khajehpiri 2014; Mohammadi 2004; Shang 2015; see supplementary file S61);
3. decreased appetite was 31.1% (95% CI 26.5% to 36.2%; 84 studies, 11,594 participants; see supplementary file S62);
4. decreased weight was 8.60% (95% CI 4.90% to 14.7%; 28 studies, 5182 participants; see supplementary file S63);
5. diarrhoea was 4.70% (95% CI 2.00% to 10.9%; 8 studies, 809 participants; Abbasi 2011; Blader 2010; Hammerness 2009; Khajehpiri 2014; Kordon 2011; Kratochvil 2002; Mohammadi 2004; Mohammadi 2010; see supplementary file S64);
6. dry mouth was 17.8% (95% CI 9.60% to 30.6%; 9 studies, 221 participants; Abbasi 2011; Amiri 2008; Blader 2010; Davari-Ashtiani 2010; Işeri 2007; Mohammadi 2004; Mohammadi 2010; Mohammadi 2012a; Mohammadi 2012b; see supplementary file S65);

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7. gastrointestinal adverse events was 2.80% (95% CI 1.10% to 7.30%; 3 studies, 1487 participants; Dittmann 2014; Gau 2008; Valdizán Usón 2013; see supplementary file S66);
8. nausea was 7.60% (95% CI 5.30% to 10.6%; 41 studies, 5612 participants; see supplementary file S67);
9. upset stomach was 11.0% (95% CI 7.00% to 17.0%; 3 studies, 217 participants; Arnold 2004; Hulvershorn 2012; Na 2013; see supplementary file S68);
10. vomiting was 7.30% (95% CI 3.70% to 13.9%; 20 studies, 2731 participants; see supplementary file S69);
11. dyspepsia was 2.30% (95% CI 0.20% to 22.8%; 2 studies, 1502 participants; Arnold 2004; Cortese 2015; see supplementary file S70); and
12. gastroenteritis was 1.80% (95% CI 0.70% to 4.40%; 2 studies, 276 participants; Arnold 2004; Wigal 2015; see supplementary file S71).

Two studies also provided data on different gastrointestinal adverse events (Blader 2010; Khajehpiri 2014).

1. In Blader 2010 (65 participants), the proportion of participants on methylphenidate with increased appetite was 1.54% (95% CI 0.27% to 8.22%).
2. In Khajehpiri 2014 (71 participants), the proportion of participants on methylphenidate with xerostomia was 16.9% (95% CI 9.9% to 27.2%).

2.2.5 Musculoskeletal system

See Analysis 7.5. We were able to use data from 23 studies in 4 meta-analyses.

Chest pain

We combined the data from three studies (189 participants) in a meta-analysis (Arnold 2004; Hammerness 2009; Shang 2015), and found that the proportion of participants on methylphenidate with chest pain was 2.20% (95% CI 0.80% to 6.00%; see supplementary file S72).

Height

Six studies provided data on this outcome (Jensen 1999 (MTA); Kim 2010; Mohammadi 2012a; Vincent 1990; Wiguna 2012; Yalcin 2014).

Four studies reported increases in height in cohorts prescribed methylphenidate: Kim 2010 (baseline: 128.7 (SD 9.10) cm; follow-up: 129.4 (SD 9.10) cm), Mohammadi 2012a (baseline: 133.8 (SD 14.81) cm; follow-up: 135.9 (SD 15.6) cm), Wiguna 2012 (MD 0.55 cm, P = 0.06), and Yalcin 2014 (baseline: 134.6 (SD 12.32) cm; follow-up: 136.0 (SD 12.5) cm).

Vincent 1990 reported no difference in expected (158.7 (SD 10.2) cm) and observed (158.7 (SD 9.80) cm) height.

Jensen 1999 (MTA) reported no difference after 14 months in those who received methylphenidate (mean change: 5.88 (SD 1.80), n = 222), and those who did not (mean change: 6.93 (SD 2.21), n = 106), nor at 24 months (methylphenidate: mean 4.53 (SD 1.61), n = 106; no methylphenidate: mean 5.40 (SD 2.18)).

Weight

Eight studies provided data on this outcome (Davari-Ashtiani 2010; Germinario 2013; Kim 2010; Kratochvil 2002; Mohammadi 2012a; Vincent 1990; Wiguna 2012; Yalcin 2014).

Three studies reported an increase in weight in participants receiving methylphenidate. Yalcin 2014 reported weight gain in 15/33 participants while Davari-Ashtiani 2010 reported weight gain in 1/16. Germinario 2013 reported an increase in weight from 38.4 kg (SD 11.3) at baseline to 46.8 kg (SD 13.4) at 24 months.

Five studies reported no apparent increase or decrease in weight: Vincent 1990 (observed weight = 47.90 (SD 10.30) kg; expected weight = 48.1 (SD 10.6) kg); Kim 2010 (baseline: 28.5 (SD 6.40) kg; follow-up: 27.6 (SD 5.90) kg, n = 285); Kratochvil 2002 (baseline: 40.7 (SD 17.2) kg; follow-up: 40.6 (SD 18.1) kg, P = 0.20); Mohammadi 2012a (baseline: 32.7 (SD 14.7) kg; follow-up: 33.6 (SD 17.1) kg); and Wiguna 2012 (baseline: 36.20 (SD 11.9) kg; follow-up: 35.79 (SD 12.0) kg, P = 0.51).

BMI

Three studies provided data on this outcome (Gerwe 2009; Mohammadi 2012a; Yalcin 2014).

There was no apparent change from baseline BMI in all three studies: Gerwe 2009 (mean change from baseline: −0.30 (SD 0.70) kg/m^2); Mohammadi 2012a (baseline: 18.2 (SD 4.74) kg/m^2; follow-up: 18.4 (SD 4.85) kg/m^2), or Yalcin 2014 (baseline: 18.1 (SD 2.76) kg/m^2; follow-up: 17.8 (SD 2.71) kg/m^2).

Z scores

- Height

Seven studies reported that age- and sex-adjusted scores were lower after follow-up: mean 11.2 months in Moungnoi 2011 (baseline: z score = 0.09; one year: z score = 0.05, n = 83); after 14 months in Bereket 2005 (z score = −0.31 (SD 1.02)); after 18 months in Poulton 2003 (baseline: z score = 0.26 (SD 0.82), n = 19; 18 months: z score = −0.50 (SD 0.77), n = 13); 24 months in Germinario 2013 (baseline: z score = 0.36 (SD 1.21); 24 months: z score = 0.18 (SD 1.12)); 36 months in Poulton 2012 (baseline: z score = 0.34 (SD 0.81), n = 21; 36 months: z score = −0.13 (SD 0.76), n = 17). The difference in z score between baseline and follow-up was also lower in Spencer 1992 (z score difference = −0.23, SD 0.42) and marginally lower in Schertz 1996 (z score difference = −0.1).

- Weight

Five studies reported decreases in weight from baseline: −0.26 kg (SD 1.40) in Gerwe 2009; 0.04 z score at 14 months in Bereket 2005; 0.4 z score decrease at follow-up (mean follow-up 11.2 months) in Schertz 1996; a mean weight-for-age z score of 0.01 at baseline to −0.06 at one-year follow-up in Moungnoi 2011 (n = 83); from a z score of 0.44 (SD 0.97; n = 19) at baseline, to −0.15 (SD 0.98; n = 16) at 18 months, and a mean difference of −0.23 (SD 0.96; n = 17) at 36 months in Poulton 2003.

- BMI

In three studies, there was no difference in the BMI of participants receiving methylphenidate over 14 months (Bereket 2005: z scores = 0.706 (SD = 0.65)); after 24 to 36 months (Poulton 2012: z score =

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0.12 (SD = 0.43); N = 24), and over 48 months (Durá-Travé 2012: z score = −0.20 (SD = 0.99); N = 160).

Other specific adverse events

Two studies reported on the proportion of participants on methylphenidate with different musculoskeletal adverse events (Ardic 2014; Lahat 2000).

1. In Ardic 2014 (122 participants), the proportion of participants on methylphenidate with increased mobility was 18.03% (95% CI 12% to 25%).
2. Lahat 2000 (18 participants) reported on bone mineral density as follows: "...no significant difference between serum calcium, phosphorus or bone-specific alkaline phosphatase, urinary deoxypyridinoline, or bone mineral density in the two groups of children. No child deviated from his height percentile during the treatment period."

2.2.6 Immune system

See Analysis 7.6. Fourteen studies reported data on this outcome.

We conducted eight meta-analyses using data from 13 studies (Arnold 2004; Arnold 2010; Döpfner 2011b; Findling 2009; Garg 2014; Hammerness 2009; Kordon 2011; Kratochvil 2002; Lee 2007; Pierce 2010; Sangal 2006; Steele 2006; Wang 2007). We found the proportion of participants on methylphenidate with:

1. nasopharyngitis to be 8.50% (95% CI 3.50% to 19.4%; 5 studies, 521 participants; Arnold 2004; Arnold 2010; Döpfner 2011b; Findling 2009; Kratochvil 2002; see supplementary file S73);
2. pyrexia to be 12.6% (95% CI 6.60% to 22.7%; 3 studies, 412 participants; Arnold 2004; Findling 2009; Wang 2007; see supplementary file S74);
3. allergies to be 2.30% (95% CI 0.90% to 5.30%; 2 studies, 225 participants; Hammerness 2009; Pierce 2010; see supplementary file S75);
4. cold symptoms to be 11.8% (95% CI 3.40% to 33.9%; 3 studies, 154 participants; Hammerness 2009; Kratochvil 2002; Steele 2006; see supplementary file S76);
5. pharyngitis to be 5.10% (95% CI 1.70% to 14.1%; 5 studies, 834 participants; Arnold 2004; Döpfner 2011b; Kordon 2011; Kratochvil 2002; Sangal 2006; see supplementary file S77);
6. viral infection to be 6.10% (95% CI 0.30% to 58.4%; 2 studies, 674 participants; Arnold 2004; Kordon 2011; see supplementary file S78);
7. rash to be 5.50% (95% CI 3.10% to 9.70%; 3 studies, 213 participants; Arnold 2004; Garg 2014; Lee 2007; see supplementary file S79); and
8. rhinitis to be 3.10% (95% CI 0.70% to 12.6%; 2 studies, 617 participants; Arnold 2004; Kordon 2011; see supplementary file S80).

Three studies provided data on different adverse events related to the immune system (Hammerness 2009; Kordon 2011; Valdizán Usón 2013).

1. In Hammerness 2009 (57 participants), the proportion of participants on methylphenidate with ear disorders was 5.30% (95% Cl 1.80% to 14.4%).
2. In Kordon 2011 (541 participants), the proportion of participants on methylphenidate with fever was 1.70% (95% CI 0.90% to 3.30%).
3. In Valdizán Usón 2013 (689 participants), the proportion of participants on methylphenidate with infections was 1.90% (95% CI 1.10% to 3.20%)

2.2.7 Urogenital system

See Analysis 7.7. We included three studies (141 participants) in this meta-analysis (Blader 2010; Galland 2010; Tomás Vila 2010b). The proportion of participants on methylphenidate with enuresis was 9.30% (95% CI 4.10% to 19.9%; see supplementary file S81).

2.2.8 Other body systems

See Analysis 7.8. Ten studies reported data on this outcome (Abbas 2006; Arnold 2004; Congologlu 2009; Garg 2014; Ghanizadeh 2013; Haertling 2015; Khajehpiri 2014; Pierce 2010; Shang 2015; Witt 2008).

Using data from across five studies (Abbas 2006; Haertling 2015; Khajehpiri 2014; Pierce 2010; Shang 2015), we conducted two meta-analyses, in which we found the proportion of participants on methylphenidate with:

1. hair loss to be 2.80% (95% CI 0.00% to 9.00%; 2 studies, 161 participants; Abbas 2006; Khajehpiri 2014; see supplementary file S82); and
2. skin problems to be 1.80% (95% CI 0.80% to 4.00%; 4 studies, 447 participants; Haertling 2015; Khajehpiri 2014; Pierce 2010; Shang 2015; see supplementary file S83).

Five studies reported data on patients on methylphenidate with other non-serious adverse events (Arnold 2004; Congologlu 2009; Garg 2014; Ghanizadeh 2013; Witt 2008).

1. Arnold 2004 (76 participants) reported the proportion of participants on methylphenidate with accidental injury as 13.2% (95% CI 7.30% to 22.6%).
2. Congologlu 2009 suggested that "methylphenidate decreases fundamental [voice] frequency in children with ADHD, but our findings should be replicated under blind drug administration and by supporting other vocal analyses."
3. Garg 2014 (27 participants) reported the proportion of participants on methylphenidate with hypersalivation as 3.70% (95% CI 0.70% to 18.3%).
4. Ghanizadeh 2013 (26 participants) reported the proportion of participants on methylphenidate with nasal bleeding as 3.90% (95% CI 0.70% to 2.20%).
5. Witt 2008 conducted a study of chromosomal aberration and "found no evidence of changes in any of the three cytogenetic endpoints examined in the lymphocytes of children treated with methylphenidate or mixed mixed amphetamine salts (MAS) based products continuously for three months".

2.2.9 Withdrawal of treatment

Due to non-serious adverse events

See Analysis 8.1. We conducted a meta-analysis of data from 37 studies (7142 participants) that reported on the number of patients withdrawn from methylphenidate due to non-serious adverse events. The proportion of participants withdrawn from

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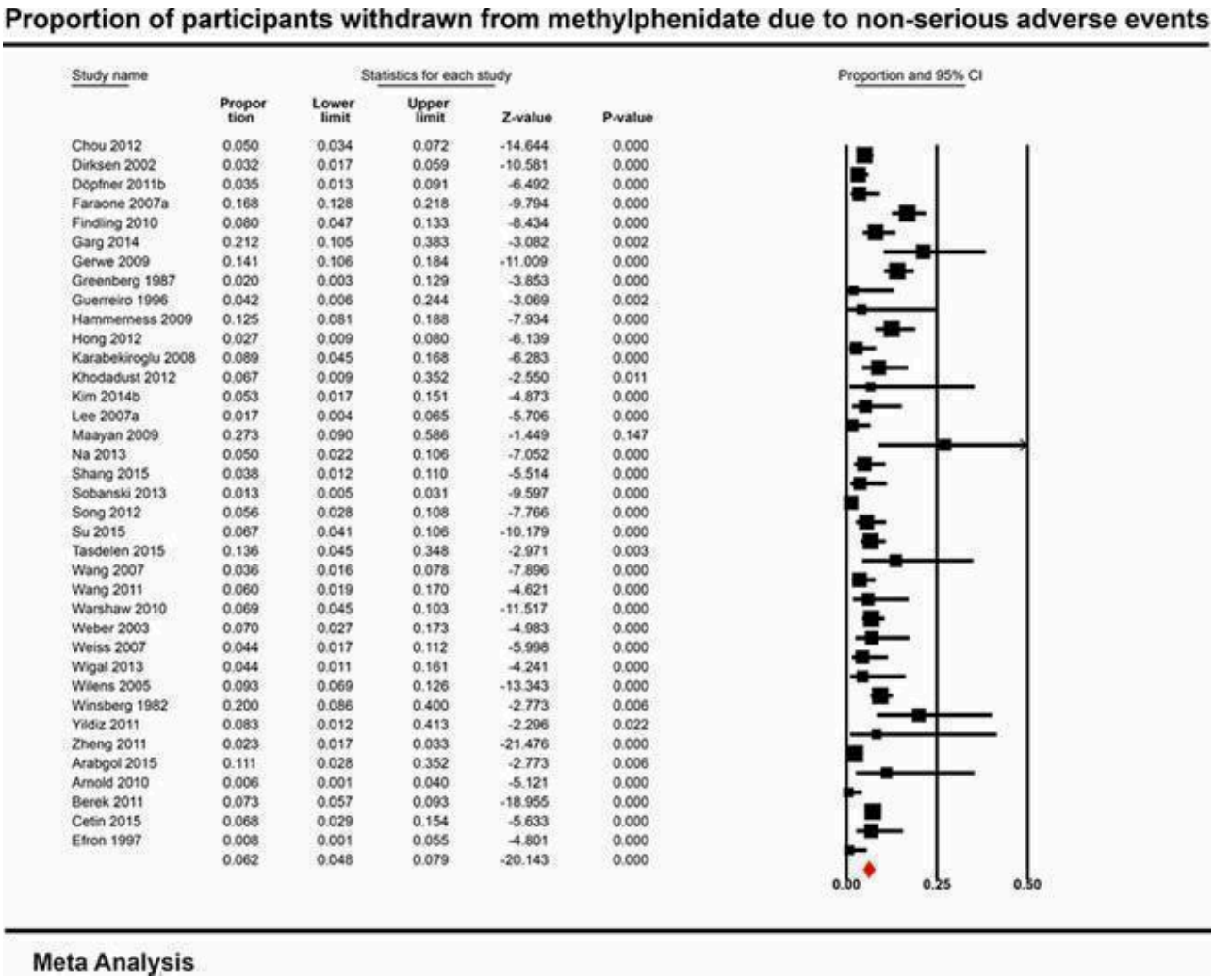
methylphenidate treatment due to non-serious adverse events was 6.20% (95% CI 4.80% to 7.90%; Figure 6).

Figure 6. Proportion of participants withdrawn from methylphenidate due to non-serious adverse events



For unknown reasons

See Analysis 8.2. We conducted a meta-analysis of data from 57 studies (8340 participants) that reported on the number of patients withdrawn from methylphenidate for unknown reasons. The proportion of participants withdrawn from methylphenidate for unknown reasons was 16.2% (95% CI 13.0% to 19.9%; Figure 7).

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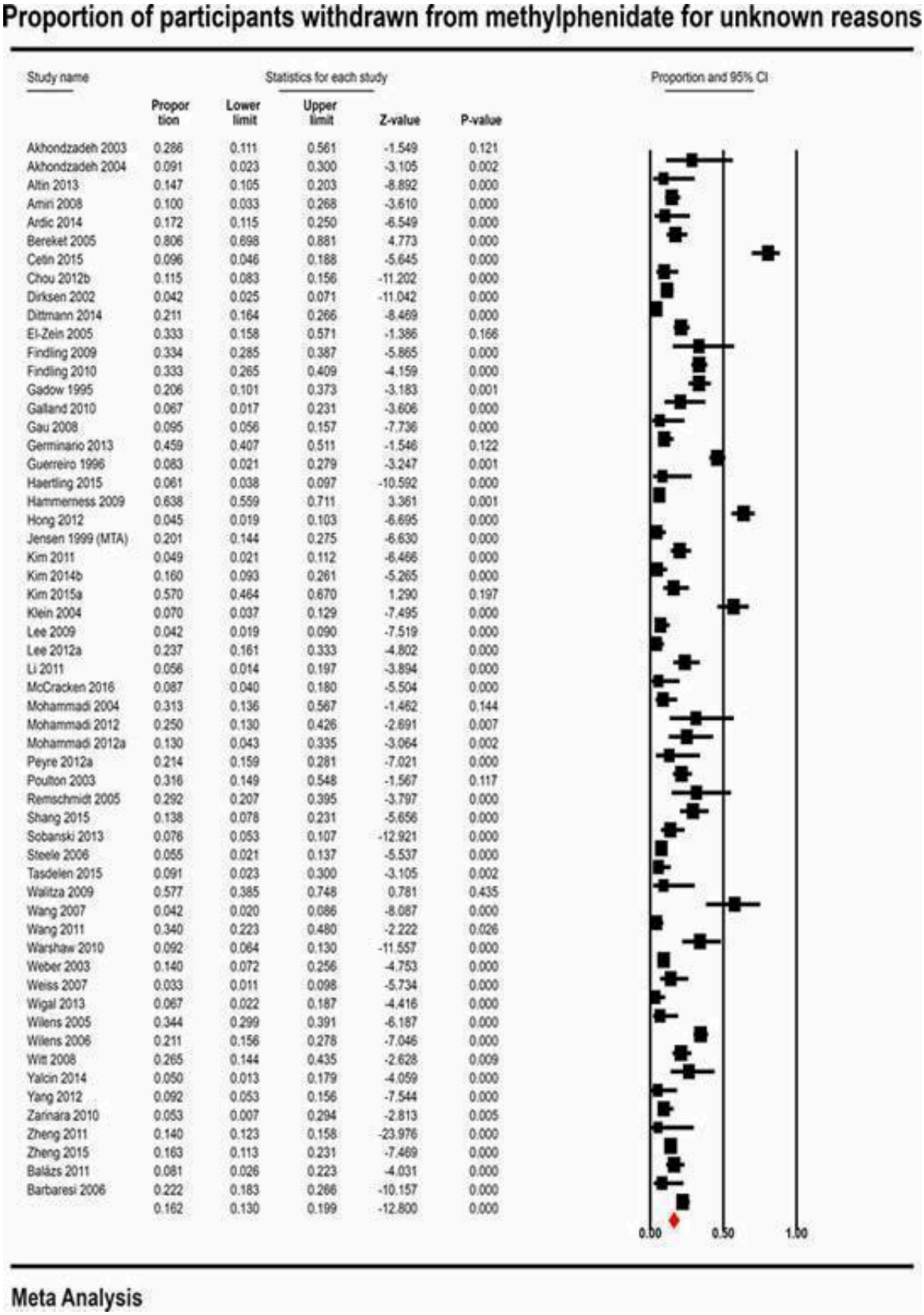
Figure 7. Proportion of participants withdrawn from methylphenidate for unknown reasons



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3. Patient reports/series

3.1. Primary outcomes: serious adverse events

3.1.1 Frequency of any serious averse events

We found 26 patient reports/series of serious adverse events and these studies reported 149 cases of serious adverse events.

3.1.2 Central nervous system

See Analysis 9.1. We found 20 patient reports/series of serious adverse events related to the central nervous system.

Psychotic conditions

Twelve patient reports/series described psychosis or psychotic symptoms related to methylphenidate.

1. Abali 2007 reported on a 14-year-old girl with ADHD, major depression, and conduct disorder. She was treated with methylphenidate (20 mg/day) and fluoxetine (20 mg/day) and developed visual and auditory hallucinations a few hours after treatment initiation.
2. Aguilera-Albesa 2010 reported on an 8-year-old boy and 6-year-old girl, both with ADHD, who developed psychosis on modified-release methylphenidate 18 mg/day (0.51 mg/kg/day) after two days, and modified-release methylphenidate 10 mg for three days then 20 mg/day on the fourth day (0.45 mg/kg/day).
3. Coşkun 2008 also reported on the development of psychosis in a 10-year-old boy with ADHD, oppositional defiant disorder, and generalised and separation anxiety, who was also treated with a combination of methylphenidate and fluoxetine. He was taking OROS methylphenidate (18 mg/day) and fluoxetine (10 mg/day) and experienced a relatively acute-onset episode of intense visual and tactile hallucinations three hours after taking the medication. In these cases, it was thought that the combination of methylphenidate and fluoxetine might have precipitated the psychoses.
4. Goetz 2011 described a girl with ADHD and oppositional defiant disorder who experienced a three-hour episode of bizarre, complex, nocturnal visual hallucinations whilst taking OROS methylphenidate (18 mg/day). Authors reported a reduction of REM (rapid eye movement) sleep and two episodes of confusional arousals, hypothesising that her pre-existing sleep impairment made her vulnerable to methylphenidate-induced, adverse sleep effects.
5. Gross-Tsur 2004 described three children with ADHD treated with low-dose methylphenidate, who developed complex visual and tactile hallucinations that appeared soon after ingestion of methylphenidate and resolved after its withdrawal. In one patient, the hallucinations reappeared after an inadvertent challenge.
6. Halevy 2009 reported on a 15-year-old boy with ADHD who presented with complex visual hallucinations of rats running around and touching and smelling him soon after receiving a first low dose of methylphenidate. The hallucinations resolved upon discontinuation of the drug. Reintroduction of the drug seven years later at an even lower dose had the same effect. The authors suggested that the occurrence of hallucinations after a very low dose of methylphenidate on two occasions may suggest an idiosyncratic reaction. It could also be explained by a drug-induced dysfunction of the monoamine transmitters. Given the wide use of methylphenidate, clinicians should be aware of this possible adverse event.
7. Irmak 2014 reported a nine-year-old boy who developed phobias and visual hallucinations during OROS methylphenidate titrated to 1 mg/kg/day.
8. Mino 1999 described a 16-year-old girl with hyperkinetic disorder who developed a psychosis after initially becoming depressed following three weeks of 10 mg/day of methylphenidate. Methylphenidate was stopped, but six weeks later she developed a psychosis with delusions of reference, thought block, and other psychotic features. These resolved on antipsychotic medication after two months. The authors highlighted the risk of methylphenidate precipitating psychosis. However, there had been a history of diagnostic uncertainty beginning with behavioural difficulties from the start of school and then treatment with antipsychotics for mania when she was 12 years old. This might suggest that methylphenidate treatment in a patient with possible additional vulnerability could precipitate psychosis.
9. Porfirio 2011 reported an episode of complex visual hallucinations three years after initiation of methylphenidate treatment (30 mg/day (0.5 mg/kg)).
10. Rashid 2007 reported a 10-year-old boy with ADHD and chronic somatisation who developed intensified somatic hallucinations with a change in methylphenidate dosage from 36 mg OROS methylphenidate a day to 15 mg immediate-release methylphenidate twice daily.
11. Shibib 2009 describes four patients (a 14-year-old girl, a 14-year-old boy, an 8-year-old boy and a 10-year-old boy), all of whom were treated with methylphenidate in normal therapeutic doses and all of whom developed psychoses that resolved on cessation of methylphenidate treatment. Three of the four patients were taking modified-release methylphenidate.
12. Tomás Vila 2010a described the development of psychosis in a 10-year-old patient with ADHD who was treated with 30 mg of methylphenidate (50% immediate release, 50% modified release). The patient experienced visual hallucinations (insects on hands, feet, abdomen and thorax) with associated itching. It resolved on stopping methylphenidate and treatment with risperidone.

Seizures

Two patient reports/series described seizures related to methylphenidate.

1. Feeney 1997 reported on a 13-year-old boy with ADHD and depressive disorder (not otherwise specified) who developed seizures a week after sertraline, 50 mg/day, was added to his 80 mg/day dose of methylphenidate (1.8 mg/kg/day). He had been established on 80 mg/day of methylphenidate for seven months; initially, this had been gradually titrated upwards to achieve symptom control, without significant adverse events. He was treated with cognitive behavioural therapy and family interventions for depression, but when this deteriorated after eight months of treatment, sertraline 25 mg/day was prescribed for a week and then increased to 50 mg/day. A week later he experienced a tonic-clonic event witnessed by his father, which lasted a few seconds. All investigations were normal apart from a serum pH value of 7.20. The sertraline was discontinued and methylphenidate treatment continued unchanged without seizure recurrence.

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2. Hemmer 2001 reported seizures in a boy aged six, and two girls aged six and seven, receiving 0.30 mg/kg/day to 1 mg/kg/day of methylphenidate for six weeks, 10 months and 3 months, respectively.

Cerebral arteritis

One patient report/series described cerebral arteritis related to methylphenidate (Trugman 1988). This study reported on cerebral arteritis and infarction thought to have been caused by chronic oral methylphenidate use in a 12-year-old boy. The cerebrospinal fluid profile and angiogram at the time supported the diagnosis of inflammatory arteritis, yet laboratory evaluation revealed no identifiable cause. Magnetic resonance imaging (MRI) six years on was compatible with an old infarction. In the six years since the stroke, while not on methylphenidate, there was no evidence of active, central nervous system or systemic vasculitis.

Self-harm and suicidal behaviour

Three patient reports/series described self-harm and suicidal behaviours related to methylphenidate.

1. Arun 2014 reported on two children with ADHD who developed suicidal ideation, which abated after discontinuation of methylphenidate. Neither child had depressive symptoms, and the suicidal ideation could not be explained on the basis of impulsivity.
2. Gökce 2015 reported on a 12-year-old boy who made a suicide attempt after switching from 27 mg to 36 mg of OROS methylphenidate: the patient reported irritable mood when he took the first dose of 36 mg of long-acting methylphenidate. This might be the cause of the suicide attempt. He had a full recovery after withdrawal from methylphenidate.
3. Strandell 2007 reported concerns about suicidal behaviour, including suicide, based on information retrieved from the WHO Collaborating Centre for International Drug Monitoring (Uppsala, Sweden). A total of 116 reports of methylphenidate related to 'suicide attempts', although this term is not explicitly defined. The data included reports of methylphenidate and atomoxetine. They summarised reports on methylphenidate as: suicide (n = 7), suicide attempt (n = 25), depression, suicidal (n =1), intentional overdose (n = 0), intentional self-injury (n = 8), non-accidental overdose (n = 8), suicidal tendency (n = 21), thoughts of self-harm (n = 0).

Death

Tølløfsrud 2006 reported a 17-year-old boy who died of heart failure (acute dilated cardiomyopathy) during methylphenidate treatment.

Dyskinesia

We found one patient report/series on dyskinesia related to methylphenidate (Yilmaz 2013). This study reported a patient having involuntary movements that started about five hours after methylphenidate ingestion, including lip-licking, lip-smacking and tongue-rolling movements, as well as dyskinetic tongue movements inside and outside the mouth, and involuntary bilateral arm swinging while sitting and standing. Furthermore, he opened and closed his fingers without complete extension and made occasional repetitive movements of the feet, such as beating them against each other while sitting. About 15 hours after methylphenidate ingestion, both hand-mouth movements and excessive mobility had significantly resolved. Dyskinetic symptoms had completely disappeared on the second day of hospitalisation, and the patient was discharged.

3.1.3 Cardiovascular and respiratory system

See Analysis 9.2. We found three patient reports/series on adverse events related to the cardiovascular and respiratory system (Munk 2015; Nymark 2008; Saieh 2004).

Cardiovascular events

Two patient reports/series described cardiovascular events related to methylphenidate.

1. Munk 2015 reported a case of myocardial infarction related to methylphenidate exposure in a cardiac-healthy, 11-year-old boy without any cardiovascular risk factors, who was being treated with methylphenidate 54 mg/day. Treatment duration was two years. The boy experienced a cardiac arrest following exercise, without any prior complaints about chest discomfort or shortness of breath. A week before the event, he had a short episode of tachycardia. The examination showed that the myocardial infarction was of an older date (more than weeks), due to thinning of the myocardium and an adversely remodelled left ventricle. A pacemaker was inserted and methylphenidate treatment was discontinued. The boy was very thoroughly examined and the only thing that stands out is the methylphenidate treatment.
2. Nymark 2008 reported a case of serious cardiomyopathy during methylphenidate treatment; a serious adverse event (hospitalisation) relating to hypoxia and dyspnoea following 11 months of methylphenidate treatment. On investigation, signs of liver, renal, and heart failure were found.

Hypertension

One patient report/series, Saieh 2004, described hypertension related to methylphenidate. Saieh 2004 described a patient who was hospitalised due to hypertension during methylphenidate treatment. Abdominal pain with intermittent accentuation for hours was present for four days prior to hospitalisation. Secondary hypertension: persistent hypertension (158/88 mmHg to 170/105 mmHg; pulse: 78 bpm to 98 bpm). The study authors reported normal physical examination, normal eye fundus, and normal cardiological examination. After discontinuation of methylphenidate, hypertensive treatment was only necessary for 24 hours. There was also normal blood pressure after one week.

3.1.4 Gastrointestinal system

Hepatoxicity

See Analysis 9.3. We found one patient report/series on hepatoxicity related to methylphenidate (Bernhard 2009). The study authors reported a hepatotoxic reaction; liver enzymes were elevated in a four-year-old boy prior to therapy. Vomiting started five weeks after onset of methylphenidate therapy and increased over three days. Abdominal pain increased in intensity. Liver transaminases were elevated over 30 times the normal level, and creatine kinase (CK) level also increased (Bernhard 2009).

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3.1.5 Urogenital system

Priapism

See Analysis 9.4. We found two patient reports/series on priapism related to methylphenidate.

1. In Cakin-Memik 2010, a 14-year-old boy with ADHD reported three to four episodes of priapism per day, lasting 40 to 45 minutes for three days after receiving 20 mg/day of immediate-release methylphenidate.
2. In Schwartz 2004, a 15-year-old boy with ADHD also experienced intermittent painful erections two weeks after initiating OROS-methylphenidate, which recently had been increased to 36 mg/day. The symptoms had not reoccurred two weeks or six months following cessation of methylphenidate.

No [patient reports/series] reported adverse outcomes related to the musculoskeletal, immune or other body systems,or on withdrawal of treatment due to serious adverse events, or adverse events of unknown severity.

3.2 Secondary outcomes: non-serious adverse events

3.2.1 Frequency of any non-serious adverse events

We found 45 patient reports/series of non-serious adverse events and these studies reported 55 cases of non-serious adverse events.

3.2.2. Central nervous system

See Analysis 10.5. We found 23 patient reports/series of non-serious adverse events related to the central nervous system.

Movement-related outcomes

See Analysis 10.1

- Tics

Two patient reports/series described tics related to methylphenidate.

1. Adrian 2001 showed the presence of clinically explosive outbursts of tics in a 10-year-old boy boy with ADHD receiving 20 mg/day of methylphenidate at seven years, which over a two-to-three-year period was increased to 40 mg/day.
2. Chandler 1989 described two ADHD patients: a boy aged 12 years receiving 0.2 mg/kg of methylphenidate twice a day who reported motor and vocal tics one month after treatment, and a 9-year-old boy treated with the same dose of methylphenidate and subsequent nortriptyline, who reported severe facial grimacing and vocal tics.

- Involuntary movements or dyskinesia

Three patient reports/series described involuntary movements or dyskinesia related to methylphenidate.

1. Machado 2010 reported choreoathetoid movements of orofacial muscles, arms and legs, and dystonic postures of the right arm in a 6-year-old girl with ADHD after an initial dose of 18 mg of extended-release methylphenidate.
2. McLaren 2010 showed spasmodic muscular contractions in the jaw of a boy aged 11 years old with ADHD after receiving a dose of 108 mg of OROS methylphenidate.
3. Hollis 2007 showed acute and transient dyskinesia within hours after treatment with 36 mg of modified-released methylphenidate in a 7-year-old, stimulant-naïve boy who had recently stopped taking risperidone.

Mood disorders

See Analysis 10.2

- Depression and disturbed mood

Three patient reports/series described depression and disturbed mood related to methylphenidate.

1. Hechtman 2011 gave an account of a 5-year-old boy with ADHD receiving 35 mg of OROS methylphenidate titrated to 54 mg over one to two months who was exhibiting frequent crying, marked irritability and many tantrums, which subsided after methylphenidate treatment was discontinued.
2. Mino 1999 reported depressed mood three weeks after initiating methylphenidate treatment (10 mg/day) in a 16-year-old girl with ADHD.
3. Niederhofer 2009 found depressed mood and appetite loss in a boy aged 11 years after two months of daily dosages of 20 mg of methylphenidate.

- Irritability

Two patient reports/series described irritability related to methylphenidate.

1. In Hechtman 2011, emotional mood, frequent crying, marked irritability and multiple tantrums were observed in a patient report/series of a 5-year-old boy with ADHD receiving 54 mg of OROS methylphenidate once a day for one to two months.
2. In Sabuncuoglu 2007, another three reports of irritability and agitation were reported in one boy and two girls aged 5, 6 and 15 years (all diagnosed with ADHD), upon switching from 1 mg/day of risperidone to 15 mg/day of methylphenidate.

- Aggression

Two patient reports/series described aggression related to methylphenidate.

1. In Coignoux 2009, a 14-year-old boy receiving 54 mg/day of extended-release methylphenidate for two years developed gestural stereotypes and verbal aggression towards his parents.
2. In Niederhofer 2011, two boys aged 10 and 11 years, who were receiving 20 mg/day of methylphenidate for two months, exhibited aggression and emotional instability.

- Mania/euphoria

Two patient reports/series described mania/euphoria related to methylphenidate.

1. Corrigall 1996 reported euphoria in a 11-year-old boy with ADHD and hyperkinetic disorder, who received 10 mg/day of methylphenidate for four weeks, which subsequently increased to 15 mg/day for five days.
2. In Ghanizadeh 2009, hypertalkativity (scaled 7 to 9 on a 10-point visual analogue scale) was found 45 minutes after taking 10 mg/day of methylphenidate in a 5-year old boy, continuing for three to four hours. Re-challenge was attempted more than 20 times, with hypertalkativity reoccurring on every consecutive attempt.

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Sleep problems

See Analysis 10.3

- Disturbed sleep

One patient report/series described disturbed sleep related to methylphenidate (Langevin 2012). This controlled before-and-after study showed a significant baseline difference (P = 0.008) between the number of nocturnal movements in a group of five ADHD children receiving an unspecified methylphenidate dosage and five ADHD children not on stimulant treatment.

- Other sleep problems

Two patient reports/series described sleep problems related to methylphenidate. Arun 2014 observed impaired sleep onset in an eight-year-old boy with ADHD who was receiving 5 mg/day of immediate-release methylphenidate for two days. In Coşkun 2010, the following problems were reported in a patient series of seven children with ADHD who were receiving 10 mg to 54 mg or immediate-release/OROS methylphenidate for 4 to 30 months: sleep problems (n = 4), worsening of pre-existing sleep problems (n = 2), and no worsening of such problems (n = 1).

Voice and speech disorders

See Analysis 10.4

- Voice problems

One patient report/series described voice problems related to methylphenidate (Yalcin 2012). In this study, a 10-year-old boy with ADHD who was receiving 5 mg of immediate-release methylphenidate, exhibited disturbances of voice quality, hoarseness, bifurcation-strain and voice over-vibrations beginning on the first day of treatment, which was scheduled to last for two weeks.

- Stuttering

One patient report/series described stuttering related to methylphenidate (Alpaslan 2015). This study found stuttering in a 7-year-old boy with ADHD 10 days after receiving 10 mg/daily of immediate-release methylphenidate. The treatment was ended immediately, and one week later the stuttering ended.

Other specific adverse events

See Analysis 10.5

- Anorexia

One patient report/series described anorexia related to methylphenidate (Findling 1996). In this study, an 11-year-old girl with ADHD received 5 mg of methylphenidate twice a day for three months and experienced mild and transient anorexia, resulting in a weight loss of 2 kg after treatment.

- Obsessive compulsive disorder (OCD) symptoms

Two patient reports/series described OCD related to methylphenidate.

1. Coşkun 2011 found symptoms of OCD, facial grimaces, nail picking and biting in a 10-year-old girl with ADHD who was receiving 27 mg/day of OROS methylphenidate for six weeks. The symptoms gradually disappeared upon discontinuation of methylphenidate and reoccurred when re-administering the same dosage at a later stage.
2. Woolley 2003 found obsessions and compulsions with anxiety, such as excessive handwashing, ritual checking and emetophobia, in an 11-year-old boy with ADHD and comorbid OCD upon receiving 40 mg/day of immediate-release methylphenidate for more than 15 months. These symptoms decreased rapidly upon methylphenidate withdrawal and increased when it was later reintroduced.

- Headache

One patient report/series described headache related to methylphenidate (Mize 2004). This study reported headache and mild depression in a 12-year-old boy after a methylphenidate dosage of 26 mg.

- EEG changes

One patient report/series described EEG changes related to methylphenidate (Dupuy 2008). In this study, elevated frontal coherence in all frequency bands was shown on the EEG-measurements of nine girls with ADHD who were administered methylphenidate over six months with unreported dosages.

3.2.3 Cardiovascular and respiratory system

See Analysis 10.6. We found four patient reports/series of non-serious adverse events related to the circulatory and respiratory system (Grossman 1985; Karaman 2010; Yu 2010; Gracious 1999).

Vasculopathy

One patient report/series described vasculopathy related to methylphenidate (Yu 2010). This study observed signs of vasculopathy in three male patients. First, a 16-year-old boy was diagnosed with "decreased circulation but not Raynaud's syndrome", occurring when his methylphenidate (Concerta) dose was increased from 54 mg/day to 90 mg/day for three months while on a constant dose of dexmethylphenidate (Focalin) (10 mg/day). Second, Raynaud's syndrome with finger pain and colour changes was observed in a 10-year-old boy on 30 mg/day of methylphenidate hydrochloride (Ritalin LA) and 2.5 mg/day of dexmethylphenidate for five years. Third, reddish and purple colour changes in the hands and feet of an 11-year-old boy were observed whilst on a daily dose of 20 mg of dexmethylphenidate hydrochloride (extended-release capsules) and 10 mg of immediate-release dexmethylphenidate for one year.

Cardiovascular problems

One patient report/series described cardiovascular problems related to methylphenidate (Karaman 2010). In this study, a 15-year-old with ADHD developed pulmonary arterial hypertension (PAH) after 18 months of treatment with 54 mg/day of OROS-methylphenidate. One month following a decision to discontinue OROS methylphenidate, the symptoms disappeared.

Bleeding

One patient report/series described bleeding related to methylphenidate (Grossman 1985). This study reported on a 7-year-old girl with ADHD receiving 10 mg of methylphenidate three times a day for seven months, who experienced idiopathic thrombocytopenic purpura (ITP). One week following a decision

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to end methylphenidate treatment, the petechia began to fade, and one year later there had been no reoccurrence of petechiae or bruising.

Tachycardia

One patient report/series described tachycardia related to methylphenidate (Gracious 1999). In this study, a 13-year-old girl with ADHD, who was administered 20 mg of methylphenidate twice daily for three months and subsequently 20 mg of sustained-release methylphenidate for 11 months once daily, developed atrioventricular nodal re-entrant tachycardia during treatment.

3.2.4 Gastrointestinal system

See Analysis 10.7. We found five patient reports/series of non-serious, gastrointestinal adverse events (Agarwal 2008; Coşkun 2009a; Ghanizadeh 2008a; Rappaport 2004; Yalcin 2012).

Loss of appetite

All five patients reports described loss of appetite related to methylphenidate.

1. Agarwal 2008 found decreased appetite in an 8-year-old boy with ADHD on 50 mg/day of immediate-release methylphenidate and atomoxetine for six months.
2. Coşkun 2009a found loss of appetite but no weight decrease in an 6-year-old boy receiving 10 mg/day to 20 mg/day of immediate-release methylphenidate and 400 mg/day valproate for two months.
3. Ghanizadeh 2008a reported significant decreases in appetite in a 8.5-year-old boy with ADHD and oppositional defiant disorder on 20 mg/day of methylphenidate for one month.
4. Rappaport 2004 found loss of appetite whilst on an unspecified dose of immediate-release methylphenidate in a 14-year-old boy with ADHD and various comorbidities, who was comedicated with olanzapine.
5. Yalcin 2012 observed significant appetite loss in a 11-year-old boy with ADHD and comorbid specific learning disorder and social anxiety, who was receiving 18 mg/day of OROS methylphenidate for two weeks. The symptoms disappeared on drug-free days.

Nausea and vomiting

One patient report/series also described nausea and vomiting related to methylphenidate (Rappaport 2004). This study found nausea and vomiting in the same 14-year-old whilst on an unspecified dose of extended-release methylphenidate.

3.2.5 Musculoskeletal system

Growth

We found one patient report/series on reduced growth related to methylphenidate (Holtkamp 2002). This study found growth impairment in a 7-year-old boy with ADHD on 20 mg/day to 25 mg/day of methylphenidate for 19 months (Analysis 10.8).

3.2.6 Immune system

Allergic reactions

See Analysis 10.9. We found two patient reports/series on allergic reactions related to methylphenidate.

1. Confino-Cohen 2005 reported pruritic maculopapular skin rash during 10 mg/day methylphenidate treatment for one week in an 8-year-old girl with ADHD. The rash improved with antihistamines and, while re-challenge at a lower dose caused reappearances of rash, the symptoms were less severe the second time around.
2. In Vashi 2011, a 9-year-old girl with ADHD receiving an unknown dosage of methylphenidate patches for eight months presented with pruritic dermatitis, with itchy, burning, red lesions on her arms, legs, abdomen and back, lasting two months following methylphenidate discontinuation. Similar rashes later reoccurred upon re-testing methylphenidate treatment.

3.2.7 Urogenital system

See Analysis 10.10. We found five patient reports/series related to the urogenital system (Ramasamy 2014; Coşkun 2009b; Tang 2010; Ghanizadeh 2008b; Williamson 2011).

Testicular failure

We found one patient report/series on testicular failure related to methylphenidate (Ramasamy 2014). In this study, a 20-year-old male patient with ADHD, treated with methylphenidate for approximately 17 years at various doses, reported testicular failure and poor erectile function.

Sexual adverse events

One patient report/series described serious adverse events related to methylphenidate (Coşkun 2009b). This study reported multiple, daily, painless erections unrelated to any sexual stimuli and without ejaculation in a 15-year-old boy with ADHD administered 10 mg/day to 30 mg/day of immediate-release methylphenidate for one month, 18 mg/day of OROS methylphenidate for one month and 36 mg/day of OROS methylphenidate for three weeks. They also found hypersexual behaviour and morning erections prior to ingesting methylphenidate, with no such behaviour on drug-free days, on 18 mg/day of OROS-methylphenidate, which were dramatically reduced on 10 mg/day to 20 mg/day of immediate-release methylphenidate, only to return in fluctuations on 18 mg/day of OROS methylphenidate (with no hypersexual behaviour on drug-free days).

Incontinence

One patient report/series described incontinence related to methylphenidate (Tang 2010). In this study, almost daily urinary incontinence on 36 mg/daily of OROS methylphenidate for two weeks was observed in an 8-year-old boy with ADHD, which was rapidly and completely resolved after discontinuation of the treatment dose.

Enuresis

Two patient reports/series described enuresis related to methylphenidate.

1. In Ghanizadeh 2008b, 20 mg/day of methylphenidate was titrated and discontinued three times for an 11-year-old boy with nocturnal enuresis occurring and ceasing each consecutive time.
2. Williamson 2011 also found resolution of daily enuresis in a 9-year-old boy with ADHD on 54 mg/day of extended-release methylphenidate and an 11-year-old girl with ADHD on 10 mg/

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daily of extended-release dexmethylphenidate for a short-term period.

3.2.8 Other body systems

See Analysis 10.11. We found five patient reports/series of other, non-serious adverse events (Cohen 1992; Coşkun 2009a; Ghanizadeh 2008c; Lewis 2012; Ririe 1997).

Skin reactions

Two patient reports/series described skin reactions related to methylphenidate.

1. Cohen 1992 found severe swelling and redness of the scrotum in an 8-year-old boy with ADD, which spontaneously resolved four days after the methylphenidate dose of 10 mg/day was discontinued. Eighteen hours after methylphenidate retesting, the same skin eruption was documented, which again was resolved after another discontinuation of treatment. A 10-year-old boy from the same study, who was given the same methylphenidate dose, reported six hours of severe swelling and skin eruption of the scrotum within two days following treatment. The reactions were resolved upon drug withdrawal.
2. Coşkun 2009a found maculopapular pruritic skin eruption in an 8-year-old boy with ADHD following treatment with 18 mg/day of OROS methylphenidate and 400 mg/day of valproate. When the medication was discontinued, the skin lesion abated within weeks, and did not reoccur upon when restarting 10 mg/day to 20 mg/day of immediate-release methylphenidate and 300 mg/day of gabapentine.

Problems with sedation

One patient report/series described sedation problems related to methylphenidate (Ririe 1997). This study reported difficulty with conscious sedation in a 6-year-old boy with ADHD on 10 mg/day of immediate-release methylphenidate, who had a comorbid history of William's syndrome and supravalvar aortic stenosis. He remained alert and unable to lie still despite being given oral doses of sedatives, pointing to a potential interaction between methylphenidate and the anaesthetic agents.

Eye problems

Two patient reports/series described eye problems related to methylphenidate.

1. In Ghanizadeh 2008c, photophobia occurred a few days after initiation of 35 mg/day of methylphenidate treatment in a 7-year-old boy. The symptoms ceased and reoccurred upon discontinuation and readministration of methylphenidate.
2. In Lewis 2012, during 18 mg/day of extended-release methylphenidate, which was titrated to 54 mg/day over six months, a 10-year-old girl with ADHD showed intraocular pressure in the 16 mmHg to 19 mmHg range bilaterally in one study.

No [patient reports/series] reported on withdrawal of treatment due to non-serious adverse events or for unknown reasons.

Subgroup analyses

We conducted the subgroup analyses below using the Comprehensive Meta Analysis software (analyses not shown).

Duration of methylphenidate treatment

We found no significant difference (P = 0.83) between the proportion of participants on methylphenidate with any serious adverse events in short-term (less than six months: 1.20%, 95% CI 0.7% to 2.1%; 41 studies, 159,407 participants) versus long-term (six months or more: 1.1%, 95% CI 0.3% to 3.4%; 10 studies, 3015 participants) non-comparative studies.

We found no significant difference (P = 0.74) between the proportion of participants on methylphenidate with any non-serious adverse events in short-term (less than six months: 52.3%, 95% CI 52.3% to 39.6%; 35 studies, 11,411 participants) versus long-term (six months or more: 48.9%, 95% CI 33.7% to 64.3%; 14 studies, 2567 participants) non-comparative studies.

Comorbidity

We found no significant difference (P = 0.21) in the proportion of participants experiencing non-serious adverse events between those with ADHD and any comorbidity (54.2%, 95% CI 42.7% to 65.5%; 40 trials, 13,039 participants) versus those with ADHD and no comorbidities (40.4%, 95% CI 24.5% to 58.7%; 9 trials, 939 participants) in non-comparative cohort studies of methylphenidate.

We could not carry out the subgroup analysis on serious adverse events due to insufficient data on comorbidity.

Concurrent medication-intervention

We found a significant difference (P = 0.011) in the proportion of participants with ADHD experiencing any non-serious adverse events between those taking methylphenidate and no other medication (53.6%, 95% CI 42.9% to 64.0%; 43 trials, 12547 participants) versus those also taking other medications (27.1%, 95% CI 14.8% to 44.3%; 6 trials, 1431 participants) in non-comparative cohort studies.

We could not carry out the subgroup analysis on serious adverse events due to insufficient data on concurrent medication.

Dose of methylphenidate

We found no significant difference (P = 0.062) in the proportion of participants experiencing any non-serious adverse events between those on low-dose (less than 20 mg/day: 45.3%, 95% CI 33.7% to 57.5%; 35 studies, 159,278 participants) versus high-dose (20 mg/day and above: 64.4%, 95% CI 48.4% to 77.7%; 14 studies, 3144 participants) methylphenidate in non-comparative studies.

We could not carry out the subgroup analysis on serious adverse events due to insufficient data on dose of methylphenidate.

Age of participants

We found no significant difference (P = 0.23) in the proportion of participants on methylphenidate with any non-serious adverse events between non-comparative studies where the mean participant ages are 10 years or more (53.8%, 95% CI 37.2% to 69.5%; 22 studies, 159,278 participants) versus those where the mean participant ages are less than 10 years (47.1%, 95% CI 36.0% to 57.8%; 27 studies, 3144 participants) in non-comparative studies.

We could not carry out the subgroup analysis on serious adverse events due to insufficient data on age of participants.

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Study design

We found a significant difference (P = 0.01) between the proportion of participants on methylphenidate with any serious adverse events in the non-comparative, classic cohort studies (1.10%, 95% CI 0.60% to 2.00%; 32 studies, 159,761 participants) versus those in cohort studies from RCTs assessing methylphenidate versus other intervention for ADHD (1.60%, 95% CI 1.00% to 2.30%; 18 studies, 2661 participants)

We found no significant difference (P = 0.17) between the proportion of participants on methylphenidate with any non-serious adverse events in the non-comparative, classic cohort studies (47.10%, 95% CI 35.6% to 58.9%; 36 studies, 13,035 participants), compared to those in cohort studies from RCTs assessing methylphenidate versus other intervention for ADHD (62.1%, 95% CI 44.4% to 77.1%; 13 studies, 943 participants)

Study funding

We found no significant difference (P = 0.22) between the proportion of participants on methylphenidate with any serious adverse events in non-comparative cohort studies funded by industry (1.0%, 95% CI 0.6% to 1.6%; 30 studies, 137,152 participants) versus those not funded by industry (1.80%, 95% CI 0.80% to 4.10%; 20 studies, 25,270 participants); however, when looking only at the point estimate there seems to be 0.8% more serious adverse events in the group of studies not funded by industry.

On the other hand, in non-comparative cohort studies we did find a significant difference (P = 0.02) in the proportion of participants on methylphenidate with any non-serious adverse events between studies funded (41.6%, 95% CI 32.8% to 51.0%; 27 studies, 7981 participants) versus those not funded (64.2%, 95% CI 46.9% to 78.5%; 22 studies, 5997 participants) by industry.

Sensitivity analyses

We conducted a sensitivity analysis to test the robustness of our findings using the alternative, fixed-effect model, for the outcome of non-serious adverse events. In most analyses, there were no significant differences between the two statistical models. In cases where there was a statistical difference, the fixed-effect model mostly showed a higher proportion of adverse events. Therefore, the decision to report the results of the random-effects model was a conservative one.

We also conducted a sensitivity analysis to test the robustness of our findings to the removal of patient-control studies from the analysis, for the outcome of any serious adverse events; we found no statistical difference (Analysis 1.1).

DISCUSSION

Summary of main results

Our search found 260 relevant non-randomized studies from 431 reports consisting of: 7 comparative cohort studies, 4 patient-control studies, 177 non-comparative cohort studies, 70 patient reports/series, and 2 cross-sectional studies. We reported adverse events data from 2,283,509 participants worldwide, of both genders, aged between 3 and 20 years. The risk of bias in the comparative studies ranged from moderate to critical, whereas all non-comparative studies were at critical risk of bias. The quality of evidence for all outcomes was very low according to GRADE standards. We found that the occurrence of serious adverse events in the comparative cohort and patient-control studies was 1.36 times more frequent in participants that used methylphenidate when compared to controls. In cohort studies without a control group, we found a low proportion (1.20%) of any serious adverse events. Out of these, 22 studies had adverse events data for the central nervous system, 5 studies for the cardiovascular and respiratory system, 2 studies for the musculoskeletal system, and 1 study apiece for the gastrointestinal and immune systems. The largest proportion (51.2%) of non-serious adverse events due to methylphenidate use were found in cohort studies without a control group. However, this can be interpreted as an imprecise finding due to the large CI. In non-comparative cohort studies, the proportion of participants withdrawn from methylphenidate treatment due to: serious adverse events was 1.20%; adverse events of unknown severity, 7.30%, non-serious adverse events, 6.20%; and unknown reasons, 16.2%.

Subgroup analyses

We conducted subgroup analyses for studies that included children who:

1. received concurrent medication versus no concurrent medication;
2. had comorbidities versus those who had none;
3. were younger versus older than 10 years of age;
4. received methylphenidate for six months or more versus less than six months; and
5. received a higher dosage of methylphenidate (20 mg/day and above) versus a lower dosage.

We also conducted a subgroup analysis in which we compared studies with higher-quality designs (i.e. RCTs) to those of lower quality (cohorts). We concluded that adverse events reported in observational studies do not seem to depend on comorbidity or age of participants, dose or duration of methylphenidate treatment, or study design (non-serious adverse events). However, we observed fewer adverse events in concurrent-medication users. These subgroup analyses suggest that the most common confounding factors do not affect the proportions of adverse events. We discovered differences when comparing the proportion of participants on methylphenidate with any serious adverse events in the non-comparative classic cohort studies to the proportion of participants on methylphenidate with any serious adverse events in the cohort studies from the RCTs, and thus reported these separately.

Finally, we conducted subgroup analyses investigating whether there were differences in the proportions of adverse events in the studies funded versus not funded by pharmaceutical companies. We found that studies funded by pharmaceutical companies had a much lower proportion of both serious and non-serious adverse events. This is worrying, as it shows that adverse events are underestimated in industry-sponsored studies, confirming findings from previous systematic reviews (Lundh 2012; Lundh 2017). This underpins our statements in this review that the proportions of adverse events are likely underestimated and that the proportions would likely have been higher if all studies had been conducted without industry funding.

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Overall completeness and applicability of evidence

To our knowledge, this is the first systematic review that assesses adverse events of methylphenidate in children and adolescents from non-randomised studies. The included studies investigated adverse event profiles of children in different countries, settings, time periods and clinical practice. Studies were conducted over approximately 10 years with a great deal of inconsistency in reporting and classifying adverse events. In addition, there are limited data on comorbidities and medicine use.

Surprisingly, we found few comparative non-randomised studies. Many of the comparative studies had healthy controls and therefore could not be included as comparative studies. From these studies, however, we included those receiving methylphenidate as an observational cohort study. Accordingly, most of the data in this review come from non-comparative cohort studies (including methylphenidate groups from RCTs assessing methylphenidate versus other interventions for ADHD, and follow-up periods from RCTs), comprising 2,207,751 participants. These data may therefore be biased due to the absence of a control group and through uncontrolled confounding factors. Thus, readers should consider the very low quality of the included studies when interpreting the findings of this review.

Cortese 2015 reported headache and sleep disorders as serious adverse events. Whilst these may usually be considered non-serious adverse events, it is in keeping with their definition of adverse events: "Serious adverse events (AEs) were classified as severe if their occurrence was followed by active notification by clinical centers to the Italian Medicines Agency; otherwise, they were labelled as mild. The Italian Medicines Agency requires active notification when an AE [adverse event] results in death, is life-threatening, requires hospitalisation or prolongation of existing inpatients' hospitalisation, results in persistent or significant disability or incapacity, or leads to a congenital anomaly or birth defect." This definition is 100% in accordance with the ICH-GCP definition of serious adverse events (ICH 1996).

To expand our understanding of adverse events, particularly where these are rare or take time to become apparent, it is necessary to bolster the limited data from RCTs by including data from non-randomised studies (Storebø 2015). There are a number of advantages to non-randomised studies.

Despite the fact that these non-randomised studies may have a higher risk of bias as regards adverse events, they are the only data available and should still be considered in the evaluation of methylphenidate as a treatment. One may debate whether controlling for confounders is necessary when determining adverse events, given that they are less likely to occur when an outcome is unintended, as opposed to an intended exposure effect (Golder 2011).

The findings from this review underscore the fact that information on long-term adverse events in the use of methylphenidate is very limited. The increased use of methylphenidate, therefore, raises concerns about possible harms, particularly regarding unknown long-term risks.

We found new data on unexpected adverse events, and this information is important with regard to identifying unrecognised harmful effects. Most reported adverse events were non-serious. This information is now available to regulators so they may update the SPC with respect to frequency estimates and completeness of adverse event information.

Few scales were used to define and/or evaluate adverse events. Assessment of causality of adverse events was also poorly reported.

Quality of the evidence

Due to the presence of a large number of cohort studies without a comparator, it was only possible to evaluate the quality of the evidence for a small number of studies. These evaluations confirmed that non-randomised studies monitoring adverse events are at critical risk of bias. The high degree of under-reporting in these studies, particularly within cohort studies, is of great concern.

High risk of bias in RCTs has been shown to overestimate benefits and underestimate harms, and this is especially common in trials funded by industry (Lundh 2017). Thus, one can presume that the proportions we found are at the lower side of the estimate spectrum (Gluud 2008; Kjaergard 2001; Lundh 2017; Moher 1998; Savović 2012; Schulz 1995; Wood 2008); pharmaceutical companies funded 53 out of the 177 non-comparative cohort studies included in our review. Furthermore, 11 other studies had authors with connections to pharmaceutical advisory boards, whilst 45 of 177 studies did not report source of funding.

In non-randomised studies, a number of biases can indeed affect the estimation of the efficacy outcome. However, adverse events are not usually influenced by these sources given their unpredictable nature (Loke 2011).

Furthermore, the use of rating scales to more reliably assess adverse events was uncommon, so we believe that the proportions reported here are an underestimation of the true value (Pagsberg 2017).

The findings of this review should be interpreted whilst bearing in mind the very low quality of the included studies and their methodological limitations. Many of the uncontrolled confounding factors that might limit the value of this review, for example, duration of methylphenidate treatment, dosage of methylphenidate, comorbidity, age of participants, or study design (non-serious adverse events), do not seem to affect the estimates when investigated in subgroup analyses. It is possible and even likely that the adverse event profile of methylphenidate could be worse than what we report here (Aagaard 2011).

Adverse events in non-randomised studies are often the only data available on such outcomes. This is why they are still used to evaluate adverse events (Golder 2011). Moreover, the duration of most RCTs is seldom long enough to detect adverse events that may only appear after a lengthy duration (Ioannidis 2009). Schroll 2016 showed that only 3% to 33% of the total number of investigator-reported adverse events from RCTs were reported in the clinical study reports. This further underlines the need to include non-randomised studies when assessing harms.

Our aggregation and assessment of patient reports/series revealed a number of serious adverse events occurring during treatment with methylphenidate. We included patient reports/series of serious adverse events that developed over several years of treatment. These reports indicate a need for more comprehensive

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monitoring in order to allow early detection of possible serious adverse events.

Additionally, most study authors call for increased screening before commencing methylphenidate treatment. Examples of such procedures could be obtaining an ECG or an extensive family history of somatic and psychiatric illness. These measures cannot prevent all patients from developing serious adverse events as these can still occur in apparently healthy, screened patients. We therefore highlight the 'best practice' of both thorough pre-treatment screening and continuous monitoring of the individual patient during treatment.

It is important to acknowledge the limitations of patient reports/series. Again, we must stress the fact that patient reports/series are not representative and do not necessarily reflect a cause-effect relationship. As such, we cannot generalise data based on our included patient reports/series. The quality of our included patient reports/series also varied, and they rarely followed the standards set by CARE (CAse REport) Guidelines (Gagnier 2013). This is a common issue relating to patient reporting that has repercussions in terms of their utility as a source of evidence to inform clinical practice. It is crucial to expand both the knowledge and use of reporting guidelines to enhance the quality of published patient reports/series in the future.

One of the merits of patient reports/series is their ability to stimulate the generation of hypotheses. Based on the results of this review, one could hypothesise that the unknown severity of adverse events (which is likely to be higher than is currently recognised) and their heterogeneous characteristics, needs to be weighed up against the possible benefits of methylphenidate.

It is also central to good practice that clinicians and researchers improve their formal reporting of adverse events in order to assess more accurately the extent of adverse events experienced. Such reporting, combined with more methodologically sound research, could ensure informed, clinical decision-making by health professionals, patients, and the public.

Not all clinical studies get published, leading to publication bias (Papanikolaou 2004). This is especially so in older studies with negative results for efficacy and safety (Ioannidis 1998). As methylphenidate was licensed in the 1960s, publication bias may well be significant, especially as many of the included studies were funded by pharmaceutical companies (Lundh 2017).

Potential biases in the review process

We excluded 112 studies (121 reports) because outcomes were outside the focus of this review (e.g. visual attention test, reaction time, memory skills, and functional abnormalities, see Excluded studies). This raises the issue of bias in our review process as we did not write to these authors asking whether they collected data on other outcomes. This potential bias, however, is not likely to change our conclusions.

With respect to identifying unpublished studies, we contacted relevant pharmaceutical companies, but none of them responded to our requests. The letter sent to pharmaceutical companies can be seen at Zenodo.org (see supplementary file 'Letter to pharmaceutical companies').

We excluded methylphenidate treatment groups from placebo-controlled trials because these are published in our systematic review comparing methylphenidate versus placebo or no intervention (Storebø 2015). While this was done to avoid duplicate reporting (Storebø 2015), it potentially introduces bias by reducing the amount of data available for analysis. It is noteworthy that the RR for the harms outcomes from placebo-controlled trials indicate that methylphenidate carries similar risks of serious and non-serious adverse events as placebo (Storebø 2015). We found an increased likelihood of rare and serious harms in the present study, which differs from our previous work. There are two possible explanations for this. The first is that it could be due to confounders. The second is that the average exposure to methylphenidate in these studies is longer, given that they are observational studies rather than the relatively short durations of the RCTs. It is possible that longer average exposure to methylphenidate could have given rise to this increased likelihood of rare and serious harms (or both).

We decided to combine different types of study designs in the cohort study group; classic cohort studies, treatment groups from RCTs (similar to classic cohort studies), and cross-sectional studies. The differences between these study designs have been investigated in subgroup analyses and reported separately when necessary.

We conducted systematic literature searches over a long period and continuously revised our search strategy in order to detect all possible relevant studies. We excluded many studies due to a lack of information about adverse events despite efforts to contact the authors for these data. We therefore assume that the current systematic review is the most up-to-date and comprehensive one in this area of research.

We included a few new brand names in the January 2016 search. We only searched for the new terms in the revised adverse event strategy from 2016, so there is a small risk that we might have missed a few studies.

One limitation of our review is that we were not able to assess the quality of all of the non-comparative cohort studies using ROBINS-I. We have, however, assessed all of these studies as being at critical risk of bias. Another limitation arises from the lack of some sensitivity analyses. However, we performed many subgroup analyses to investigate various possible sources of heterogeneity.

In many countries there has been a large increase in the abuse of methylphenidate. It is therefore important to warn the scientific community about possible methylphenidate abuse, especially in individuals with drug dependence (Frauger 2016). In Iceland, intravenous methylphenidate abuse is very common in patients with substance use disorder. This suggests that methylphenidate has high abuse potential (Bjarnadottir 2015). It is a limitation that we did not collect data on methylphenidate abuse in this review.

We did not identify any other potential biases in the review process.

Agreements and disagreements with other studies or reviews

In this study, we reported on a small number of serious adverse events affecting a substantial proportion of participants, which is concerning.

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Methylphenidate exposure in children and adolescents with a diagnosis of ADHD is associated with arrhythmia and potentially with myocardial infarction during periods of use. It may also be associated with psychotic disorder (Ramstad 2018).

The high proportion of withdrawals due to adverse events of unknown severity affected almost 10% of participants. This contrasts with the findings in our systematic review of 185 RCTs, in which fewer than 10% reported serious adverse events and fewer than a third reported adverse events at all (Storebø 2015). We observed many of the previously described adverse events, including abdominal pain, decreased appetite, tics, and headache in our present review. These findings are consistent with the results of our Cochrane Review investigating the short-term effects of methylphenidate use in RCTs (Storebø 2015).

We found evidence for previously reported serious adverse events, including psychosis, arrhythmia, myocardial infarction, seizures, and hypertension. The large cohort study by Hennessy 2010 reported no risk of serious adverse events, including cardiac problems. We excluded this large cohort study because it included children who were not diagnosed with ADHD. As an industry-sponsored cohort study it may well be biased (Lundh 2017). Furthermore, the median follow-up for the control group was 611 days versus only 91 days for methylphenidate users. This could increase the potential for under-reporting of adverse events in the methylphenidate group. The Shin 2016 study suggests that the relative risk of myocardial infarction and arrhythmias was increased in the early period after initiation of methylphenidate treatment. Their findings should be interpreted with caution, according to the authors themselves, due to the potential inaccuracies in coding and incompleteness of records. The outcome measures were limited to patients with diagnoses of cardiovascular adverse events, and they could have missed such outcomes where cardiovascular events were present but not diagnosed. A great strength of this study, however, is that it included the entire South Korean population and used the national health insurance claims database for all patients with ADHD. A large cohort study including 1.8 million pregnancies found a small increase in the risk of cardiac malformations (adjusted relative risk 1.28, 95% CI 0.94 to 1.74) associated with intrauterine exposure to methylphenidate (Huybrechts 2018).

In our systematic review of RCTs, we found the proportion of participants with one or more serious adverse events to be 2.80% (95% CI 1.70% to 4.80%; 9 trials, 613 participants) in the control group, and only 1.9% (95% CI 1.10% to 3.20%; 9 trials, 919 participants) in the methylphenidate group (Storebø 2015). In the present review, we found that the proportion of serious adverse events was 1.20% (95% CI 0.70% to 2.00%; 50 studies, 162,422 participants) for non-comparative studies.

One of the excluded studies suggested an association between the use of stimulants and sudden unexplained death among children and adolescents (Gould 2009). This was a patient-control study using a control group of healthy participants, so it did not meet our inclusion criteria (see Criteria for considering studies for this review). However, it is an important study regarding sudden death among children using methylphenidate, supporting our findings regarding this risk.

To get an idea of the clinical relevance of the proportion of non-serious adverse events in the uncontrolled cohort studies, we compared the data with the methylphenidate and placebo groups in our Cochrane Review of RCTs (Storebø 2015). We also compared our results with the official SPC from Denmark (Danish Health and Medicines Authority 2017), the UK (MHRA 2017), and the USA (US Food and Drug Administration (FDA) 2017) (Table 2). It is striking that there is no information about total non-serious adverse events in any of these countries. This is worrying and comparable to the findings in our published Cochrane Review, where only a small number of the included RCTs reported on non-serious adverse events. Some would say that this is due to the fact that there are very few non-serious adverse events, but we are concerned that we simply do not know this because the data to determine it are lacking.

We included in our present review the methylphenidate-treated groups from 49 RCTs that compared methylphenidate with other ADHD medications in randomised head-to-head trials. We excluded these RCTs from our first review assessing methylphenidate versus placebo or no intervention (Storebø 2015). When one assesses the proportions of serious adverse events in the methylphenidate groups, originating from the two groups of RCTs and from the non-randomised studies, the proportions appear comparable. However, when one assesses the proportions of non-serious adverse events as well as individual non-serious adverse events in Table 2, we see an emerging picture. Either the proportions of patients with non-serious adverse events are the same or raised in the cohort studies (where investigators knew that the patient received methylphenidate) compared to the methylphenidate groups of the placebo- or no intervention-controlled RCT (where investigators were not supposed to break the blinding, but where we previously have declared that we think the blind was broken (Storebø 2015)). However, any non-serious adverse events and individual non-serious adverse events (headache; anxiety; sleep difficulties; irritability; tics; drowsiness; sadness; abdominal pain; decreased appetite; and decreased weight) were about two to three times higher in the methylphenidate-exposed group from the 49 RCTs that compared this drug versus other interventions also aimed at treating ADHD. The investigators were probably less prone to breaking the blind in the latter trials. Moreover, these proportions are likely closer to the real-life, adverse events of methylphenidate. Therefore, authors, editors, regulators, and others have not been aware of the potential harms of this drug.

In summary, we found higher proportions of adverse events during methylphenidate treatment than have been reported previously. It would be appropriate for our findings to be incorporated into treatment guidelines so as to encourage better awareness of the risk of adverse events during methylphenidate treatment. It is sometimes not possible to distinguish between an adverse event and symptoms that are part and parcel of the underlying ADHD. For example, tics or sleep difficulties are commonly found in children with ADHD, and we do not know whether there is a causative effect or a chance association when such symptoms appear during methylphenidate treatment. We are aware that for many of the proportions of adverse events we describe, there was no comparator group or other data for comparison. Another possibility is that both ADHD and methylphenidate could act as 'shared partners'; a synergistic effect on the emergence of different symptoms.

A qualitative review investigated the occurrence of harmful effects from methylphenidate use in 16 empirical studies using both

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randomised and non-randomised study designs (Aagaard 2011). Its findings, with respect to the type and share of serious adverse events and quality of included studies, were in agreement with the observations made in our present systematic review.

The clinical expert opinion of Graham and colleagues, on behalf of the Guideline Group for the European Network for Hyperkinetic Disorders (EUNETHYDIS), concluded that, "some of the effects examined appeared to be minimal in impact or difficult to distinguish from risk to untreated populations", whilst acknowledging that "several areas require further study to allow a more precise understanding of the risks" (Graham 2011).

The research evidence, however, is at best uncertain, as the studies we found were of very low quality, and there were many dropouts for unexplained reasons. Some of these may well have occurred due to serious adverse events. We therefore believe that better-quality research evidence should be presented before such reassuring conclusions are accepted. We are also aware that conscious or unconscious bias may have arisen through pharmaceutical-industry sponsorship linked to many of these authors (Lundh 2017).

AUTHORS' CONCLUSIONS

Implications for practice

Our findings suggest that methylphenidate may be associated with a number of serious adverse events. In addition, a large number of non-serious adverse events are reported in children and adolescents, often leading to withdrawal of treatment. Although our results suggest adverse events may be more common than previously reported, included studies were of very low quality. Therefore, we cannot be confident that the size of the effects are significantly higher compared with other treatments. Given the high rates of reported adverse events, clinicians need to carefully balance the potential risks to the potential benefits for each individual patient when considering methylphenidate for the treatment of ADHD.

In view of the possible relationship between adverse events and discontinuation of treatment, it may be necessary to record the presence or absence of sleep difficulties, appetite suppression, cardiovascular problems, psychosis and tics prior to commencement of medication, with active monitoring after medication has been prescribed. Recording family history of neuro-developmental disorders and other physical health problems may also help to inform decisions to commence and persist with treatment.

Adverse events reported in observational studies do not seem to depend on dose or duration of methylphenidate treatment, comorbidity, age of participants, or use of cointerventions. It remains unclear how medications used just prior to methylphenidate intervention may influence the development of adverse events.

Studies funded by pharmaceutical companies reported a much lower proportion of both serious and non-serious adverse events, confirming previous studies and systematic reviews on industry bias.

Implications for research

Methyphenidiate may be associated with a number of serious adverse events as well as a large number of other adverse events in children and adolescents with ADHD. The increasing use of methylphenidate in childhood and adolescence, often continuing into adulthood, also supports the need for more certainty about the true amount of serious adverse events (Bachmann 2017). In order to investigate this, we need to undertake large-scale, high-quality RCTs along with studies aimed at identifying responders and non-responders.

Better designed non-randomised studies are needed to assess possible rare and unexpected adverse events occurring from methylphenidate use in the paediatric population.

Future observational studies must include a comparator group of untreated participants more often; otherwise it will not be possible to distinguish between harms related to the drug studied and harms related to the patients' disease.

The study duration ranged from 1 day to 11 years, yet most included studies were less than six months. Therefore, we need to conduct large, long-term observational studies to be able to detect adverse events across paediatric populations and differences in prescribing practice and patterns. The ICH Guideline (E17) on the general principles for planning and design of multi-regional clinical trials should be consulted when planning new studies in this field.

Future studies should publish depersonalised, individual participant data and report all outcomes, including adverse events (Skoog 2015). This will enable researchers conducting systematic reviews to assess differences between intervention effects according to sex, age, type of AHDH, presence of comorbidities, and use of comedications (especially antipsychotics and antidepressants). Future studies should also screen for potential adverse events. Such screening has been recently shown to increase the reporting of adverse events in adolescents on antipsychotic medication from about 50% to 100% (Pagsberg 2017).

Adverse events should be monitored through the use of structured tools in order to ensure consistency of practice amongst clinicians.

Systematic analyses of adverse events reported to national databases are also necessary, as these databases constitute an underestimated source of important data, particularly information about serious and unexpected reactions from medicine use (Aagaard 2010a; Aagaard 2010b).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abali 2007

Methods	A patient report of hallucinations during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 14 years old IQ: 99 Sex: female Methylphenidate naïve: not stated Ethnicity: not stated Country: Turkey Comorbidity: depression, behavioural disorder Comedication: fluoxetine (20 mg/day) Sociodemographics: not stated
Interventions	Methylphenidate dosage: 20 mg/day Administration schedule: 10 mg in the morning and 10 mg in the afternoon Duration of treatment: 15 days Treatment compliance: not stated
Outcomes	Serious adverse events: Methylphenidate for 15 days: audio-visual hallucinations. Occurrence 30 minutes after ingestion. Duration: 30 minutes Cessation of methylphenidate: no hallucinations

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Abali 2007 *(Continued)*

	Further trials with methylphenidate caused hallucinations, which immediately disappeared after discontinuation
Notes	*Key conclusions of the study authors*: here, we report a 14-year old girl with a diagnosis of ADHD, major depression and conduct disorder. During her treatment with methylphenidate 20 mg/day and fluoxetine 20 mg/day, she developed visual and auditory hallucinations. It may be concluded that methylphenidate in some cases may cause hallucinations in patients *Supplemental information* regarding IQ received through personal email correspondence with the authors in November 2013 (Abali 2013 [pers comm])

Abbas 2006

Methods	A cohort study with 2 study samples (N = 60 and N = 30) where participants were part of a 6-month audit regarding the use of methylphenidate and to determine if the NICE guidelines were followed
Participants	Number of participants screened: 420 Number of participants included: 90 Number of participants followed up: not stated Number of withdrawals: not stated Sex: 85 males, 5 females Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 10 years old IQ: none with intellectual disability Methylphenidate-naïve: not stated Ethnicity: not stated Country: UK Setting: not stated Comorbidity: 28.8% general learning difficulties, 21% sleeping problems, 28.8% mental health problems Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. Children with a diagnosis of ADHD according to DSM-IV who were prescribed MP after October 2000
Interventions	Methylphenidate dosage: most were treated with Ritalin Administration schedule: not stated Duration of intervention: 6 months Treatment compliance: not stated
Outcomes	Non-serious adverse events: 12% reported side effects on methylphenidate, most were transient

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Abbas 2006 *(Continued)*

	In 3 cases, medication was stopped due to side effects
Notes	Sample calculation: not stated Any withdrawals due to adverse events: for 3 patients the side effects resulted in medication stop. 2 patients stopped because of headaches and 1 because of hair loss Ethics approval: not stated Funding: none Vested interest/authors' affiliations: not stated *Key conclusions of the study authors*: the guidelines were followed, but not fully. However this was improved significantly in the second part due to increased professional awareness about ADHD because we held many seminars on this subject. The mental health team worked more closely than before with community paediatricians via joint ADHD clinics with child and adolescent psychiatrists. Families were getting better support via the ADHD family project which was jointly funded by health, education, and social services. The audits lead to a better provision of services for children with ADHD via specialist ADHD clinics *Comments from the review authors*: the reference was a poster, and no full text article has been published on the subject *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* regarding study information received through personal email correspondence with the authors in December 2013 (DeSoysa 2013 [pers comm])

Abbasi 2011

Methods	A 6-week, parallel group, RCT with 2 arms 1. Methylphenidate plus Acetyl-L-carnitine (ALC) 2. Methylphenidate plus placebo
Participants	Number of participants screened: 68 Number of participants included: 40 Number of participants randomised: ALC + MPH: 20, P + MPH: 20 Number of participants followed-up: MPH + P: 19 Number of withdrawals: MPH + P: 1 **Methylphenidate + placebo** Diagnosis of ADHD: DSM-IV-TR (combined type: 100%) Age: mean 8.36 (1.53), range: 7-13 years old Sex: 25 males, 5 females Methylphenidate-naïve: 100% Ethnicity: Persian Country: Iran Comorbidity: not stated

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Abbasi 2011 *(Continued)*

	Comedication: not stated IQ: > 70 Sociodemographics: not stated *Inclusion criteria*: 1. DSM-IV-TR diagnostic criteria for ADHD 2. Total and/or subscale scores on Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version being ≥ 1.5 SD above norms for patient's age and gender 3. Parents and children had to be willing to comply with all requirements of the study *Exclusion criteria*: 1. A history or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders (DSM-IV axis I) 2. Any current psychiatric comorbidity that required pharmacotherapy 3. Any evidence of suicide risk 4. Any evidence of mental retardation (IQ < 70) 5. A clinically significant chronic medical condition, including organic brain disorder, seizures or current abuse or dependence on drugs in the last 6 months 6. Hypertension or hypotension
Interventions	Participants were randomly assigned to MPH and ACL or MPH and placebo Methylphenidate type: not stated Methylphenidate dosage: 20-30 mg/day depending on weight (20 mg/day for < 30 kg and 30 mg/day for > 30 kg) Administration schedule: morning and midday Duration of intervention: 6 weeks Titration period: 3 weeks after randomisation Treatment compliance: not stated
Outcomes	Non-serious adverse events: 1. Side effect checklist administered by a child psychiatrist on days 7, 21 and 42 2. Haematology tests, baseline and weeks 2, 4 and 6 3. Serum chemistry, urinalysis, 12-lead ECG, and physical examinations at baseline and week 6 4. Body weight and vital signs, baseline and weeks 1, 2, 4, and 6
Notes	Sample calculation: yes Any withdrawals due to adverse events: no Ethics approval: yes Funding: this study was supported by a grant from Tehran University of Medical Sciences *Key conclusions of the study authors:* the principal measure of outcome was the Teacher and Parent attention deficit/hyperactivity disorder Rating Scale- IV. No difference was observed between the 2 groups. Side effects consisting of headache and irritability were observed more frequently in the methylphenidate plus placebo group. The results of this study do not support the application of ALC as an adjunctive therapy to methylphenidate in children and adolescents with ADHD. *Comments from the review authors:* patients are randomised to receive MPH plus acetyl-L-carnitine (ALC) or MPH plus placebo: no outcome measures regarding effect are relevant, because the study does

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Abbasi 2011 *(Continued)*

	not include a placebo or no-intervention group. The co-intervention (ALC/placebo) is not the same in the 2 groups, and therefore we can only use AE data regarding group 2 (MPH+P group). *Supplemental data* has not been possible to receive from the authors through email correspondence in August and October 2013. No reply

Adrian 2001

Methods	A patient report of a 10-year-old boy referred to a tertiary neurodevelopmental assessment clinic for a second opinion on the management of his ADHD, with particular concern being expressed about aggressive outbursts and poor tolerance of methylphenidate
Participants	Diagnosis of ADHD: ICD-10 (subtype: unknown) Age: 10 years old IQ: average intelligence Sex: male Methylphenidate naïve: not stated Ethnicity: not stated Country: UK Comorbidity: not stated Comedication: not stated Sociodemographics: Uneventful pregnancy
Interventions	Methylphenidate type: not stated Methylphenidate dosage: started 20 mg/day at 7 years and gradually increased to 40 mg/day Duration of treatment: 2-3 years Treatment compliance: treatment was administered until 9 to 10 years of age when parents discontinued treatment due to obsessive compulsive symptoms
Outcomes	Non-serious adverse events: 1. Tics (both motor and vocal). Started at 40 mg/daily and subsided spontaneously after a year of treatment 2. Obsessive compulsive symptoms (predominantly about symmetry) started about 6 months after tics and lasted 2.5 years and resolved at age 10 3. Sudden and severe aggressive and violent outbursts. The explosive outbursts paralleled the development of preoccupation with symmetry 4. Sedation/semi-catatonia 5. Increased impulsivity The other adverse events were not found at the assessment 10 months after he stopped methylphenidate treatment
Notes	*Key conclusions of the study authors*: clinically explosive outbursts can be induced by the pharmacological treatment of ADHD and should not be mistaken for a symptom of the disorder Comments from the study authors: explosive episodes were coincident with a period of treatment with methylphenidate

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Adrian 2001 *(Continued)*

	Funding/vested interest: not stated
	Authors' affiliations: Great Ormond Street Hospital London
	Supplemental information regarding diagnostic criteria and treatment duration obtained through personal email correspondence with the authors in October 2013 (Adrian 2013 [pers comm])

Agarwal 2008

Methods	A patient report of the combination of atomoxetine and methylphenidate in the treatment of ADHD
Participants	Diagnosis of ADHD: DSM-III-R/DSM-I (subtype: combined)
	Age: 8 years old
	IQ: normal (attends school)
	Sex: male
	Methylphenidate naïve: no
	Ethnicity: not stated
	Country: India
	Comorbidity: not stated
	Comedication: not stated. No atomoxetine (in the period relevant for this review)
	Sociodemographics: not stated
Interventions	Immediate release methylphenidate gradually increased to 50 mg/day
	Administration schedule: 3-4 divided dosages
	Duration of intervention: 6 months
	Treatment compliance: not stated
Outcomes	*Non-serious adverse events*:
	Decreased appetite and delayed sleep onset
Notes	*Key conclusions of the study authors*: the combination of atomoxetine and methylphenidate may be used more often in patients who are not able to tolerate high doses of methylphenidate or develop tolerance to it

Aguilera-Albesa 2010

Methods	2 patient reports of the appearance of hallucinations few hours after methylphenidate ingestion
Participants	**Case 1**
	Diagnosis of ADHD: DSM-IV (subtype: inattentive)
	Age: 8 years old
	IQ: > 85

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Aguilera-Albesa 2010 *(Continued)*

	Sex: male Methylphenidate naïve: not stated Ethnicity: white Country: Spain Comorbidity: procedural learning disorder Comedication: not stated Sociodemographics: not stated **Case 2** Diagnosis of ADHD: DSM-IV (subtype: inattentive) Age: 6 years old IQ: > 85 Sex: female Ethnicity: white Country: Spain Comorbidity: none Comedication: none Sociodemographics: not stated
Interventions	**Case 1** Extended release methylphenidate 18 mg/day (0.51 mg/kg/day) Administration schedule: once daily Duration of intervention: 2 days Treatment compliance: not stated **Case 2** 50% extended release, and 50% immediate release methylphenidate 10 mg/day (0.45 mg/kg/day) for 3 days and 20 mg/day (0.9 mg/kg/day) for 1 day Administration schedule: once daily Duration of intervention: 4 days Treatment compliance: not stated
Outcomes	*Serious adverse events*: **Case 1** After the first dose: irritability, emotional lability, motor restlessness and facial motor tics After the second dose: added auditory hallucinations (noise and unintelligible verbal expressions), and visual hallucinations (shadows approaching and receding) 24 hours after discontinuation: the symptoms remitted **Case 2**

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Aguilera-Albesa 2010 *(Continued)*

	After the first dose and the following days: intermittent visual hallucinations (insects, especially flies, flying around her). The symptoms improved at night After increased dose (20 mg) on day 4: visual hallucinations were associated with dread of going outside and cries of panic 1 day after discontinuation: the symptoms remitted
Notes	*Key conclusions of the study authors*: these patient reports suggest an individual susceptibility to psychotic symptoms after taking methylphenidate. This side effect is considered idiosyncratic, extraordinary and unpredictable. Case 2 suggests the existence of a dose-effect relationship *Supplemental information* regarding diagnostic criteria and IQ received through personal email correspondence with the authors in July 2013 (Aguilera-Albesa 2013 [pers comm])

Akhondzadeh 2003

Methods	A 4-week randomised, double-blind, clinical trial, parallel-design where children with ADHD are randomised to methylphenidate or selegiline
Participants	Number of participants screened: not stated Number of participants included: 28 Number of participants randomised: selegiline: 14; methylphenidate: 14 Number participants followed-up in each arm: selegiline: 13; methylphenidate: 10 Number of withdrawals in each arm: selegiline: 1; methylphenidate: 4 **Methylphenidate group** Diagnosis of ADHD: DSM-IV (subtype: combined) Age: mean 7.37 years old (SD 1.59) IQ: above 70 Sex: 10 males, 4 females Methylphenidate-naïve: 100% Ethnicity: Persian Country: Iran Setting: outpatient clinic Comorbidity: not stated Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. DSM-IV 2. IQ > 70 3. Parents and children had to be willing to comply with all requirements of the study 4. Minimum score of 20 on the teacher and parent ADHD rating scale *Exclusion criteria*

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Akhondzadeh 2003 *(Continued)*

1. Previously diagnosed with a psychiatric disorder
2. Clinically significant chronic medical condition, incl. a past history of cardiovascular disease, organic brain disorder, or seizures
3. Current abuse or dependence on drugs within 6 months
4. Current treatment with psychotropic medications

Interventions	Participants were randomly assigned to receive treatment using either selegiline 5 mg/day (under 5 years of age) and 10 mg/day (over 5 years of age) or methylphenidate 1 mg/kg/day for a 4-week double-blind clinical trial Methylphenidate type: not stated Administration schedule: not stated Titration period: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: 1. Anxiety: 3 2. Decreased appetite: 5 3. Increased appetite: 0 4. Difficulty falling a sleep: 4 5. Abdominal pain: 3 6. Nausea: 2 7. Headache: 6
Notes	Sample calculation: not stated Any withdrawals due to adverse events: not stated Ethics approval: not explicitly stated but inferred: informed consent (parent and children) was received before the administration of any study procedure or dispensing of study medication in accordance with the ethical standards of the investigative site's institutional review board and with the Helsinki Declaration of 1975, as revised in 2000 Funding/vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: the results of the study must be considered preliminary, but they do suggest that selegiline may be beneficial in the treatment of ADHD. In addition, a tolerable side effect profile may be considered as one of the advantages of selegiline in the treatment of ADHD *Supplemental information* requested from the study authors twice in June 2013 with no answer

Akhondzadeh 2004

Methods	A 6-week double-blind, placebo-controlled, parallel group trial with 2 interventions: 1. Methylphenidate + zinc sulfate 2. Methylphenidate + placebo
Participants	Number of participants screened: not stated Number of participants included: 22 Number of participants followed up: 20 Number of withdrawals: 2

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Akhondzadeh 2004 *(Continued)*

	Diagnosis of ADHD: DSM-IV (subtype: combined (100%)) Age: mean: 7.73 (1.63), range: 5-11 IQ: > 70 Sex: 12 males, 10 females Methylphenidate-naïve: 100% Ethnicity: Persian Country: Iran Setting: outpatient clinic Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Exclusion criteria* 1. Previously diagnosed with a psychiatric disorder 2. Mental retardation (IQ < 70) 3. Clinically significant chronic medical condition, including a past history of cardiovascular disease, organic brain disorder, seizures, current abuse or dependence on drugs within 6 months 4. Current treatment with psychotropic medications
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 1 mg/kg/day (+ placebo: sucrose, 55 mg) Administration schedule: twice daily, 7 am and 3 pm Duration of each medication condition: 6 weeks Treatment compliance: not stated
Outcomes	Systematically recorded throughout the study and were assessed using a checklist administered by a resident of psychiatry on days 7, 14, 21, 28 and 42 *Non-serious adverse events*: 1. Anxiety: 3 2. Decreased appetite: 7 3. Difficulty falling asleep: 6 4. Abdominal pain: 4 5. Nausea: 3 6. Headache: 9 7. Metallic taste: 0
Notes	Sample calculation: not stated Any withdrawals due to adverse events: none Ethics approval: not explicitly stated but inferred: informed consent (parent and children) was received before the administration of any study procedure or dispensing of study medication in accordance with the ethical standards of the investigative site's institutional review board and with the Helsinki Declaration of 1975, as revised in 2000 Funding/vested interests/authors' affiliations: not stated

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Akhondzadeh 2004 *(Continued)*

Key conclusions from study authors: this double-blind, placebo-controlled study demonstrated that zinc as a supplementary medication might be beneficial in the treat- ment of children with ADHD. However, further investigations and different doses of zinc are required to replicate these findings in children with ADHD.

Comments from the study authors: the limitations of the present study, including lack of a full placebo group, using only a moderate dose of methylphenidate, the small number of participants, short period of follow-up and lack of plasma zinc concentration should be considered so further research in this area is needed

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no

Alpaslan 2015

Methods	A patient report of stuttering associated with the use of methylphenidate
Participants	Diagnosis of ADHD: DSM-5 (subtype: predominantly hyperactive-impulsive) Age: 7 years old IQ: 94 Sex: male Methylphenidate naïve: yes Ethnicity: white/Turkish Country: Turkey Comorbidity: none Comedication: none Sociodemographics: both parents had advanced no further than elementary school. The parents' history was unremarkable
Interventions	Short-acting methylphenidate 10 mg/daily Administration schedule: not stated Duration of treatment: 4 weeks Treatment compliance: good according to regular visits record
Outcomes	*Non-serious adverse events*: 10 days after beginning short-acting methylphenidate treatment, the client began to stutter. Treatment was stopped. 1 week later, the patient's speech was back to normal. 4 weeks later atomoxetine treatment was started with no reoccurrence of stuttering
Notes	*Key conclusions of the study authors*: evidence for stuttering associated with the use of short-acting methylphenidate is presented. Clinicians should be aware that an additional adverse effect of methylphenidate may be a beginning of a stutter Funding/vested interest: the authors received no financial support for the research and/or authorship of this article. The authors report no conflicts of interest *Supplemental information* regarding IQ, ethnicity and treatment compliance received through personal email correspondence with the authors in April 2016 (Alpaslan 2016 [pers comm])

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Altin 2013

Methods	A observational, prospective and non-interventional study of methylphenidate, atomoxetine and nootropic medication use for 12 months
Participants	Number of participants screened: not stated Number of participants included: 546 Number of participants randomised: methylphenidate: 221. Atomoxetine: 234. Nootropic medicine: 91 Number followed-up in each arm: methylphenidate: 133 (60.2%). Atomoxetine: 146 (62.4%). Nootropic med: 77 (84.6%) Number of withdrawals in each arm: methylphenidate: 52. Atomoxetine: 59. Nootropic med: 16 Diagnosis of ADHD: DSM-IV-TR (subtype: not stated) Age: mean: 9.6 (2.8) + 9.9 (2.7) + 9.4 (2.5), range: 6-17 years old IQ: not stated Sex: male: 206 (88.0%) 180 (81.4%) 70 (76.9%) Methylphenidate-naïve: not stated Ethnicity: white 129 (55.1%) + 93 (42.1%) + 91 (100.0%); Asian: 102 (43.6%) + 128 (57.9%) + 0 (0.0%); Black or African American: 2 (0.9%) + 0 (0.0%) + 0 (0.0%); other: 1 (0.4%) + 0 (0.0%) + 0 (0.0%). Country: Russian Federation, China, Taiwan, Egypt, United Arab Emirates, and Lebanon Setting: outpatient clinic Comorbidity: yes Comedication: yes Sociodemographics: not stated *Inclusion criteria*: 1. Attending school for at least the previous 4 weeks 2. Continue to attend classes for ≥ 4 weeks before summer vacation 3. Initiating or switching ADHD treatment (monotherapy with methylphenidate, atomoxetine or nootropic agent) 4. Without significant or unstable mental or general medical comorbidities 5. Not involved in a current clinical trial *Exclusion criteria*: Discontinuation of the original prescribed monotherapy
Interventions	Methylphenidate type: not stated Methylphenidate dosage: not stated Administration schedule: not stated Duration of intervention: 12 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*:

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Altin 2013 *(Continued)*

	3 patients discontinued treatment in the methylphenidate group due to headache, anxiety and depressed mood
Notes	Sample calculation: yes Ethics approval: yes Funding/vested interest: sponsored by Eli Lilly Authors' affiliations: Eli Lilly Neuroscience, Eli Lilly & Company Turkey; Eli Lilly Egypt; Eli Lilly Canada; Lilly Research Laboratories, Indianapolis; Eli Lilly and Company, Hungary; Dept. of Neurology, Neurosurgery and Medical Genetics of Pediatric Faculty, Moscow, Russian Federation; Dept of Psychological Medicine, Children's Hospital of Fudan University, Shanghai, China *Key conclusions of the study authors*: after 12 months of treatment, clinical and functional outcomes were improved in children and adolescents from non-Western countries who initiated and remained on their prescribed pharmacological monotherapy *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* requested from the study authors twice in June 2016 with no answer

Amiri 2008

Methods	A 6-week, parallel group, randomised controlled trial with 2 arms: 1. Modafinil 2. Methylphenidate
Participants	Number of patients screened: not stated Number included: 60 Number randomised to methylphenidate: 30 and (modafinil): 30 Number followed-up: MPH: 27 Number of withdrawals: MPH: 3 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (100%)) Age: mean 8.96 years old IQ: > 70 Sex: 24 males, 6 females Methylphenidate-naïve: not stated Ethnicity: Persian Country: Iran Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. Between the ages of 6-15 2. DSM-IV-TR diagnostic criteria for ADHD

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Amiri 2008 *(Continued)*

	3. Total and/or subscale scores on Attention-Deficit/Hyperactivity DisorderRating Scale IV (ADHD-RS-IV) School Version ≥ 1.5 SD above norms for patient's age and gender 4. Parents and children had to be willing to comply with all requirements of the study *Exclusion criteria*: 1. History or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders (DSM-IV axis I) 2. Any current psychiatric comorbidity that required pharmacotherapy 3. Any evidence of suicide risk or mental retardation (IQ < 70 based on clinical judgement) 4. A clinically significant chronic medical condition, including organic brain disorder, seizures and, current abuse or dependence on drugs within 6 months 5. Hypertension, hypotension and habitual consumption of more than 250 mg/day of caffeine
Interventions	Participants were randomly assigned to methylphenidate or modafinil Metylphenidate type: not stated Methylphenidate dosage: 20-30 mg/day depending on weight (20 mg/day for < 30 kg and 30 mg/day for > 30 kg) Administration schedule: not stated Duration of intervention: 6 weeks Titration period: 3 weeks, initiated after randomisation Treatment compliance: not stated
Outcomes	Side effect checklist (20 side effects) administered by a child psychiatrist on days 7, 21 and 42 Haematology tests, baseline and weeks 2, 4 and 6 serum chemistry and urinalysis, baseline and week 6 Body weight and vital signs, baseline and weeks 1, 2, 4, and 6 12-lead ECG and physical examinations, baseline and week 6 *Non-serious adverse events*: Abdominal pain, anxiety/nervousness, decreased appetite, sadness, difficulty falling asleep, weight loss, nausea, dry mouth, irritability, headaches
Notes	Sample calculation: yes Ethics approval: yes Funding/vested interest: this study was supported by a grant (grant number: 3317) from Tehran University of Medical Sciences Authors' affiliations: no affiliations to pharmaceutical companies stated *Key conclusions of the study authors*: no significant differences were observed between the 2 groups (modafinil vs methylphenidate) on the Parent and Teacher Rating Scale scores. Side effects of decreased appetite and difficulty falling asleep were observed more in the methylphenidate group. The results of this study indicate that modafinil significantly improved symptoms of ADHD and was well tolerated and it is beneficial in the treatment of children with ADHD *Comments from the study authors:* the limitations of the present study, including lack of a placebo group, using only ADHD Rating Scale for measuring outcome and the small number of participants should be considered so further research in this area is needed *Comments from the review authors*: checklist with 20 possible side effects administered, but only the 10 observed side effects are reported *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

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Amiri 2008 *(Continued)*

	Supplemental adverse event data has not been possible to receive through personal email correspondence with the authors in June-August 2013

Arabgol 2015

Methods	A 6-week double-blind clinical trial comparing methylphenidate and risperidone
Participants	Number of participants screened: 38 Number of participants included: 33 Number of participants randomised: methylphenidate: 18; risperidone: 20 Number of participants followed-up in each arm: methylphenidate: 15; risperidone: 18 Number of withdrawals in each arm: methylphenidate: 3; risperidone: 2 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (57.57%), hyperactive-impulsive (33.33%), inattentive (9.09%)) Age: mean for the methylphenidate group: 4.73 (SD 0.77) years old (range 3-6) IQ: > 70 Sex (in the methylphenidate group): 12 males, 3 females Methylphenidate-naïve: not stated, but all were with no drug history since 2 weeks ago Ethnicity: not stated Country: Iran Setting: outpatient clinic Comorbidity: not stated Comedication: none Sociodemographics: not stated *Inclusion criteria*: 1. Outpatient preschoolers 2. ADHD according to DSM-IV-TR criteria established by 2 child and adolescent psychiatrists *Exclusion criteria*: 1. Presence of any physical disease 2. Presence of mental retardation 3. Presence of any psychiatric comorbid disorders except conduct disorder and oppositional defiant disorder
Interventions	Metylphenidate was started at dose 2.5 mg/day and gradually (every week) increased based on the therapeutic response and the patient's tolerance Methylphenidate type: not stated Mean methylphenidate dosage: 12.83 (SD 0.56) mg/day Administration schedule: optimal dose was 20 mg/day in 2 divided doses Duration of intervention: 6 weeks

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Arabgol 2015 *(Continued)*

	Washout prior to study initiation: 2 weeks Treatment compliance: not stated
Outcomes	Patients were assessed by a child and adolescent psychiatrist at baseline (T0); T1, 2 weeks; T2, 4 weeks and T3, 6 weeks after the intervention started. Side effects were measured using the Methylphenidate Side Effects Form *Non-serious adverse events*: One 4.5-year old girl discontinued due to severe anorexia in the second week. One 5-year old boy discontinued because of crying and sadness in the second week. One 5-year old boy discontinued due to increased symptoms and aggression More common side effects were anorexia (55.55%), nervousness (33.33%) and disturbed sleep (27.77%)
Notes	Sample calculation: no Any withdrawals due to adverse events: 3 Ethics approval: yes, the Hospital's Institutial Review Board and Iranian Randomized Clinical Trial Funding/vested interest: none. Funded by Behavioral Sciences Research Center affiliated with Shahid Beheshti Medical University Authors' affiliations: not stated *Key conclusions of the study authors*: this double-blind, randomised and controlled study suggests risperidone is effective in alleviating total symptoms of ADHD and related co-morbid symptoms in preschoolers and that there is no statistically significant difference between the 2 groups in alleviating ADHD symptoms *Comments from the study authors*: our study assessed a relatively small sample of patients in a short-term intervention. ADHD is a generally chronic neuropsychiatric condition that may last many years, we do not know whether therapeutic effects of risperidone last for a long term or not. Also further investigations are needed to assess long-term safety when risperidone is prescribed for very young children, regarding the possibility of adverse effects on the developing brain. Also trials are needed to evaluate eventual metabolic and cardiovascular adverse effects of risperidone in very young children. We recommend further future studies to assess the therapeutic efficacy of risperidone in preschooler ADHD with different co-morbidities *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Ardic 2014

Methods	A retrospective chart review of osmotic release oral system methylphenidate and immediate release methylphenidate use for 8 weeks
Participants	Number of participants screened: not stated Number of participants included: 122 (68 in the OROS-MPH group and 54 in the IR-MPH group) Diagnosis of ADHD: DSM-IV (subtype: combined (89.00%), hyperactive-impulsive (0%), inattentive (11%)) Age: mean 9.1 (1.7), range: 7-15 years old IQ: OROS-MPH: 98.2 (SD 16.5). IR-MPH: 99.4 (SD 12.8) Sex: 98 males, 24 females (OROS-MPH: 58 males, 10 females; IR-MPH: 40 males, 14 females) Methylphenidate naïve: not stated Ethnicity: not stated Country: Turkey

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Ardic 2014 *(Continued)*

	Comorbidity: none Comedication: none Sociodemographics: not stated *Inclusion criteria*: 1. Children and adolescents admitted to the Child and Adolescent Psychiatry Department of Ege University Medical Faculty between January and June 2010 2. ADHD diagnosis according to the schedule for affective disorders and schizophrenia for school aged children (Kiddie-SADS) *Exclusion criteria*: 1. Psychotic disorder, bipolar disorder or pervasive developmental disorder 2. Mental retardation (defined as having an IQ lower than 80) 3. Not taking another medication for anxiety, depression, or other disruptive behaviour disorders
Interventions	Methylphenidate type: osmotic release oral system (OROS) and immediate release Mean methylphenidate dosage: OROS-MPH 30.8 (SD 11.5) mg/day; IR-MPH 27.5 (SD 6.1) mg/day Administration schedule: OROS-MPH once daily, IR-MPH twice daily Duration of intervention: 8 weeks Treatment compliance: not stated
Outcomes	*Serious adverse events*: No severe or life-threatening adverse effects were reported in either group *Non-serious adverse events*: ≥ 1 adverse effect in 76% of the OROS-MPH group and in 79.6% of the IR-MPH group. 88% adverse events disappeared/decreased over time. Emotional changes were more frequent in IR-MPH than OROS-MPH group (51.9% and 32.4%, respectively; P = 0.03)
Notes	Sample calculation: not stated Ethics approval: local approval was obtained from hospital administration for using the data on the Hospital Information System retrospectively Funding/vested interest/authors' affiliations: while making the study no support has been taken. Eyup Sabri Ercan is in charge in the advisory board of Lilly and Janssen-Cilag, and the other authors declare no competing financial interests *Key conclusions of the study authors*: OROS-MPH was effective and safe for Turkish children and adolescents, compared to MPH-IR *Comments from the study authors*: an important limitation of our study is our inability to assess treatment adherence in both medication groups. 88% of the adverse effects in the OROS-MPH group and 86% of those in the IR-MPH group decreased or disappeared over time *Comments from the review authors*: adverse events rating scale was created by study authors, but it seems to be very similar to Barkley rating scale. According to the Methods section, heart rate, blood pressure, and weight were measured but are not reported in the paper *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not explicitly stated, but it seems that only methylphenidate-responders were included *Supplemental information* regarding heart rate, blood pressure and weight has not been possible to receive from the authors. We have written twice in June 2016 without reply

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Arman 2013

Methods	A cohort study measuring heart rate and cardiac abnormalities at the second to fourth week of treatment with methylphenidate
Participants	Number of participants screened: not stated Number of participants included: 15 Number of participants followed-up: 15 Number of withdrawals: 0 Diagnosis of ADHD: not stated (subtype: combined (53%), inattentive (47%)) Age mean: 9.08 years (range: 7-13 years) IQ: not stated Sex: 11 males, 4 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: Turkey Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: None stated *Exclusion criteria*: 1. Participants with cardiac and neurologic diseases affecting the autonomic nervous system were excluded
Interventions	Methylphenidate dosage: 0.25-1 mg/kg/day Mean methylphenidate dosage: 0.6 mg/kg/day Administration schedule: not stated Duration of intervention: not stated, but the outcome measures were monitored from week 2 to 4 Treatment compliance: not stated
Outcomes	Serious adverse events: Cardiac rhythm abnormalities monitored by 12-lead-surface electrocardiogram and 24-hour-ambulatory Holter monitorisation *Non-serious adverse events*: Heart rate variability (HRV) monitored by 12-lead-surface electrocardiogram and 24-hour-ambulatory Holter monitorisation
Notes	Sample calculation: not stated Ethics approval: not stated

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Arman 2013 *(Continued)*

Funding/vested interest/authors' affiliations: not stated

Any withdrawals due to adverse events: not stated

Key conclusions of the study authors: our study showed a significantly increased heart rate and decreased heart rate variability due to methylphenidate treatment in children with ADHD, suggesting an increased sympathetic tonus especially at the daytime. Risk of sudden cardiac death and serious arrhythmia has not been demonstrated

Comments from the review authors: no full text available, only an abstract. No information on ADHD diagnosis so we are only able to use data on serious adverse events

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: not stated

Supplemental information requested through personal email correspondence with the authors in August 2014. They were not able to provide further information

Arnold 2004

Methods	A 7-centre US study consisting of a 6-week, open-label, dose-titration phase (Part A) and a 2-week, double-blind, randomised, parallel, placebo-controlled withdrawal study (Part B) with 2 arms: 1. Dexmethylphenidate 2. Placebo
Participants	**Part A** Number of participants screened: 116 Number of participants included: 89 Number of participants followed up: 76 Number of withdrawals: 13 Diagnosis of ADHD: DSM-IV (subtype: combined (80%)) Age: range 6-16 years old Sex: 72 males, 17 females IQ: not stated Methylphenidate-naïve: 71,9% Ethnicity: not stated Country: USA Comobidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. 6-17 years of age 2. Enrolled in school 3. DSM-IV diagnosis of ADHD any subtype 4. Within 30% of normal body weight

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Arnold 2004 *(Continued)*

	5. Able to participate for the full 8 weeks *Exclusion criteria* 1. History or evidence of cardiovascular, renal, respiratory (other than asthma/allergy), endocrine, or immune system disease 2. History of substance abuse 3. Hypersensitivity to dl-methylphenidate or other stimulants 4. Treatment with any investigational drug within 30 days of screening 5. Other significant central nervous system disorders 6. Treatment with antidepressants, neuroleptics/ antipsychotics, mood stabilisers, anticonvulsants, beta blockers, alpha2 agonists, other stimulants, thyroid medications, chronic oral steroids, or sedatives/hypnotics 7. Concurrent treatment with other psychoactive drug
Interventions	**Part A** Methylphenidate type: dexmethylphenidate Methylphenidate dosage: 2.5 to 10 mg twice daily depending on individual participants' prior medication experience Children who had received dl-MPH began with half their total daily dl-MPH dose administered as d-MPH, but not more than 20 mg/day; those who had not previously received dl-MPH started d-MPH at 2.5 mg twice daily Duration of intervention: 6 week Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Part A and B: monitoring AEs and changes from baseline in vital signs (pulse and blood pressure), physical examination, and clinical laboratory parameters throughout the study
Notes	Sample calculation: not stated Ethics approval: not stated Funding: not stated Vested interests/authors' affiliations: *Key conclusions of the study authors*: d-MPH is safe, tolerable, and effective, with a 6-hour duration of effect suggested by the significant difference from placebo at 6 hours on a double-blind discontinuation *Comments from the study authors*: limitations: study design (withdrawal): treatment effects in such trials may be larger than those seen in unselected populations, because randomised, withdrawal phase preselected responders to the drug from the open-label titration phase. Another possible limitation is the duration of the discontinuation (2 weeks) *Supplemental information* received through email correspondence with the authors in October 2013 (Arnold 2013b [pers comm]) However, authors advise us to contact the sponsoring drug company for additional information. We contacted them in November 2013 (Jones 2013 [pers comm]), but did not succeed in getting further information.

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Arnold 2010

Methods	A multisite cohort study of transdermal methylphenidate following abrupt withdrawal of extended release methylphenidate with follow-up of 4 weeks
Participants	Number of participants screened: 194 Number of participants included: 171 Number followed-up: 150 but 164 in ITT analysis Number of withdrawals: 21 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (77%), hyperactive-impulsive (2%), inattentive (21%)) Age: mean 9.4 years IQ: normal Sex: 117 males, 47 females Methylphenidate-naïve: none Ethnicity: white (79%), African American (12%), Asian (0.6%), others (9%) Country: USA Comorbidity: none Comedication: none Sociodemographics: not stated *Inclusion criteria*: 1. Children aged 6-12 years 2. Any type of ADHD (DSM-IV-TR) 3. On a stable dose of an oral extended release methylphenidate (not exceeding 54 mg/day) for ≥ 30 days and total scores of or less than 1.5 SDs from age appropriate norms on the ADHD Rating Scale-IV 4. Normal laboratory parameters, vital signs, electrocardiogram (ECG), and a body mass index (BMI) not exceeding the 90th percentile 5. Whose parent/legally authorised representative was considering a change in treatment based on efficacy, tolerability, or compliance 6. Females of childbearing potential must have a negative serum beta Human Chorionic Gonadotropin pregnancy test *Exclusion criteria*: 1. Children with a comorbid psychiatric disorder (excepting ODD), intellectual disability, concurrent illness or skin disorder that might compromise tolerability or study assessments 2. Taken clonidine, atomoxetine, antidepressants, antihypertensives, medications with CNS effects, sedatives, antipsychotics, anxiolytics, anticonvulsants, or other investigational medications within the previous 30 days 3. A recent history of suspected substance abuse or dependence disorder
Interventions	Transdermal methylphenidate following abrupt withdrawal of extended release methylphenidate Week 1: predefined dose-transition schedule based on previous daily dose of oral extended release methylphenidate Week 2 + 3: transdermal methylphenidate titration Week 4: stable dose transdermal methylphenidate

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Arnold 2010 *(Continued)*

	Mean final transdermal methylphenidate dosage: 26.63 mg/day Administration schedule: patches were applied to alternating hips once daily in the morning and were worn for up to 9 hours per day Duration of intervention: 28 days Treatment compliance: compliance with the treatment regimen was measured by patch counts weekly. Data not stated
Outcomes	Participant and/or parent reporting of adverse events, application site reactions (assessed on a scale ranging from 0 (no irritation) to 7 (strong reaction)), physical examinations, vital signs and ECGs. Adverse events were recorded throughout the study and for 30 days after the last dose of study drug *Serious adverse events*: No deaths were reported No reports of sudden death, stroke, or other serious cardiovascular events 1. One 12 year old girl experienced acute depression and suicide attempt which was considered possibly related to transdermal methylphenidate treatment, 30 mg for 16 days *Non-serious adverse events*: 1. Application site reaction 2. Other adverse event
Notes	Sample calculation: yes Ethics approval: yes Funding: Shire Development Inc, USA Vested interest/authors' affiliations: multiple authors are employees or have received research support from pharmaceutical companies, including Shire, Novartis, Ortho-McNeil Pharmaceuticals and Neuropharm *Key conclusions of the study authors*: abrupt conversion from a stable dose of oral ER-MPH to transdermal MPH was accomplished using a predefined dose-transition schedule without loss of symptom control; however, careful titration to optimal dose is recommended. Most AEs were mild to moderate and, with the exception of application site reactions, were similar to AEs typically observed with oral MPH This study demonstrates that MTS, when carefully titrated to optimal dose, may further improve child and family HRQL, as well as behavioural, medication worry, and economic impact item scores in participants switching to MTS from a stable dose of routinely prescribed oral ER-MPH after a short treatment period. Furthermore, following the abrupt conversion from oral ER-MPH to MTS, the majority of caregivers reported being highly satisfied with MTS as a treatment option for their children with ADHD. (Bukstein 2009) *Comments from the study authors*: study limitations: open-label, with no control group, non-randomised design. Relatively short duration. Spontaneous AE reporting. These results may not be generalisable to participants who are not on a stable dose of oral methylphenidate or who have a poor response *Supplemental information* regarding adverse outcome data received through personal email correspondence with the authors in September 2013 (Arnold 2013 [pers comm])

Artul 2014

Methods	A patient report of severe recurrent pancreatitis during methylphenidate treatment

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Artul 2014 *(Continued)*

Participants	Diagnosis of ADHD: DSM (version and subtype: not stated) Age: 10 years old IQ: > 70 Sex: male Ethnicity: Arabic Country: Israel Comorbidity: none Comedication: none Sociodemographics: good socioeconomic status
Interventions	Methylphenidate dosage: 30 mg daily Administration schedule: not stated Duration of treatment: 3 weeks Treatment compliance: not stated
Outcomes	*Serious adverse events*: After 3 weeks of treatment at 30 mg/daily: severe relapsing pancreatitis, 3 times in 2 months within 3 weeks after starting treatment with methylphenidate. Discontinuation: free of symptoms
Notes	*Key conclusions of the study authors*: acute pancreatitis in paediatric age could be due to the use of methylphenidate Funding/vested interests: the authors have no conflicts of interest to disclose Authors' affiliations: Department of Radiology, Nazareth Hospital, EMMS, Faculty of Medicine, Bar-Ilan University, Israel. Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel Department of Nuclear Medicine, Meir Hospital, 44410 Betah Tekva, Israel. Department of Internal Medicine, EMMS Hospital, 16100 Nazareth, Israel. Pediatric Department, Nazareth Hospital, Israel *Supplemental information* regarding IQ, ethnicity, comorbidity and comedication received through personal email correspondence with the authors in August 2016. No information regarding exact IQ level was available, but authors state that it was above 70 (Artul 2016 [pers comm])

Arun 2014

Methods	2 patient reports of suicidal ideation during methylphenidate treatment
Participants	**Case 1** Diagnosis of ADHD: DSM-IV TR (subtype: combined) Age: 8 years old IQ: > 70 Sex: male Ethnicity: Hindu Country: India

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Arun 2014 *(Continued)*

	Comorbidity: none Comedication: none Sociodemographics: living in joint family **Case 2** Diagnosis of ADHD: DSM-IV TR (subtype: combined) Age: 7 years old IQ: average Sex: male Ethnicity: Hindu Country: India Comorbidity: none Comedication: none Sociodemographics: living in nuclear family
Interventions	**Case 1** Immediate release methylphenidate dosage: 5 mg/day Administration schedule: once daily in the morning Duration of treatment: 2 days Treatment compliance: not stated **Case 2:** Methylphenidate type: not stated Methylphenidate dosage: 10 mg/day Administration schedule: once daily Duration of treatment: 12 days Treatment compliance: not stated
Outcomes	*Serious adverse events* Suicidal ideation *Non-serious adverse events* Impairment in sleep onset for 1 night
Notes	*Key conclusions of the study authors*: depressed mood or affective symptoms may occur as an adverse effect during Methylphenidate treatment, and impulsivity may result in attempted suicide even in ADHD children without depression. In view of the current findings and existing literature, clinicians need to be alert to the adverse effects of methylphenidate during examination of every case. Equally important is ensuring that the patients' parents and teachers of the patients are appropriately educated regarding potential adverse effects of methylphenidate *Comments from the study authors*: there was no depressive symptoms reported along with it, and the ideation could not be explained on the basis of impulsivity either Funding/vested interest: nil, none otherwise declared

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Arun 2014 *(Continued)*

Authors' affiliations: Department of Psychiatry, Government Medical College and Hospital, Chandigarh, India

Supplemental information received through personal email correspondence with the authors in September 2014 (Arun 2014 [pers comm])

Ashkenasi 2011

Methods	A single-centre, open-label, randomised cross-over study of transdermal methylphenidate effect on sleep disturbance, where participants were randomised to 1 of 4 groups with different sequences of patch wear time (9,10,11,12 hours a day) Phases: 1. Titration period to optimal dose 2. RCT for 4 weeks with a different sequence of patch wear time
Participants	Number of participants screened: not stated Number of participants included: 26 Number of participants followed up: 24 Number of withdrawals: 2 Diagnosis of ADHD: DSM-IV (subtype: combined (77%)) Age: mean 9.3 years, range 6-12 years old IQ: > 70 Sex: 19 males, 7 females Methylphenidate-naïve: not stated Ethnicity: not stated Comorbidity: sleep disturbances Comedication: none Sociodemographics: not stated *Inclusion criteria*: 1. Children aged 6-12 years 2. Met the DSM-IV criteria for attention deficit hyperactivity disorder (any subtype) 3. Demonstrated difficulty sleeping (as reported by the caregiver) *Exclusion criteria*: 1. Patients with previous intolerance, adverse response, or allergy to methylphenidate or skin sensitivity to the methylphenidate transdermal system 2. Severe comorbid psychiatric disorders (e.g. psychosis, bipolar illness, pervasive developmental disorders, severe obsessive compulsive disorder, severe depression, or severe anxiety disorder) or other symptomatic manifestations that would, in the opinion of the examining physician, contraindicate the use of methylphenidate or confound efficacy or safety assessments (i.e., common, less severe comorbidities of attention deficit hyperactivity disorder were permitted) 3. A history of seizure disorder, tics/Tourette syndrome, known structural cardiac abnormalities, hypertension, hyperthyroidism, glaucoma, and pregnancy/lactation

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Ashkenasi 2011 *(Continued)*

	4. Use of psychotropic medications (other than study medications) and medications that might affect sleep (e.g. antihistamines or decongestants)
Interventions	Participants were randomly assigned to different drug condition orders Methylphenidate type: methylphenidate transdermal system Mean methylphenidate dosage: 20 mg Administration schedule: once daily in the morning, switching between 9, 10, 11 and 12 hour alternating wear time across 4 consecutive weeks. Patch wear times were maintained Monday through Thursday of each week. Patients followed the standard 9-hour wear time schedule on weekends (i.e. Friday through Sunday) Duration of intervention: 4 weeks Washout before study initiation: 1 week before titration period to optimal dose. And a minimum of 12 hours between 2 consecutive days during the trial Titration period: before randomisation Treatment compliance: 1 participant discontinued because of non-compliance. No information about the others
Outcomes	*Serious adverse events*: Hallucinosis: 1 child "withdrew after completing the randomization phase because of a significant medication side effect that emerged later in the study (i.e., hallucinosis)". No hospitalisation, symptoms withdrew after medication was discontinued *Non-serious adverse events*: Skin reactions were coded on a 3-point scale, where 0 ¼ no change, 1 ¼ slight pink/pink, and 2 ¼ slight red/ red. Rated by caregivers Sleep was assessed according to a daily sleep diary, with entries for time of patch application and removal, sleep timing (e.g. bedtime, time to fall asleep, number of awakenings, time awake at night, and final wake time), and ratings of sleep quality (on a 5-point scale). Entries were recorded at baseline, after determination of the optimal patch dose, daily during wear time titration, and at endpoint. The sleep diary was documented by caregivers Monday through Sunday of every week throughout the wear time titration
Notes	Funding: investigator-sponsored grants from Shire Pharmaceuticals, Inc. and Noven Pharmaceuticals, Inc. Vested interest/authors' affiliations: Shire Pharmaceuticals, Noven Pharmaceuticals. "..these companies were not involved in the conduct of the study or the preparation of the manuscript" *Key conclusions of the study authors*: patch wear time exerted no significant effect on sleep latency or total sleep time, although a trend toward improved sleep quality was evident (P ¼ 0.059) with longer patch wear times. Sleep parameters were not adversely affected by longer methylphenidate transdermal system patch wear times *Comments from the study authors*: limitations of the study: small sample size, for instance resulting in a weaker randomisation to patch wear time sequence that was not completely effective in balancing baseline covariates *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes. Children with previous intolerance or adverse events on methylphenidate were excluded *Supplemental information* received through personal email correspondence with the authors in September 2013. Not possible to get the necessary supplemental information on non-serious adverse events (Ashkenasi 2013 [pers comm])

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Atzori 2009

Methods	A cohort study of methylphenidate use for 36 months and factors influencing compliance and persistent use
Participants	Number of participants screened:187 Number of participants included: 134 Number of participants followed up: 134 Number of withdrawals: 72 (were followed up but had stopped treatment at 36 months follow-up) Diagnosis of ADHD: DSM-IV (subtype: combined (83.6%), hyperactive-impulsive (4.5%), inattentive (11.9%)) Age: mean 9 (SD 2), range 4-16 IQ: 83 (SD 16), range 51-114; 88 (SD 19), range 54-129; 84 (SD 18), range 41-124 Sex: 122 males, 12 females Methylphenidate-naïve: none Ethnicity: not stated Country: Italy Comorbidity: 80.6% Comedication: not stated Sociodemographics: double parents: 74.6%. Urban residence: 56% *Inclusion criteria*: 1. ADHD diagnosis using DSM-IV 2. Taking ≥ 1 dose of methylphenidate between 1998-2005 *Exclusion criteria*: 1. Severe side effects after test dose 2. Lack of symptom improvement after ≥ 1 week of treatment 3. Parental decision immediately after test dose or during the first 2 weeks of treatment
Interventions	Methylphenidate type: immediate release methylphenidate Methylpenidate dosage: mean 0.42 mg/kg/per dose, range 0.3-0.5 Administration schedule: 2-3 daily doses of maximum 1 mg/kg per dose Duration of intervention: 36 months (15.5 months in those suspended for functional remission, 14.7 months in those suspended for other reasons) Treatment compliance: 14.9% non-adherent (non-adherence as taking less than 80% of medication for ≥ 8 months per year)
Outcomes	Clinician-designed questionnaire asking for the adverse events reported in the Switzerland SPC, self-reported, unclear 53 children did not start chronic treatment due to side effects
Notes	Sample calculation: none

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Atzori 2009 *(Continued)*

Ethics approval: not stated

Funding/vested interests: supported in part by Sardinian Public Health Secretariat and by the Agenzia Italiana del Farmaco

Authors' affiliations: Dr Zuddas has received research grants from Eli Lilly and Shire Laboratories and has been a speaker for Eli Lilly and Sanofi-Synthelabo and has an advisory or consulting relationship with Eli Lilly, Shire Laboratories, UCB, and Astra Zeneca

Key conclusions of the study authors: clinical outcome of ADHD treatment is heterogeneous. Specific clinical and social predictive parameters for long-term methylphenidate use and compliance can be identified. An accurate tailoring of clinical intervention to the individual child appears crucial for good outcome

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: yes

Ayaz 2014

Methods	A case-control study of methylphenidate use for 12 months
Participants	Number of participants screened: 2171 Number of participants included: 1348 Number of participants followed up: 877 (methylphenidate only: 788) Number of withdrawals: 195 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean continuing: 9.01 (SD 2.36); mean discontinuing: 9.52 (SD 2.37). Range: 6-18 years old IQ: > 70 Sex: 687 males, 132 female Methylphenidate-naïve: 100% Ethnicity: not stated Country: Turkey Comorbidity: ODD, CD, learning disorders, mood disorders, anxiety disorders, tic, elimination disorders Comedication: atomoxetine Sociodemographics: low educational level of mother: children continuing: 67.9%; children discontinuing: 73.4%, low educational level of father: children continuing: 54.3%; children discontinuing: 56.9% *Inclusion criteria* 1. ADHD medication first administered ≥ 12 months prior beginning study 2. Evaluation of efficacy and side effects *Exclusion criteria* 1. Previous ADHD treatment 2. ADHD treatment from another clinic after initiating medication 3. > 18 years old 4. Treatment discontinued by clinicians 5. Insufficient data, or evaluation scores not appropriately calculated

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Ayaz 2014 *(Continued)*

	6. Adopted, living in institutions, or not living with parents 7. Mental retardation, pervasive developmental disorders, psychosis, substance abuse/addiction, bipolar disorder
Interventions	Methylphenidate type: immediate and extended release Methylphenidate dosage: not stated Administration schedule: not stated Duration of intervention: 12 months Treatment compliance: 265 continued treatment 12 months after the initiation of the prescription
Outcomes	Since data includes atomoxetine no outcomes are usable
Notes	Sample calculation: no Any withdrawals due to adverse events: yes Ethics approval: yes Funding/vested interest/authors' affiliations: none stated *Key conclusions of the study authors*: medication persistence, in Turkish children, can be influenced by younger age, higher hyperactivity/impulsivity scores, use of long acting MPH, addition of another ADHD medication, and addition of other psychotropic medications, absence of adverse events, efficacy level perceived by the parents *Comments from the study authors*: limitations due to retrospective approach of the study, the determination of medication persistence, lack of sufficient data about the treatment efficacy and side effects after each medication was switched, and information obtained on the side effects spontaneously by parental reports. *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes, methylphenidate responders only *Supplemental information* requested from the study authors in April 2016. No answer

Balázs 2011

Methods	A cohort study of dyskinesia in children routinely using methylphenidate after a single dose of methylphenidate compared to community controls
Participants	Number of participants screened: 94 Number of participants included in the ADHD group: 37 Number of cases followed up: 34 Number of withdrawals: 3 Diagnosis of ADHD: DSM-IV (subtype: combined (67.6%), hyperactive-impulsive (10.8%), inattentive (21.6%)) Age: mean 10.8 years, range 7-17 years old IQ: normal Sex: 32 males, 5 females Methylphenidate-naïve: 0%. Median prior exposure to methylphenidate: 1074 days

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Balázs 2011 *(Continued)*

	Ethnicity: not stated Country: Hungary Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Aged 6-18 years 2. ADHD DSM-IV diagnosis (using the Mini International Neuropsychiatric Interview Kid 2.0) 3. Receiving methylphenidate 4. Recruited from a child and adolescent psychiatric hospital and outpatient clinic *Exclusion criteria*: 1. Past or present mental or neurological disorders
Interventions	Methylphenidate type: not stated Methylphenidate dose: not stated Administration schedule: single dose, the same dose which they had been prescribed for their regular treatment Duration of treatment: 1 day Treatment compliance: 3 children left the study after baseline measurements were taken
Outcomes	*Non-serious adverse events*: Dyskinesia measured before and 90-120 minutes after administration of a single dose of methylphenidate by using the Abnormal Involuntary Movement Scale (AIMS) (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe)
Notes	Sample calculation: not stated Ethics approval: yes, the study was approved by the Regional Ethics Committee Funding: none reported Vested interest/authors' affiliations: the authors report no conflict of interest *Key conclusions of the study authors:* methylphenidate-treated children with ADHD had more dyskinesia than children in the control group. Dyskinesia did not worsen after a single dose of methylphenidate Higher dyskinesia scores in the methylphenidate-treated younger age group warrant caution in the methylphenidate treatment of ADHD; however, further studies are needed to clarify the possible causal relationship between dyskinesia and methylphenidate treatment and/or age and/or the disease itself *Comments from the study authors:* we found no relationship between prior methylphenidate exposure of the children with ADHD and the total severity of dyskinesia. We believe that this lack of association is because most of our patients had been receiving long-term methylphenidate treatment before enrolment in the study. Limitations: no inclusion of treatment-naïve children with ADHD *Comments from the review authors:* none of the participants were methylphenidate-naïve, and the results from the measurements before methylphenidate administration (baseline) are therefore in fact reflecting long-term use (median prior exposure to methylphenidate: 1074 days). This needs to be taken into account when assessing the results from the measurements after methylphenidate administration in the study (short-term challenge).

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Barbaresi 2006

Methods	A study of stimulant use for ADHD in a birth cohort born between 1976 and 1982
Participants	Number of participants screened: 5718 Number of participants included: 379 Number of participants followed up: 295 using stimulants which included 251 receiving methylphenidate Number of withdrawals: 84 Diagnosis of ADHD: DSM-IV (subtype: combined (67.5% stimulants, 72.1% MPH), hyperactive-impulsive (7.4%, 4.8%), inattentive (24.6%, 21.1%)) Mean age at onset stimulant treatment: 10.4 (SD 3.6). Age at last follow-up: 17.6 years IQ: not stated Sex: 284 males, 95 females (stimulant treatment). 198 males, 53 females (MPH) Methylphenidate-naïve: not stated Ethnicity: not stated Country: USA Comorbidity: not stated Comedication: yes, 2 stimulants Sociodemographics: not stated *Inclusion criteria*: 1. ADHD symptoms 2. Positive results in ADHD questionnaires 3. Documented diagnoses of ADHD *Exclusion criteria*: 1. Diagnosis of pervasive developmental disorder 2. Severe mental retardation 3. Schizophrenia, or other psychotic disorder
Interventions	Methylphenidate type: not stated Methylphenidate dosage: the dose of each stimulant was initially converted to methylphenidate equivalent units (MEUs) and then each dose was weighted by the duration of use. 24.4 (11.1) mg/day Administration schedule: not stated Duration of intervention: 33.8 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: 63 (22.3%) of the 283 children treated with stimulants had ≥ 1 side effect Dextroamphetamine were significantly more likely to be associated with a side effect compared to methylphenidate (10.0% vs 6.1%, OR 1.8, 95% CI 1.1 to 3.0; P = 0.034)

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Barbaresi 2006 *(Continued)*

	6.1% of 717 MPH treatment episodes (i.e. period of time during which participant was treated with MPH at a specific dose) were associated with a side effect
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interest: the project was supported by research grants from the Public Health Service, National Institutes of Health and by an investigator-initiated research grant from McNeil Consumer and Specialty Pharmaceuticals Authors' affiliations: Department of Pediatric and Adolescent Medicine, Division of Developmental and Behavioral Pediatrics, Mayo Clinic College of Medicine. Department of Health Sciences Research, Division of Clinical Epidemiology, Mayo Clinic College of Medicine. Department of Psychiatry and Psychology, Mayo Clinic College of Medicine. Department of Health Sciences Research, Division of Biostatistics, Mayo Clinic College of Medicine *Key conclusions of the study authors*: clinicians made appropriate treatment decisions; there are disparities in the rates ADHD treatment for boys/girls; efficacy was comparable to clinical trials *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated

Barrickman 1995

Methods	Double-blind, cross-over study comparing methylphenidate and bupropion
Participants	Number of participants screened: not stated Number of participants included: 18 patients Number of participants followed up: 15 Number of withdrawals: 3 Diagnosis of ADHD: DSM-III-R (subtype: not stated) Age: 11.8 (SD 3.3), range 7-16 IQ: full scale WISC-R score 106 (SD 10), range 84-123 Sex: 12 males, 3 females Methylphenidate-naïve: 5 (33.33%) Ethnicity: white Country: USA Comorbidity: conduct disorder (n = 2), oppositional defiant disorder (n = 2), developmental learning disorder (n = 5) Comedication: none. Before washout methylphenidate (n = 9), methylphenidate + imipramine (n = 1) Sociodemographics: not stated *Inclusion criteria*: 1. ADHD diagnosis according to DSM-III-R 2. Aged 7-17 years *Exclusion criteria*: 1. IQ < 70

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Barrickman 1995 *(Continued)*

	2. Any other major Axis I, II or III diagnoses 3. Seizure disorders (bupropion contraindication) or history of seizures, eating disorders (predisposed to bupropion seizures), current use of an MAOI
Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders, methylphenidate or bupropion. Mean methylphenidate dosage: 31 (n = 11) mg/day (20-60 mg/day) or 0.7 (n = 0.2) mg/kg/day (0.4-1.3 mg/kg/day) Administration schedule: morning, noon, and 4 pm if needed Duration of intervention: 6 weeks Washout prior to study initiation: 14 days Medication-free period between intervention: 14 days Titration period: methylphenidate was administered in a dose of 0.4 mg/kg per day during the first week and the to the maximum effective dose during the next 2 weeks. Dosage was fixed for the final 3 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Adverse effects checklist monitored by a physician by the end of each week. Physical examination Children's Depression Inventory (CDI), rated each week by physician. Revised Children's Manifest Anxiety Scale (R-CMAS), rated each week by physician
Notes	Sample calculation: yes Ethics approval: not stated Funding: not stated Vested interest/authors' affiliations: not stated *Key conclusions of the study authors*: bupropion and methylphenidate were both effective and did not differ in their overall efficacy as treatment for ADHD. Thus, results of nearly all of the rating scales trended in favour of methylphenidate. There is a possibility that this insignificant difference might be a function of the relatively small dose of bupropion used in this study *Supplemental information* requested through personal email correspondence with the authors in June 2014. No reply

Berek 2011

Methods	A multicentre, prospective, open-label, single-arm, non-interventional study of methylphenidate use for 3 months. 5 visits: baseline, 1, 3 and 6 weeks of treatment, as well as after 3 months or upon premature termination
Participants	Number of participants screened: not stated Number of participants included: 822 Number of participants followed up: 74% completed the 12-week trial Number of withdrawals: total number of dropouts was not reported, 60 dropped out due to AEs Diagnosis of ADHD: ICD-10 (subtype: F90.0: n = 519 (63.14%). F90.1: n = 316 (38.44%). F90.8: n = 14 (1.70%). F90.9: n = 21 (2.55%). Others: n = 65 (7.91%) Age: mean 11.1, range 6-18 (6-9 years old (n = 251, 30.54%), 10-12 (n = 332, 40.39%), 13-15 (n = 197, 23.97%), 16-18 (n = 42, 5.11%))

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Berek 2011 *(Continued)*

	IQ: not stated Sex: 698 (84.91%) males, 124 (15.09%) females Methylphenidate-naïve: not stated Ethnicity: not stated Country: Germany Comorbidity: F91.X: n = 187 (22.75%). F91 incl. F91.3: n = 140 (17.03%). F41: n = 32 (3.89%). F42: n = 15 (1.82%). F1X: n = 6 (0.73%). None: n = 496 (60.34%). Other: n = 73 (8.88%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Children and adolescents aged 6-18 2. Confirmed diagnosis of ADHD (any subtype) by ICD-10 3. In whom treatment with OROS methylphenidate was medically indicated and planned by the treating physician
Interventions	Methylphenidate type: OROS methylphenidate Methylphenidate dosage: starting dose 31.53 (SD 13.52) mg/day. Min: 18, med: 36, max: 108. Final dose: 35.47 (SD 14.04) mg/day Administration schedule: once daily Duration of intervention: 84.10 (SD 29.49) days Treatment compliance: not stated
Outcomes	Blood pressure and heart rate measured at baseline and all visits (week 1, 3, 6 and 12 or last visit), weight measured at first and last visit Adverse events were coded according to WHO Adverse Reaction Terminology (WHOART) Sleep quality and appetite were assessed at each visit, using a 5-point scale with categories: very good, good, satisfactory, sufficient and insufficient
Notes	Sample calculation: not stated Ethics approval: independent ethics committee, Freiburg, Germany Funding: the study was funded by Janssen-Cilag GmbH, Neuss Germany Vested interest/authors' affiliations: KR is a consultant working for GEM, Meerbusch, Germany, who was hired by Janssen-Cilag to carry out the statistical analyses. LS and BS are employees of Janssen-Cilag; at the time the study was conducted, MG was also an employee of Janssen-Cilag. MG is currently employed by Ipsen Pharma. AL has, in the past 3 years, been a speaker for Shire and Novartis. He is not an employee or a shareholder of any of these companies and has no other financial or material support, including expert testimony, patents or royalties *Key conclusions of the study authors*: our study suggest a clinically meaningful increase in efficacy upon transitioning onto OROS methylphenidate in the treatment of children/adolescents with ADHD who had insufficient response to and/or poor tolerability with extended release methylphenidate or atomoxetine *Comments from the review authors*: the data extraction is based on Berek (2011), rather than an independent synthesis of the many articles published on this study

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Berek 2011 *(Continued)*

	Supplemental information requested through personal email correspondence with the authors in August 2014. No reply

Bereket 2005

Methods	A longitudinally study of 16 months of methylphenidate treatment in newly diagnosed and untreated children
Participants	Number of participants screened: not stated Number of participants included: 72 Number of participants followed up: 14 Number of withdrawals: 58 Diagnosis of ADHD: DSM-IV (subtypes: not stated) Age: mean 8.12 years, range 6.47-10.32 IQ: none with mental retardation Sex: 10 males, 4 females Methylphenidate-naïve: 100% Ethnicity: Turkish Country: Turkey Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. ADHD according to DSM-IV, confirmed by 2 child psychiatrists *Exclusion criteria*: 1. Prematurity 2. Low birth weight 3. Any systemic disease
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 0.75 mg/kg Administration schedule: not stated Duration of intervention: 16 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Height measured with a Harpenden stadiometer. Performed every 4 months Weight measured "with minimal clothing". Performed every 4 months

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Bereket 2005 *(Continued)*

	Height and weight measurements were transformed to SDs before the statistical analyses using normative data for Turkish children. BMI values were transformed to SDs according to data from Cole 2007
Notes	Sample calculation: no Ethics approval: approved by local ethics committee Funding: supported by a TUBITAK grant Vested interest/authors' affiliations: not stated *Key conclusions of the study authors*: prepubertal children with ADHD had normal height, weight, BMI, serum IGF-I and IGFBP-3 and thyroid functions. Methylphenidate treatment had no sustained effects on growth parameters, IGF-I and IGFBP-3 during the follow-up period of this study. However, it caused a mild decrease in total and free T4, which may warrant further monitoring *Supplemental information* received through personal email correspondence with the authors in January 2014 (Bereket 2014 [pers comm])

Bernhard 2009

Methods	A patient report of a 4-year-old boy with T-cell acute lymphoblastic leukemia and in maintenance therapy with purinethol and methotrexate experiencing a hepatotoxic reaction after onset of methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: hyperactive-impulsive) Age: 4 years and 6 months old IQ: unknown Sex: male Ethnicity: not stated Country: Germany Setting: outpatient clinic Comorbidity: T-ALL; severe damage to white matter induced by chemo- and radiotherapy Comedication: purinethol and methotrexate Sociodemographics: unknown
Interventions	Methylphenidate type: short acting Ritalin Methylphenidate dosage: 10 mg, 0.6 mg/kg Administration schedule: once daily in the morning Duration of treatment: 3 weeks titration. 6 weeks treatment in total. Treatment compliance: not stated
Outcomes	*Serious adverse events*: A hepatotoxic reaction: liver enzymes were elevated prior to therapy. Vomiting starting 5 weeks after onset of methylphenidate therapy and increased within the next 3 days. Abdominal pain increased in intensity. Liver transaminases elevated over 30 times of the normal level, CK level also increased

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Bernhard 2009 *(Continued)*

Notes	*Key conclusions of the study authors*: hepatotoxicity of methylphenidate can be considered minimal. However, methylphenidate therapy in children with prior or possible hepatic damage should be monitored clinically and by laboratory testing in short intervals *Comments from the study authors*: liver enzymes elevated prior to treatment Funding/vested interests: none Authors' affiliations: Hospital for Children and Adolescents, University of Leipzig, Leipzig, Germany

Blader 2010

Methods	A non-randomised trial with no placebo group of methylphenidate use and the factors associated with aggression that is responsive versus refractory to individualised optimisation of stimulant monotherapy
Participants	Number of participants screened: 304 Number of participants included: 68 Number of participants followed up: 65 Number of withdrawals: 3 Diagnosis of ADHD: not stated (subtype: not stated) Age: mean: 8.95, range: 6-13 years old IQ: > 70 Sex: 50 males, 15 females Methylphenidate-naïve: none Ethnicity: white: 72%, African American: 12%, Hispanic: 8%, others: 8% Country: USA Setting: outpatient clinic Comorbidity: ODD: 94%; CD: 6%; anxiety disorder: 29%; depressive disorder: 65% Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Aged between 6 and 13 2. Fulfill diagnostic criteria for ADHD 3. Fulfill criteria for ODD or CD 4. Obtain parent reported ratings of clinically significant aggression (R-MOAS) 5. Previous stimulant treatment at a minimum of methylphenidate dosage 30 mg/day or equivalent with insufficient response *Exclusion criteria* 1. Major depression, bipolar disorder, Tourette syndrome, psychotic disorders, pervasive developmental disorder, mental retardation and aggressive behaviour arising chiefly as a complication of an anxiety disorder 2. Contraindications to stimulant treatment

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Blader 2010 *(Continued)*

	3. Seizure disorders 4. Pregnancy
Interventions	Methylphenidate type: triphasic-release methylphenidate Methylphenidate dosage: 64 mg (refractory) and 52 mg (non-refractory) Administration schedule: weekly dosage adjustments from 18 mg of normally 18 mg increments to reach best tolerated dosage associated with greatest overall improvement in ADHD symptoms and aggression to a maximum dosage of 90 mg/day; once daily after waking but no later than 8.30 am Duration of intervention: average 63.26 days (SD 23.98) Treatment compliance: 3 withdrawals due to low adherence
Outcomes	*Non-serious adverse events*: Weight, observer, weekly Height, observer, weekly Blood pressure, observer, weekly Heart rate, observer, weekly Barkley Behaviour and Adverse Events Questionnaire Modified, parent, weekly A BBAEQ-M item was considered present when the parent rated it at least moderate
Notes	Sample calculation: no Ethics approval: no, approved by institutional review boards of 2 clinical sites Funding/vested interests: National Institutes of Health Grants K23MH064975 and M01RR10710, a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression and a grant for investigator-initiated research from Abbot Laboratories Authors' affiliations:*a*ll authors have received research support in the past from pharmaceutical companies and/or consulting and/or speaking fees. *Key conclusions of the study authors:* among children whose aggressive behaviour develops in the context of ADHD and of oppositional defiant disorder or conduct disorder, and who had insufficient response to previous stimulant treatment in routine clinical care, systematic, well-monitored titration of stimulant monotherapy often culminates in reduced aggression that averts the need for additional agents *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes, according to exclusion criteria no. 2

Buchmann 2007

Methods	A cohort study of methylphenidate use for 10-14 days
Participants	Number of participants screened: not stated Number of participants included: 18 Number of participants followed up: 18 Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (subtype: not stated)

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Buchmann 2007 *(Continued)*

	Age: mean: 11 years, SD: 1.91 years old IQ: > 85 Sex: 15 males, 3 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Germany Comorbidity: no psychiatric comorbidity Comedication: none Sociodemographics: not stated *Inclusion criteria*: 1. Over 7 years old 2. Diagnosis of ADHD (DSM-IV) *Exclusion criteria*: 1. Any other psychiatric disorder, including ODD, dyslexia, dyscalculia, and OCD 2. Any combinations with neurological diseases, including tic disorder/Tourette syndrome
Interventions	Methylphenidate type: extended release methylphenidate Mean methylphenidate dosage: 0.78 (SD 0.26) mg/kg/day Administration schedule: once a day in the morning Duration of intervention: 10-14 days Treatment compliance: children were inpatients for the duration of the study and received supervision when taking their medication
Outcomes	Data on adverse events were not systematically collected, so we could not use this data
Notes	Sample calculation: not stated Any withdrawals due to adverse events: not stated Ethics approval: not stated Funding/vested interest: not stated Authors' affiliations: Department of Child and Adolescence Psychiatry and Neurology University of Rostock, Rostock, Germany. *Key conclusions of the study authors*: the methylphenidate group had the short interval cortical inhibition, intracortical facilitation and long interval cortical inhibition changes restored by the medication - this was a very similar finding, compared to control group *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: all participants were methylphenidate-naïve *Supplemental information* regarding methods received through personal email correspondence with the authors in June 2014 (Buchmann 2014 [pers comm])

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Cakin-Memik 2010

Methods	A patient report of a 14-year-old male with ADHD who presented with priapism after administration of immediate-release methylphenidate. When the usage of immediate-release methylphenidate was terminated, priapism spontaneously disappeared
Participants	Diagnosis of ADHD: not stated (subtype: not stated) Age: 14 years old IQ: not stated Sex: male Ethnicity: not stated Country: Turkey Comorbidity: no Comedication: no Sociodemographics: not stated
Interventions	Immediate-release methylphenidate started at 10 mg/day and after 2 months increased to 20 mg/day Administration schedule: not stated Duration of treatment: 2 months and 3 days Treatment compliance: not stated
Outcomes	*Serious adverse events*: Priapism: up to 3-4 episodes per day lasting 40 to 45 minutes beginning 3 days after the dose was increased to 20 mg/day
Notes	Funding/vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: in the case of immediate-release methylphenidate prescription to adolescent male patients, the probability of the development of priapism should not be ignored The lack of inquiry and reporting of this side effect can lead to potentially irreversible impotence. Thus, it is important that the clinician be aware of this side effect and counsel the children/adolescents and their families about its occurrence in order to improve the adaptation of methylphenidate treatment *Comments from the study authors*: it is important to note that, as in this case, adolescent males may be too embarrassed to report this side effect particularly when they do not know it may be linked to methylphenidate

Chandler 1989

Methods	A patient report of 2 boys on methylphenidate treatment. 1 with preexisting tics that were aggravated by stimulants and 1 with stimulant induced tics
Participants	**Case 1** Diagnosis of ADHD: DSM-III (subtype: not stated) Age: 12 years old IQ: > 70

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Chandler 1989 *(Continued)*

	Sex: male Ethnicity: not stated Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: not stated **Case 2** Diagnosis of ADHD: DSM-III (subtype: not stated) Age: 9 years old IQ: > 70 Sex: male Ethnicity: not stated Country: USA Comorbidity: none Comedication: not stated Sociodemographics: not stated
Interventions	**Case 1** Methylphenidate type: not stated Methylphenidate dosage: 0.2 mg/kg Administration schedule: twice daily Duration of treatment: 1 month Treatment compliance: not stated **Case 2** Methylphenidate type: not stated Methylphenidate dosage: 0.2 mg/kg Administration schedule: twice daily Duration of intervention: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: **Case 1**: after a month, the child's mother reported motor and phonic tics again **Case 2**: he was treated first with methylphenidate, and then with nortriptyline, with both drugs he manifested severe facial grimacing and phonic tics. Apparently, the tics had only occurred in the past when the child was treated with methylphenidate
Notes	Funding/vested interests/authors affiliations: not stated

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Chandler 1989 *(Continued)*

Key conclusions of the study authors: we report 2 cases of AD/HD children, 1 with pre-existing tics that were aggravated by stimulants and 1 with stimulant induced tics. With combined stimulant/L-tryptophan treatment there was sustained improvement in AD/HD symptoms and no motor or phonic tics.

Side effects such as hypomania, hyperreflexia, and diaphoresis have been reported in patients on the combination of a monoamine oxidase inhibitor and tryptophan. By itself, L-tryptophan may be mildly sedating. In light of such a favorable side effect profile, and no evidence for adverse interaction with stimulants, and at least some rationale from preclinical research, it should be investigated further as a means of alleviating some of the harsh consequences of psychostimulant treatment in AD/HD

Supplemental information regarding diagnosis and IQ received through personal email correspondence with the authors in September 2013 (Gualtieri 2013 [pers comm])

Chazan 2011

Methods	An open clinical trial of methylphenidate use for 6 months
Participants	Number of participants screened: 189 Number of participants included: 130 Number of participants followed up: 125 Number of withdrawals: 5 Diagnosis of ADHD: DSM-IV (subtype: combined (63.1%), hyperactive-impulsive (7.7%), inattentive (23.1%)) Age: mean 9.8 (2.8) years (range 5-17) IQ: mean 92.34 (12.61) Sex: 96 males, 34 females Methylphenidate-naïve: 86.9% Ethnicity: white: 77.7% Country: Brazil Comorbidity: ODD (46.9%); CD (13.1%); any mood disorder (13.1%); any anxiety disorder (40.8%) Comedication: yes Sociodemographics: classes: A + B (55%); C + D (45%) *Inclusion criteria* 1. Age between 5 and 17 years 2. ADHD diagnosis according to DSM-IV 3. Primary indication of treatment with methylphenidate *Exclusion criteria* 1. Refusal or contraindication for methylphenidate use 2. Estimated IQ < 70
Interventions	Methylphenidate type: immediate release and extended release Mean methylphenidate dosage: 0.48 mg/kg/day (SD 0.22) Administration schedule: not stated

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Chazan 2011 *(Continued)*

	Duration of intervention: 6 months Treatment compliance: 76.4% adherence
Outcomes	Barkley side effects rating scale
Notes	Sample calculation: no Ethics approval: yes Funding: this work was supported by research grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil; Edital MCT/CNPq 02/2006-Universal, 478202/2006-7) and Hospital de Clínicas de Porto Alegre Vested interests/authors' affiliations: Prof Rohde has served as a speaker and/or consultant for Eli-Lilly, Janssen-Cilag, and Novartis for the last 3 years. Currently, his only industry-related activity is taking part in the advisory board/speakers' bureau for Eli Lilly, Novartis, and Shire (USD 10,000 per year and reflecting 5% of his gross income per year). The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Abbott, Bristol-Myers Squibb, Eli-Lilly, Janssen-Cilag, Novartis, and Shire. Prof Polanczyk has served as a speaker for Novartis. Drs Chazan, Borowski, Pianca, and Ludwig report no conflict of interest *Key conclusions of the study authors*: our results suggest that ADHD combined subtype, maternal ADHD symptoms, and social adversities are independent negative predictors of methylphenidate response in children and adolescents with ADHD. Our study provides evidence for the involvement of clinical characteristics, maternal psychopathology, and environmental stressors in the response to methylphenidate *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated

Cherland 1999

Methods	A retrospective cohort study conducted as a chart review
Participants	Number of participants screened: 192 Number of participants included: 98 Number of participants followed up: 98 Number of withdrawals: not stated Diagnosis of ADD and ADHD: DSM-III-R and DSM-IV (subtype: not stated) Age: range 4-17 IQ: not stated Sex: not stated Methylphenidate-naïve: not stated Ethnicity: not stated Country: Canada Comorbidity: not stated Comedication: 2%

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Cherland 1999 *(Continued)*

	Sociodemographics: not stated *Inclusion criteria*: 1. ADHD diagnosis of DSM-III-R ADD or DSM-IV 2. Stimulant treatment
Interventions	Methylphenidate type: not stated Methylphenidate dosage: range 5-80 mg per day Administration schedule: not stated Duration of treatment: mean 1 year and 9 months Treatment compliance: not stated
Outcomes	*Serious adverse events*: The reviewers rated whether the symptoms suggesting psychosis were side effects of the medication or part of the child's psychopathology. DSM-IV criteria for definitions for psychotic and mood-congruent psychotic symptoms were used 98 children treated with stimulant medication • 9 children developed psychotic symptoms • 3 children had amphetamine intoxication • 1 had psychotic symptoms • 3 had mood-congruent psychotic symptoms • 1 was unclassifiable because information about the event was insufficient • 11 children developed either mood-only symptoms or mood-congruent psychotic symptoms while being treated with MPH (11.7%) • 1 child with severe depression required hospitalisation
Notes	Sample calculation: no Any withdrawals due to adverse events: methylphenidate was withdrawn from all children and adolescents experiencing psychotic symptoms Ethics approval: not stated Funding/vested interests: not stated Authors' affiliations: no affiliations to pharmaceutical companies stated *Key conclusions of the study authors*: awareness of the potential for psychotic side effects from stimulant medications is important when prescribing for children. A large prospective study would be useful to predict the frequency and classification of the side effects in children *Comments from the study authors*: most of the children and adolescents improved upon withdrawal of the methylphenidate *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* regarding IQ, sex distribution, comedication and safety data were requested through personal email correspondence with the authors in February 2014. No reply

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Cho 2012

Methods	A 12 week prospective, exploratory, open-labeled cohort study to achieve symptomatic remission by OROS-methylphenidate. The purpose of the study was to investigate a possible association between norepinephrine genes and cardiovascular side effects of OROS-methylphenidate in Korean children with ADHD
Participants	Number of participants screened: not stated Number of participants included: 101 Number of participants followed up: 101 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (67.6%), hyperactive-impulsive (5.8%), inattentive (26.4%)) Age: 8.73 (SD 1.78) years, range 6-12 IQ: 102.3 (SD 11.9) Sex: 81 males, 20 females Methylphenidate-naïve: 100% Ethnicity: Asian Country: South Korea Comorbidity: anxiety disorders (8.8%), ODD (6.8%), transient tic disorder (6,8%), enuresis (5.9%) Comedication: not stated *Inclusion criteria*: 1. ADHD according to DSM-IV-TR 2. Aged 6-12 years 3. Severity of symptoms equal to or more than 'moderate degree' on the Clinical Global Impression-Severity (CGI-S) scale and severe enough to warrant medication treatment 4. The absence of any history of exposure to psychostimulants such as methylphenidate *Exclusion criteria*: 1. Other mental disorders than transient tic disorder, oppositional defiant disorder, mild anxiety disorder and enuresis 2. A past or present history of brain damage or convulsive disorder 3. Mental retardation, autism, language difficulties or developmental problems including learning disabilities
Interventions	Methylphenidate: osmotic release oral system Mean methylphenidate dosage: 0.98 (SD 0.52) mg/kg Administration schedule: not stated Duration of intervention: 12 weeks Titration: initial dosage was determined by child's body weight: if ≥ 30 kg, 27 mg was administered; if < 30 kg, 18 mg was administered. The dosages were increased every 2 weeks for 9 weeks until they were sufficient to achieve a therapeutic effect, on the basis of the investigators and parents' assessments of symptoms and side effects, and then these doses were maintained until the 12th week. Treatment compliance: not stated

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Cho 2012 *(Continued)*

Outcomes	Electrocardiographic (ECG) parameters, including QT interval. Resting heart rate, seated pulse, blood pressure. All measures collected at 12 weeks after treatment. These measurements were obtained 60-120 minutes after a dose was given. The cardiovascular parameters for all participants were measured manually
Notes	Sample calculation: yes Ethics approval: approved by the institutional review board (IRB) for human subjects at the Seoul National University Hospital and at 5 other hospitals in South Korea. Parents/guardians provided written informed consent, and the children or adolescents provided verbal assent regarding participation in this study. Funding: BN Kim was supported by a Korea Research Foundation Grant funded by the Korean Government (MOEHRD) and by the Korean Janssen Pharmaceutical Company Vested interest/authors' affiliations: Janssen Korea *Key conclusions of the study authors*: the overall cardiovascular effects of OROS-methylphenidate were modest. However, our findings show a positive association between norepinephrine-related gene polymorphisms and cardiovascular response induced by methylphenidate in Korean children with ADHD. Consideration must be given to such children or adults with specific norepinephrine-related genotypes, especially if they show significant changes in heart rate or diastolic blood pressure after OROS-methylphenidate administration *Comments from the study authors*: monitoring only occurred at baseline and after 12 weeks of methylphenidate treatment. 9% of the study participants with ADHD had co-morbid anxiety disorders which may have affected cardiovascular measures. As this study was exploratory we did not apply multiple comparison corrections for the 3 cardiovascular outcomes; future studies may strengthen and perhaps extend the current findings by applying such corrections in larger samples. According to the inclusion and exclusion criteria, no children enrolled in this study had clinical histories of hypertension, hypotension or cardiovascular disease. Therefore, no conclusions can be made about the use of methylphenidate in children with significant cardiovascular dysfunction or risk factors *Supplemental information* regarding outcome measures and protocol requested twice in January 2014 with no answer

Chou 2012a

Methods	A 10-week non-comparative observational study in 6 outpatient clinics identifying the optimal dose of OROS-methylphenidate
Participants	Number of participants screened: not stated Number of participants included: 521 Number of participants followed up: 439 Number of withdrawals: 82 Diagnosis of ADHD: DSM-IV (subtype: combined (65.6%), hyperactive-impulsive (3.1%), inattentive (31.3%)) Age: mean 10.4 years (range 7-17) IQ: normal Sex: 461 males, 60 females Methylphenidate-naïve: none Ethnicity: Asian

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Chou 2012a *(Continued)*

	Country: Taiwan Comorbidity: ODD (4.4%), anxiety disorder (0.2%), other disorders (3.5%) Comedication: clonidine (0.6%), antipsychotics (0.4%) Sociodemographics: not stated *Inclusion criteria*: 1. Age 6-19 years 2. ADHD according to DSM-IV 3. Treatment with immediate-release methylphenidate (< 70 mg/day) for ≥ 1 month, without severe adverse events or possible contraindications 4. Participant/parent written informed consent 5. Participants must be living with the parent/caregiver who can complete the questionnaires during the study 6. Participants or parent/caregivers without any psychotic disease or any mental situation which may cause the concern to properly complete the questionnaires *Exclusion criteria*: 1. Any systemic disease or clinically significant gastrointestinal problem 2. Any comorbid psychiatric disorders, except for conduct disorder and oppositional disorder 3. Known to be non-responders to methylphenidate 4. Known or suspected mental retardation or significant learning disorder 5. Glaucoma or ongoing seizure disorder
Interventions	Methylphenidate type: osmotic release oral system Methylphenidate dosage: participants receiving an immediate release methylphenidate dosage < 15 mg, 15-30 mg, and > 30 mg day were converted to 18, 36, and 54 mg once daily Administration schedule: morning Duration of intervention: 10 weeks Treatment compliance: not stated
Outcomes	Parents or caregivers completed the Chinese version of the Barkley Side Effect Scale at each visit. An adverse event was any undesirable sign, symptom, or medical condition occurring after starting the therapy and was reported by investigators. Pre-existing medical conditions/diseases were also considered adverse events if they worsened during treatment
Notes	Sample calculation: no Any withdrawals due to adverse events: not stated Ethics approval: approved by the Joint Institute Review Board, Taipei, Taiwan Funding: the study was supported by Janssen-Cilag, Taipei, Taiwan Vested interests/authors' affiliations: Janssen-Cilag. 5 authors had conducted clinical trials on behalf of Eli & Lilly Co and 1 on behalf of Janssen-Cilag. 9 were speakers and consultants for Janssen-Cila *Key conclusions of the study authors*: the findings suggest remission as a treatment goal for ADHD therapy by providing an optimal dosage of medication for children and adolescents with ADHD through using an effective and tolerable forced-titration scheme *Comments from the review authors*: data are not pertinent to our review.

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Chou 2012a *(Continued)*

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: yes

Supplemental information received through personal email correspondence with the authors in February 2014 (Chou 2014 [pers comm])

Chou 2012b

Methods	A prospective, single-arm, open-label, 8-week, multicentre cohort study of methylphenidate use for 8 weeks
Participants	Number of participants screened: not stated Number of participants included: 296 Number of participants followed up: 230 Number of withdrawals: 66 Diagnosis of ADHD: DSM-IV (subtype: combined (67.9%), hyperactive-impulsive (1%), inattentive (30.4%)) Age: mean 9.5 (SD 2.4), range 6.0-17.0 years old IQ: not stated Sex: 247 males, 49 females Methylphenidate-naïve: none Ethnicity: not stated Country: Taiwan Comorbidity: participants with serious or unstable medical illness, or who have clinically significant gastrointestinal problems, glaucoma, ongoing seizure disorders, or a psychotic disorder are excluded Comedication: participants who are taking concomitant medication that is likely to interfere with safe administration of methylphenidate are excluded. Sociodemographics: not stated *Inclusion criteria* 1. Participants who are diagnosed with ADHD according to DSM-IV 2. Participants who have been treated with immediate-release methylphenidate for ≥ 4 weeks before enrolment, but previous treatment is considered unsatisfactory due to ≥ 1 of the following reasons: lack of effectiveness, lack of tolerability or safety, lack of compliance, and/or other reasons 3. Participants who are able to comply with the study visit schedule and whose parents/caregiver and community school teacher are willing and able to complete the protocol-specified assessments 4. Participants who are still at school 5. Participants who are treated with ≥ 10 mg immediate release methylphenidate daily before enrollment *Exclusion criteria* 1. Cannot understand or follow the instructions given in the study 2. Serious or unstable medical illness 3. Clinically significant gastrointestinal problems, including narrowing of the gastrointestinal tract 4. Gaucoma, an ongoing seizure disorders, or a psychotic disorder

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Chou 2012b *(Continued)*

	5. Hypersensitive to methylphenidate 6. Any co-existing medical condition or are taking a concomitant medication that is likely to interfere with safe administration of methylphenidate
Interventions	Methylphenidate type: osmotic release oral system (OROS) Methylphenidate dosage: 18 mg, 36 mg or 54 mg. Dose was adjusted for each participant based on clinical responses and/or side effects Administration schedule: once daily Duration of intervention: 8 weeks Treatment compliance: not stated
Outcomes	Adverse events (AEs) data were reported for each visit as total data for AEs; not analysed. In addition to the AEs reported in the below table, a category of AEs titled 'Other' was reported, as no dictionary was used and events under this category were not further specified. Total no. affected by other AEs is minimum number of participants affected
Notes	Sample calculation: not stated Ethics approval: not stated Funding: sponsored by Johnson & Johnson Taiwan Ltd Vested interests/authors' affiliations: principal investigators are not employed by the organisation sponsoring the study. There is an agreement between principal investigators and the sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is less than or equal to 60 days. The sponsor cannot require changes to the communication and cannot extend the embargo *Key conclusions of the study authors*: comparing with the baseline, OROS-methylphenidate had been demonstrated that it could significantly improve participants' ADHD behavioural symptoms and their social adjustment at school and at home *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: participants hypersensitive to methylphenidate were excluded *Supplemental information* regarding IQ requested through personal email correspondence with the authors in August 2014 with no reply

Cockcroft 2009

Methods	A comparative cohort study of sleepiness in ADHD children treated with methylphenidate compared to methylphenidate-naïve
Participants	Number of patients screened: not stated Number of participants included: 30 Number included as cases: methylphenidate (n = 12), methylphenidate naïve (n = 11) Number followed up in each arm: methylphenidate: 12 and methylphenidate naïve: 11 Number of withdrawals: 7 in the medication group were excluded because they were taking another medication, or matches with unmedicated children could be not be made Diagnosis of ADHD: DSM-IV-TR (subtype: not stated)

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Cockcroft 2009 *(Continued)*

	Age range: 6.4-12.7 years old IQ: normal Sex: 16 male, 7 female Methylphenidate-naïve: 11 Ethnicity: not stated Country: South Africa Comorbidity: not stated Comedication: no Sociodemographics: not stated *Inclusion criteria*: Children in grades 1 through 6 from 3 South African Gauteng Department of Education (GDE) remedial primary schools ADHD diagnosis according to DSM-IV-TR *Exclusion criteria*: Children taking medications other than methylphenidate
Interventions	Methylphenidate type: immediate release Methylphenidate dosage: not known Administration schedule: twice daily, morning and lunchtime Duration of intervention: 1 day Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Parental questionnaire: formulated by the authors and rated at 2 time points during the day, between 1:00 pm and 3:00 pm and between 5:00 pm and 7:00 pm. Included the child's sleep habits, sleep patterns, total sleep time, sleep latency, night time arousals, daytime naps and comments regarding daytime sleepiness in the children from appropriate adults, as well as symptoms and signs of the common sleep disorders as delineated in the DSM-IV. It also included a visual analogue scale anchored at 'not at all sleepy' to 'very sleepy' on which the parents were requested to rate their children's general levels of sleepiness Wits Faces Sleepiness: a subjective, pictorial scale designed specifically for children which consists of 5 cartoon faces depicting increasing levels of sleepiness. Rated at 8:30 am and 1:00 pm
Notes	Sample calculation: not stated Ethics approval: approved by the Committee for Research on Human Subjects of the University of Witwatersrand Vested interest/funding/authors' affiliations: not stated *Key conclusions of the study authors*: in a group of children with ADHD taking methylphenidate, there was a significant increase in sleepiness a few hours after taking the medication, which may then have a significant impact on their learning. The data also imply that part of the mechanism of action of methylphenidate effects in these children may be by reduction of daytime sleepiness

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Cockcroft 2009 *(Continued)*

	Comments from the study authors: it is highly recommended that school-aged children diagnosed with ADHD be routinely screened for daytime sleepiness. *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* regarding IQ, duration of study and methylphenidate dosage received through personal email correspondence with the authors in October 2013 and January 2014 (Cockcroft 2014 [pers comm])

Cohen 1992

Methods	2 patient reports on fixed drug eruption of the scrotum due to methylphenidate treatment
Participants	Number of participants: 2 Diagnosis of ADD: DSM Age: 8 and 10 years old IQ: > 80 Sex: male Ethnicity: unknown Country: Israel Comorbidity: unknown Comedication: none Sociodemographics: unknown
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 10 mg Administration schedule: once daily Duration of intervention: case 1: 5 days. Case 2: 7 days Treatment compliance: unknown
Outcomes	*Non-serious adverse effects*: Fixed drug eruption (FXD) (a term used to describe a sharply localised dermatitis that characteristically recurs at the same site each time the offending drug is administered) **Case 1** 5 days of methylphenidate treatment: hospitalisation due to 2 days of severe swelling and redness of the scrotum. The skin eruption resolved spontaneously 4 days after methylphenidate was discontinued. 2 weeks later, 18 hour after methylphenidate retrial, the same skin eruption of the scrotum was documented. Discontinued once again, and followed by a complete resolution of the rash after 4 days **Case 2** 7 days of methylphenidate treatment: 6 hours of severe swelling and redness of the scrotum. Discontinuation of methylphenidate was followed by a complete resolution of rash after 3 days. Re-challenge with methylphenidate 2 months later was followed by the same skin eruption of the scrotum within 2 days. Complete resolution was seen after drug withdrawal

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Cohen 1992 *(Continued)*

Notes	*Key conclusions of the study authors*: fixed drug rash induced by methylphenidate is a possible but rare phenomenon. Because this drug is prescribed so often, it is important for physicians to be familiar with this phenomenon *Supplemental information* regarding ADHD diagnosis and IQ received through personal email correspondence with first author in July 2013 (Cohen 2013 [pers comm])

Coignoux 2009

Methods	A patient report of ADHD and schizophrenia during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: hyperactive-impulsive) Age: 14 years old IQ: 135 Sex: male Ethnicity: white Country: France Comorbidity: schizotypal personality disorder, infantile psychosis with schizophrenia, OD, CDD Comedication: risperidone Sociodemographics: high cultural level
Interventions	Methylphenidate type: extended release Methylphenidate dosage: 54 mg/day Administration schedule: once daily, morning Duration of treatment: 2 years Treatment compliance: not stated
Outcomes	*Serious adverse events*: Development of gestural stereotypes and verbal aggressiveness towards his parents on methylphenidate treatment. After 6 months 4 mg risperidone is introduced. He improves, gets a less vindictive attitude but there remains some ritualised obsessive, defensive behaviour. His IQ has dropped 20 points
Notes	Funding/vested interest: none Authors' affiliations: none *Key conclusions of the study authors*: this study revealed the limits of category-based approach and international classifications as they do not express clinical singularities or possible neurobiological continuums. It also seems to confirm the possible risk of emergence of a psychosis for schizotypal participants, due to pharmaceutical induction by psychostimulants (methylphenidate). This emergence could be stopped by a combined antipsychotic treatment *Comments from the study authors*: in our case, the cognitive exploration was not precise enough to conclude, but emphasize that the negative development of IQ in the patient illustrates quite well the assumption of risk of change in adolescents with a significant and sharp decline in IQ to a psychotic disorder in adulthood

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Coignoux 2009 *(Continued)*

	Comments from the review authors: the authors state that methylphenidate might have induced the psychosis - and therefore the patient report is included despite polypharmacy

Confino-Cohen 2005

Methods	A patient report of pruritic maculopapular skin rash developing during methylphenidate treatment. The rash improved with antihistamines, and re-challenge at a lower dose caused the reappearance of the rash, though less severe. Desensitisation through graded exposure of methylphenidate in incremental doses prevented further rash development
Participants	Diagnosis of ADHD: DSM-III (subtype: not stated) Age: 8 years old IQ: normal IQ Sex: female Ethnicity: Israeli Country: Israel Comorbidity: not stated Comedication: not stated Sociodemographics: not stated
Interventions	Methylphenidate type: Ritalin Methylphenidate dosage: 10 mg Administration schedule: once daily Duration of treatment: 1 week Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: After a week on 10 mg Ritalin the patient developed pruritic maculopapular skin rash over the back of her hands, which spread to face, chest, abdomen, and legs within the next 2 days. Ritalin was discontinued and antihistamine treatment was initiated, and the symptoms disappeared after a week. Re-challenge with 5 mg Ritalin was attempted. 2 days later the same itchy rash appeared on her face and chest. Ritalin was once again discontinued and the symptoms disappeared after 2 days. A desensitisation protocol was follow over 10 days with 10 mg RItalin on the 10th day. No further adverse events were noticed
Notes	Funding/vested interest: not stated Authors' affiliations: not stated *Key conclusions of the study authors*: allergy to methylphenidate is rare. Whenever feasible, an alternate drug should be used if a reaction to the drug occurs. When an alternative is not available or the offending drug is still the best available choice, desensitisation should be considered (for mild rather than life-threatening conditions/reactions) *Comments from the study authors*: from 4 months onwards, the patient had not taken medication at weekends (1-2 days) or holidays with no adverse reaction on readministration of the drug

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Confino-Cohen 2005 *(Continued)*

	Supplemental information regarding IQ and diagnostic criteria received through personal email correspondence with the authors in November 2013 (Confino-Cohen 2013 [pers comm])

Congologlu 2009

Methods	A cohort study of voice recordings before and after methylphenidate use
Participants	Number of patients screened: not stated Number included: 22 Number followed up: 22 Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (subtype: combined 100%) Age: mean 9.05 (SD 1.43) years (range 7-12) IQ: not stated Sex: 22 males Methylpenidate-naïve: none Ethnicity: Turkish Country: Turkey Comorbidity: no Comedication: none Sociodemographics: not stated *Inclusion criteria*: 1. Boys aged 7-12 years (prepubertal) 2. ≥ 1 year of methylphenidate use and drug-responsive 3. No history of specific speech and language impairments and voice-related disorders 4. No history of other psychiatric disorders (conduct disorder, any anxiety disorder, depressive disorder, learning disorder etc.) except oppositional defiant disorder 5. No mental retardation, neurological disorders, sensorimotor handicaps, and chronic medical illness (respiratory diseases etc.) *Exclusion criteria*: 1. Those who took medication other than methylphenidate before and at the time of recording were excluded 2. At the time of recording, none of the participants had cold, allergy, or flu symptoms
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 0.5 mg/kg 1 hour before recording voice sample Mean MPH dosage: not stated Duration of intervention: single voice measurement after single dose of methylphenidate Treatment compliance: not stated

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Congologlu 2009 *(Continued)*

Outcomes	*Non-serious adverse events*: Speech samples using Multi Dimensional Voice Program (MDVP) Model 5105 Version 2.3 of the Computerized Speech, developed by Kay Elemetrics Speech recordings for acoustic analysis were made from the participants in 2 sessions held before noon: no-medication baseline session and the medication session after methylphenidate administration of 0.5 mg/kg (approximately 60 minutes later) We have not used these data
Notes	Ethics approval: the study was approved by the Human Subject Review Committee at the Gülhane Military Medical Academy Funding/vested interest/authors' affiliations: not stated Any withdrawals due to adverse events: no *Key conclusions of the study authors*: this clinical trial is the only study that examined the effects of stimulant medication on vocal acoustic parameters in children with ADHD and evaluated a small sample on and off their clinical doses of methylphenidate. We suggest that methylphenidate decreases fundamental frequency in children with ADHD, but our findings should be replicated under blind drug administration and by supporting other vocal analyses *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Corrigall 1996

Methods	A patient report of euphoria induced by methylphenidate in an 11-year-old boy diagnosed with hyperkinetic disorder
Participants	Diagnosis of ADHD: ICD-10 hyperkinetic disorder Age: 11 years old IQ: no intellectual disability Sex: male Ethnicity: not stated Country: UK Comorbidity: not stated Comedication: not stated Sociodemographics: not stated
Interventions	Methylphenidate 10 mg/day for 4 weeks and then increased to 15 mg/day for 5 days Administration schedule: not stated Duration of treatment: 6 weeks Treatment compliance: abuse
Outcomes	*Non-serious adverse events*:

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Corrigall 1996 *(Continued)*

	Methylphenidate induced euphoria on 15 mg/day. Symptoms discontinued after methylphenidate was withdrawn
Notes	Ethics approval: not stated Funding/vested interests: not stated Authors' affiliations: Maudsley Hospital, London *Key conclusions of the study authors*: euphoria induced by methylphenidate can occur in young prepubertal children and this may lead to abuse of medication *Supplemental information* regarding the boys' intellectual functioning received through personal email correspondence with the authors in October 2013 (Corrigall 2013 [pers comm])

Cortese 2015

Methods	A cohort study using the Italian national ADHD registry of methylphenidate use from June 2007 to December 2012
Participants	Number of patients screened: 2411 Number included in methylphenidate group: 1426 Number followed up in methylphenidate group: 1414 Number of withdrawals in methylphenidate group: 12 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (86.0%), hyperactive-impulsive (2.5%), inattentive (11.6%)) Age: mean: 10.55 (SD: 2.75) years old (range: 6-18) IQ: not known Sex: 1247 (87.4%) males, 179 (12.6%) females Methylphenidate-naïve: not stated Ethnicity: not stated Country: Italy Comorbidity: oppositional defiant disorder (34.4%), conduct disorder (4.2%), depression (3.6%), anxiety (11.1%), learning disorder (35.9%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: Participants were children/adolescents (aged 6-18 years) included in the Italian National ADHD Registry from June 2007 to December 2012.The diagnosis of ADHD was based on DSM-IV-TR *Exclusion criteria*: Given the naturalistic design, no a priori exclusion criteria were applied
Interventions	Methylphenidate type: immediate release Methylphenidate dosage: 0.3-0.6 mg/kg/dose/day

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Cortese 2015 *(Continued)*

	Mean methylphenidate dosage: 18.3 mg/day Administration schedule: 2-3 times a day Duration of intervention: not stated Treatment compliance: not stated
Outcomes	*Serious adverse events*: Adverse events were classified as severe if their occurrence was followed by active notification by clinical centres to the Italian Medicines Agency; otherwise, they were labelled as mild. The Italian Medicines Agency requires active notification when an adverse event results in death, is life-threatening, requires hospitalisation or prolongation of existing inpatients' hospitalisation, results in persistent or significant disability or incapacity, or leads to a congenital anomaly or birth defect *Non-serious adverse events*: Data regarding adverse events are collected via a structured form, located in a restricted area of the website of the Italian ADHD registry (available upon request), which allows standardisation of the procedure across centres. Information about the following adverse events is collected via the aforementioned structured form: cardiovascular risk, hepatic toxicity, any neurological disorder, any psychiatric symptomatology, acute diseases of the skin, and any clinically relevant gastrointestinal events
Notes	Sample calculation: no Ethics approval: yes Funding/vested interest/authors' affiliations: Prof Curatolo has received honoraria from Shire for participation in Advisory Board Meetings. Drs. Cortese, Panei, Arcieri, Germinaro, Capuano, Margari, and Chiarotti declare no competing interests *Key conclusions of the study authors*: our naturalistic postmarketing phase IV pharmacovigilance observational study showed that while mild and severe adverse events were observed in children treated with methylphenidate and in those treated with atomoxetine, those who received atomoxetine were significantly more likely to experience adverse events *Comments from the study authors*; the results should be considered in light of the study limitations. This was not a randomised study, and data on adverse events were not available for all participants at follow-up visits following the baseline assessment and treatment assignment. Our study could not be informative with regard to adverse events occurring with extended-release formulations of methylphenidate or with other class of ADHD drugs. Average dose of methylphenidate were rather low for usual standards of treatment, the naturalistic design did not allow assessment of whether children were adequately titrated for either medications. Data on validity and reliability of measures across centres are not available, and the study did not include a control group of healthy participants *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* regarding IQ received through personal email correspondence with the authors in June 2016 (Panei 2016 [pers comm])

Coşkun 2008

Methods	A patient report of tactile and visual hallucinations with the combination of OROS methylphenidate and fluoxetine
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 10 years old

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Coşkun 2008 *(Continued)*

	IQ: intellectual capacity within normal range Sex: male Ethnicity: Turkish Country: Turkey Comorbidity: oppositional defiant disorder, generalised and separation anxiety disorders Comedication: fluoxetine 10 mg/day MPH-naïve: yes Sociodemographics: not stated
Interventions	OROS MPH 18 mg/day, comedication: fluoxetine, 10 mg/day OROS MPH 18 mg/day monotherapy, 2 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Tactile and visual hallucinations. Worsening of previous sleep disturbance and decreased appetite
Notes	Funding/vested interests: the authors have no conflict of interest with any commercial or other associations, and no financial ties to disclose in connection with the submitted article *Key conclusions of the study authors*: here we report a paediatric patient who developed tactile and visual hallucinations with the combination of OROS methylphenidate and fluoxetine *Comments from the study authors*: in conclusion, we think that the causative agent was the combination of both medications rather than either medication alone. However, in either situation, it is important to note that this distressing side effect may occur even in the absence of underlying psychotic or substance-related disorders, and clinicians' awareness is important in this issue, particularly in cases where polypharmacy is considered *Supplemental information* regarding ADHD diagnostic criteria, subtype of ADHD and ethnicity received through personal email correspondence with the authors in August 2013 (Coşkun 2013 [pers comm])

Coşkun 2009a

Methods	A patient report of decreased appetite during immediate-release methylphenidate treatment and maculopapular pruritic skin eruptions during OROS-methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 8 years old IQ: > 70 Sex: male Ethnicity: not stated Country: Turkey Comorbidity: EEG abnormalities Comedication: valproate, gabapentin

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Coşkun 2009a *(Continued)*

	Sociodemographics: not stated
Interventions	Immediate release methylphenidate 10-20 mg/day for 2 months Treatment compliance: reported forgetting to take his medication sometimes OROS methylphenidate 18 mg/day for 1 week and 9 days Treament compliance: not stated
Outcomes	*Non-serious adverse events*: Immediate release methylphenidate 10-20 mg/day and valproate 400 mg/day: decreased appetite, no weight decrease OROS-methylphenidate 18 mg/day and valproate 400 mg/day: maculopapular pruritic skin eruptions on the patient's neck, arms, and legs, 1 week after starting OROS methylphenidate treatment OROS-methylphenidate free period for 5 weeks: skin lesions were almost healed Re-administering of OROS-methylphenidate 18 mg/day and gabapentin 300 mg/day: same skin eruptions with same severity, 9 days after starting OROS-methylphenidate treatment again Discontinuation of medication: skin lesions abated within the next several weeks Restart of immediate release methylphenidate 10-20 mg/day and gabapentin 300 mg/day, 4 months: no skin eruptions
Notes	Funding/vested interests: the authors report no conflicts of interest or ties *Key conclusions of study authors*: the patient reported AEs with OROS MPH on 2 different occasions, but no AE with IR MPH at 2 different trials. Emergence of AE with OROS MPH and disappearance with discontinuation at both trials may suggest enough causality between AE and OROS MPH treatment *Comments from the review authors*: unclear whether the authors believe methylphenidate caused the adverse events

Coşkun 2009b

Methods	2 patient reports of sexual side effects during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: 50% combined, 50% unknown) Age: 15 and 8 years old IQ: > 70 Sex: 2 males Ethnicity: Turkish Country: Turkey Comorbidity: borderline mental capacity: 50% Comedication: unknown Sociodemographics: unknown
Interventions	**Case 1**

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Coşkun 2009b *(Continued)*

	Immediate release methylphenidate: 10-30 mg/day in a divided dosage, 1 month. Treatment compliance: low Osmotic release oral system methylphenidate: 18 mg/day, 1 month. Treatment compliance: unknown Osmotic release oral system methylphenidate: 36 mg/day, 3 weeks. Treatment compliance: unknown **Case 2** Osmotic release oral system methylphenidate: 18 mg/day, 10 days. Treatment compliance: unknown Immediate release methylphenidate: 10-20 mg/day, 3 weeks. Treatment compliance: unknown Osmotic release oral system methylphenidate: 18 mg/day. Treatment compliance: unknown
Outcomes	*Non-serious adverse events*: **Case 1** Immediate release methylphenidate, 10-30 mg/day: initial headache and nausea Osmotic release oral system methylphenidate, 18 mg/day: emotional side effects (sense of nervousness in the chest, occasional emotional numbing), multiple daily erections (unrelated to sexual stimuli, painless, without ejaculations, onset: a few hours after ingestion of methylphenidate, duration: 5-10 minutes) Medication-free period, 1 week: no erections unrelated to sexual stimuli Re-administering of osmotic release oral system methylphenidate, 36 mg/day, 3 weeks: reemerging of erections, longer duration compared with osmotic release oral system-methylphenidate 18 mg/day. Headache. Nausea. Same emotional side effects. Drug-free days: no erections Discontinuation of medication: no erections **Case 2** Osmotic release oral system methylphenidate, 18 mg/day: loss of appetite, headache, abdominal pain, sleep problems, and conjunctival injection. Headache and abdominal pain almost disappeared after 1 week. Hypersexual behaviours. Morning erections before ingestion of methylphenidate, duration: 1 hour. Weight loss: 1.5 kg within 2 months. Drug-free days: almost no hypersexual behaviour during the day and no erection the following morning Immediate release methylphenidate, 10-20 mg/day: morning erections and hypersexual behaviours decreased dramatically. Sleep and appetite problems improved mildly. No conjunctival injection (after 3 weeks). Possible withdrawal symptoms (increased irritability and hyperactivity, getting tearful easily), several hours after each dosage Osmotic release oral system methylphenidate, 18 mg/day: next-morning erections, hypersexual behaviour during the day. Drug-free days: almost no hypersexual behaviour Osmotic release oral system methylphenidate, 18 mg/day, 6:00 am: no morning erections, but still hypersexual behaviour. Sleep and appetite problems. Conjunctival injections. Sense of pins and needles in his legs after 10 days Discontinuation of osmotic release oral system methylphenidate: no morning erections or hypersexual behaviours
Notes	Funding: no financial ties or conflicts of interest *Supplemental information* was received through personal email correspondence with the authors in August 2013 (Coşkun 2013b [pers comm])

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Coşkun 2010

Methods	Cohort study of methylphenidate treatment in participants with ADHD and comorbid anxiety- or depressive disorders
Participants	Number of participants screened: not stated Number of participants included: 7 Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (subtype: combined (57%), inattentive (43%)) Age: mean 11.85 (SD 2.91), range: 8-16 years old IQ: normal Sex: 4 males, 3 females Methylphenidate-naïve: none Ethnicity: Turkish Country: Turkey Comorbidity: generalised anxiety (86%), social anxiety (86%), panic (29%), separation anxiety (29%), obsessive-compulsive (29%) and major depressive disorder (14%), special phobia (29%) and agoraphobia (14%) Comedication: SSRIs (57%) Sociodemographics: not stated *Inclusion criteria* 1. Meet criteria for diagnoses of ADHD, anxiety and/or depressive disorders based on DSM-IV
Interventions	Methylphenidate type and dosage: immediate release (15-20 mg/day), osmotic release oral system (18-54 mg/day), IR/OROS (10-18 mg) Administration schedule: not stated Duration of intervention: 4-30 months, mean 14.28 (SD 9.41) Treatment compliance: not stated
Outcomes	*Non-serious adverse events:* 1. Sleep problems: a. developed sleep problems (n = 4) b. worsening of pre-existing sleep problems (n = 2) 2. Appetite problems: a. significant decrease in appetite (n = 3) b. weight loss: same 3 patients (1 = −2 kg, 1 = −3 kg, 1 = −4 kg)
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interests: the authors reported no conflict of interest related to this article *Key conclusions of the study authors*: young participants with diagnosis of ADHD and comorbid anxiety and depressive disorders may benefit from mirtazepine addition particularly in the presence of methylphenidate- or SSRI-related sleep and/or appetite problems

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Coşkun 2010 *(Continued)*

Comments from the review authors: the adverse events reported here are from before the start of the mirtazepine treatment which means the participants are under no treatment but methylphenidate

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no

Supplemental information received through personal email correspondence with the authors in August 2013 (Coşkun 2013c [pers comm])

Coşkun 2011

Methods	A patient report of obsessive-compulsive symptoms during methylphenidate treatment
Participants	Diagnosis of ADHD: unknown (subtype: combined) Age: 10 years old IQ: normal Sex: female Ethnicity: Turkish Country: Turkey Comorbidity: subsyndromal social and generalised anxiety disorders Comedication: unknown Sociodemographics: unknown
Interventions	Osmotic release oral system methylphenidate, 18 mg/day, 1 year Treatment compliance: unknown Osmotic release oral system methylphenidate, 27 mg/day, 3 + 3 weeks Treatment compliance: unknown
Outcomes	*Non-serious adverse events*: Osmotic release oral system methylphenidate, 18 mg/day: decreased appetite and initial headache Osmotic release oral system methylphenidate, 27 mg/day: obsessive-compulsive symptoms, decreased appetite, facial grimace, nail picking/biting Discontinuation of medication: gradually disappearance of symptoms, still subsyndromal obsessive-compulsive symptoms Re-administering of osmotic release oral system methylphenidate, 27 mg/day: mild facial grimace, similar obsessive-compulsive symptoms. After 3 weeks: Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), total score = 21
Notes	*Key conclusions of the study authors*: clinicians treating children should be familiar with the emergence and management of these unusual side effects *Supplemental information* was received through personal email correspondence with the authors in August 2013 (Coşkun 2013d [pers comm])

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Davari-Ashtiani 2010

Methods	A 6-week randomised, parallel, double-blind clinical trial with 2 arms: 1. Methylphenidate 2. Buspirone
Participants	Number of participants screened: not stated Number of participants included: 34 Number of participants randomised to methylphenidate: 16 Number of participants followed up: 16 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (100%)) Age: mean 8.62, range 6-12 years old IQ: normal Sex: not stated Methylphenidate-naïve: 100% Ethnicity: not stated Country: Iran Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. ADHD diagnosis according to DSM-IV-TR 2. Score of or above 20 on the teacher and parent ADHD-Rating Scale 3. ADHD treatment-naïve *Exclusion criteria* 1. Evidence of a mental retardation or a major psychiatric problem other than oppositional defiant disorder and conduct disorder 2. Retrieving any psychotropic medication through 2 weeks before initiation treatment 3. Medical disorders that would preclude the safe use of MPH or buspirone
Interventions	Methylphenidate type: not stated Methylphenidate dosage: initiated at 0.5 mg/kg/day and adjusted to the optimal effect. Maximum dose: 60 mg/day. Range: 0.3-1 mg/kg/day Administration schedule: not stated Duration of intervention: 6 weeks Duration of titration period: not stated Treatment compliance: not stated
Outcomes	*Serious adverse events*: No serious adverse drug effects were observed during the trial

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Davari-Ashtiani 2010 *(Continued)*

	Non-serious adverse events Possible side effects were systematically recorded throughout the study and assessed using a checklist administered by a child psychiatrist on weeks 2, 4, 6 Decreased appetite (n = 11), decreased sleep (n = 7)
Notes	Sample calculation: statistical power calculated on the basis of the projected group size, a response rate of 30% and an alpha level of 0.05. Ethics approval: yes, approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Tehran, Iran). Funding/vested interests: this work was supported in part by the grant from the Behavioral Sciences Research Center of Shahid Beheshti University of Medical Sciences (Tehran, Iran) *Key conclusions of the study authors*: no significant differences were observed between the 2 protocols on the total scores of parent and teacher ADHD Rating Scale, but methylphenidate was superior to buspirone in decreasing the symptoms of inattention. The side effects of buspirone were mild and rare in comparison with methylphenidate *Comments from the study authors:m*ain limitations: small sample size, minimal dosage necessary for response and duration of treatment. The effect of buspirone on different DSM-IV subtypes of the disorder was not explored *Comments from the review authors*: the article in Farsi presents the preliminary results, and the article in English presents the final results. Therefore, the data reported in the Farsi article are not used in our review *Supplemental information* received through personal email correspondence with the study authors in January 2014 (Davari-Ashtiani 2014 [pers comm])

Delignieres 2011

Methods	A before-after study comparing 21 children with epilepsy and ADHD with 21 ADHD-only children using a short 'attentional capture test' after being given methylphenidate
Participants	Number of participants screened: not stated Number of participants included: 21 epilepsy + ADHD and 21 ADHD only Number of participants followed up: 21 in each group Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: range: 6-13 years old IQ: not stated Sex: not stated Methylphenidate-naïve: not stated Ethnicity: not stated Country: France Comorbidity: epilepsy Comedication: anti-epileptic drugs

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Delignieres 2011 *(Continued)*

	Sociodemographics: not stated *Inclusion criteria* 1. DSM-IV diagnosis of ADHD 2. Comorbid ADHD and epilepsy *Exclusion criteria* 1. Inattention explained by EEG abnormalities or antiepileptic medication
Interventions	Methylphenidate given to children in a before-after trial, comparing 2 groups and evaluated by an attentional capture paradigm Methylphenidate type: not stated Methylphenidate dosage: not stated Administration schedule: not stated Duration of intervention: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Safety issue reported in abstract
Notes	Sample calculation: not stated Any withdrawals due to adverse events: not stated Ethics approval: not stated Funding/vested interest: not stated Authors' affiliations: not stated *Key conclusions of the study authors*: methylphenidate is safe and effective in children with epilepsy and ADHD *Comments from the review authors*: the authors state that methylphenidate is safe and effective in children with epilepsy and ADHD, but this seems to be a general statement rather than a conclusion from their findings. No data are presented in the abstract to support either conclusions on the safety or on the efficacy of methylphenidate in epilepsy and/ or ADHD *Supplemental information* and full text article requested through email correspondence with the authors in June and November 2013. No reply

Dirksen 2002

Methods	A multicentre, open-label, cohort study of the effectiveness and tolerability of an extended release methylphenidate in treated and untreated children and adolescents with ADHD over 3 weeks
Participants	Number of participants screened: 332 Number of participants included: 310 Number of participants initiating treatment: 308 Number of participants followed up: 287

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Dirksen 2002 *(Continued)*

	Number of withdrawals: 23 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 11.0, range 6-17 years old IQ: > 80 Sex: 222 males (72.1%), 86 females (27.9%) Methylphenidate-naïve: 41% Ethnicity: white (82.1%), African American (10.4%), others: (7.5%) Country: USA Comorbidity: none Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Children and adolescents aged 6-17 years 2. A confirmed DSM-IV diagnosis of ADHD 3. Either untreated or currently receiving treatment with an approved methylphenidate product 4. Vital signs and laboratory assessments within the normal range 5. Blood pressure within the 90th percentile for height and gender 6. Females pre-menarchal, sexually abstinent, or using a medically acceptable form of birth control and having a negative pregnancy test *Exclusion criteria* 1. Comorbid psychiatric disorder 2. Concurrent illness 3. IQ less than 80 4. Inability to understand or follow directions 5. History of tic disorder, Tourette syndrome, seizures, glaucoma, hyperthyroidism or significant cardiovascular disease 6. Non-response to methylphenidate 7. Use of excluded medications or medications that affect blood pressure or heart rate 8. Personal or family history of substance abuse 9. Pregnancy or a significant risk of pregnancy 10. Participated in another drug study in the previous 30 days
Interventions	Methylphenidate type: extended release methylphenidate hydrochloride (Metadate CD) Methylphenidate dosage: 20-60 mg Administration schedule: once daily, in the morning before breakfast Duration of intervention: 3 weeks Treatment compliance: not stated Dosage was titrated on a weekly basis according to clinical judgement
Outcomes	Safety and tolerability were assessed by laboratory tests, vital signs and adverse events collected through spontaneous reports by parents, general questioning of the child, and investigators' observations. Assessed at 3 study visits with 7 days apart

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Dirksen 2002 *(Continued)*

	Adverse event data were collected as pre-study events (to assess the presence of pre-existing symptoms and events)
Notes	Sample calculation: not stated Ethics approval: approved by the Institutional Review Boards at each study centre Funding: Celltech Americas Inc. Vested interest/authors' affiliations: 3 of the 4 authors were employed by Celltech Americas Inc. *Key conclusions of the study authors:* methylphenidate hydrochloride is effective and well-tolerated for clinical use in ADHD *Comments from the study authors:* the absence of a placebo control group makes it difficult to determine whether there was bias in evaluating effectiveness or relatedness of adverse events *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes *Supplemental data* requested through personal email correspondence with the study authors with in March 2014. No reply

Dittmann 2014

Methods	An observational prospective cohort study of methylphenidate use for 12 months
Participants	Number of participants screened: not stated Number of participants included: 247 in stimulant group (short- or long-acting methylphenidate) Number of participants followed up: 191 Number of withdrawals: 56. Diagnosis of ADHD: ICD-10 (subtype: F90.0 (74.9%), F90.8 (0.8%), F98.8 (8.9%)). DSM-IV (subtype: combined (8.1%), inattentive (4.9%), hyperactive/impulsive (2.0%), combined and ODD (0.4%)) Age: mean: 9.3 (SD 2.4) years (range 6-16) IQ: low IQ (70-84) 19 (7.7%), normal IQ (85-114) 197 (79.8%), high IQ (115-129) 29 (11.7%), very high IQ (> 129) 2 (0.8%) Sex: 179 males, 68 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Germany Comorbidity: conduct disorder (14.6%), ODD (13%), anxiety disorder (5.7%), depression (4.9%), tic disorder/Tourette (4.1%), other (10.1%)) Comedication: 239 (96.8%) received no concomitant medication Sociodemographics: nuclear family (66.8%), 1 biological parent, 1 step-parent (13.8%), single mother (13.8%), foster parents (0.4%), adoptive parents (1.2%), single father (0.8%), supervised living arrangement (0.8%), family members other than parents (1.2%), unknown (1.2%) *Inclusion criteria* 1. Medication-naïve child and adolescent outpatients 2. Aged 6-17 years 3. A diagnosis of ADHD according to ICD-10 or DSM-IV criteria 4. Newly initiated on medication approved for the treatment of ADHD in Germany

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Dittmann 2014 *(Continued)*

Interventions	Methylphenidate type: any Mean methylphenidate dosage: 0.37 (SD 0.23) mg/kg Administration schedule: not stated Duration of intervention: 12 months Treatment compliance: 178 (74.2%) had a PCSR (Pediatric Compliance Self-Rating instrument) score ≥ 5 at every visit
Outcomes	Adverse events were analysed for patients on initial monotherapy only Adverse effects were rated at baseline, end of week 1, 2, months 1, 3, 6, 9, and 12
Notes	Sample calculation: not stated Ethics approval: the study was approved by the responsible Ethics Committee (ERBat Medical Faculty Mannheim, University of Heidelberg, Germany) Funding: research was funded by Lilly DeutschlandGmbH, Bad Homburg, Germany, and by Eli Lilly & Co., Indianapolis, USA Vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: all outcome parameters (effectiveness) considered in this open-label, non-interventional trial with respect to ADHD core symptoms, ADHD-related difficulties, and emotional expression significantly improved over time in children and adolescents with ADHD who were treated with pharmacotherapy (i.e. atomoxetine or psychostimulants) in a naturalistic setting with regard to their degree and time course, which corresponds with the well-established findings from double-blind controlled clinical trials *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Dodangi 2011

Methods	A 6 -week parallel trial with 2 arms: 1. Duloxetine 2. Methylphenidate
Participants	Number of participants screened: 34 Number of participants included: 34 Number of participants randomised to methylphenidate: not stated Number of participants followed up: 15 in the methylphenidate group Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: range 11-18 years old IQ: not stated Sex: not stated Methylphenidate-naïve: not stated Ethnicity: not stated Country: Iran

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Dodangi 2011 *(Continued)*

	Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* Not stated
Interventions	Methylphenidate type: immediate release Methylphenidate dosage: not stated Administration schedule: not stated Duration of intervention: 6 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Children Depressive Inventory (CDI) measured at the end of the trial Revised Children's Manifest Anxiety Scale (RCMAS) at the end of the trial Drug side effects evaluated each 2 weeks during the study
Notes	Sample calculation: not stated Any withdrawals due to adverse events: yes, 3 gastrointestinal symptoms and 1 mania Ethics approval: not stated Funding/vested interests: not stated *Key conclusions of the study authors*: our study showed that duloxetine may be as effective as methylphenidate in treatment of ADHD in adolescents. *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* regarding side effects received from the author in November 2013 (Dodangi 2013 [pers comm])

Dubnov-Raz 2011

Methods	A case-control study of 17 months of methylphenidate treatment using a chart review of computerised medical records
Participants	Number of participants screened: 529 Number of participants included: 275 Number included as cases: 135 (methylphenidate treated) and controls: 140 (untreated) Diagnosis of ADHD: DSM-IV-TR (subtype: not stated) Age: mean 10.4 years old, range 6-16 IQ: > 70 Sex: 200 males, 75 females

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Dubnov-Raz 2011 *(Continued)*

	Methylphenidate-naïve: cases (none), controls (100%) Ethnicity: multiethnic Country: Israel Comorbidity: none Comedication: none Sociodemographics: a variety of different family patterns and socioeconomic status among the groups. Those who were already methylphenidate treated were 7 months older, on average, than the methylphenidate-naïve patients, and they had a higher proportion of males. Weight, height, and body mass index z scores, which inherently correct for age and sex, did not differ significantly between these 2 subgroups. Rates of overweight and obesity were also comparable *Inclusion criteria* 1. 6-16 years old 2. DSM-IV-TR diagnosis of ADHD 3. Treated in the ADHD clinic of the Neuro-paediatric Unit, Hadassah Medical Center, from 1 January 2004 to 31 December 2008 *Exclusion criteria* 1. Presence of additional mental or somatic chronic health conditions (e.g. epilepsy, mental retardation, cerebral palsy, prior significant brain injury, hearing/visual impairments, pervasive developmental disorder, mental disorders) other than overweight 2. Use of dietary supplements or chronic medications (other than methylphenidate)
Interventions	Methylphenidate type: regular (n = 52), slow-release/long-acting (n = 61), or osmotic release oral system (n = 22) Baseline methylphenidate mean dose: 0.43 mg/kg (SD 0.22), range: 0.1-1.0 mg/kg (each 4.5 mg of osmotic release was regarded as 1 mg methylphenidate) Administration schedule: not stated Duration of intervention: not stated Treatment compliance: not stated
Outcomes	Height and weight measured by a certified nurse at baseline and follow-up visits Body mass index
Notes	Sample calculation: not stated Ethics approval: yes Funding/vested interests: the authors received no financial support for the research and/or authorship of this article *Key conclusions of the study authors*: physicians should be aware of the possibility of height and weight abnormalities in children with ADHD, with or without treatment *Comments from the review authors*: only the data on the methylphenidate-treated and untreated participants with ADHD are used in this review *Supplemental information* requested from the authors in July 2013, but they did not have the time to find the relevant information

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Dupuy 2008

Methods	A controlled before-after study investigating the effects of stimulants on EEG coherence in girls with ADHD
Participants	Number of participants screened: not stated Number of participants included: 9 Number of participants followed up: 9 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype: combined or Inattentive) Age: range 7-12 years old IQ: > 85 Sex: female Methylphenidate-naïve: 100% Ethnicity: not stated Country: Australia Comorbidity: none Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. ADHD according to DSM-IV 2. IQ > 85 3. Positive response to stimulant medication *Exclusion criteria*: 1. History of problematic prenatal, perinatal, or neonatal periods 2. A history of central nervous system (CNS) diseases 3. Convulsion or convulsive disorders 4. Evidence of a consciousness disorder 5. Head injury with cerebral symptoms 6. Paraxysmal headaches or tics 7. DSM-IV criteria for CD or ODD, an anxiety or depressive disorder, Asperger or Tourette syndrome
Interventions	Methylphenidate type: not stated Methylphenidate dosage: not stated Administration schedule: not stated Duration of intervention: 6 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: If participants experienced any problems with their medication, parent(s) were asked to contact their doctor, their medication was changed, and they were removed from the study; this did not occur with these participants

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Dupuy 2008 *(Continued)*

Notes	Sample calculation: not stated Any withdrawals due to adverse events: none Ethics approval: Illawarra area health/University of Wollongong Human Research Ethics Committee Funding/vested interest: not stated Authors' affiliations: Brain & Behaviour Research Institute and School of Psychology, University of Wollongong, Australia Sydney Developmental Clinic, Australia *Key conclusions of the study authors:* intrahemispheric and interhemispheric coherences in ADHD stimulant medicated girls. Girls had elevated frontal coherence across all frequency bands *Comments from the review authors*: only children who had a positive response on stimulants were included in the study. We can only use this study qualitatively and not in the analyses. Exclusion of MPH non-responders/children who have previously experienced adverse events on MPH: no

Durá-Travé 2012

Methods	A 4-year cohort study examining OROS-methylphenidate effects on growth conducted as a review of random medical records
Participants	Number of participants screened: not stated Number of participants included: 187 Number of participants followed up: 160 Number of withdrawals: 27 Diagnosis of ADHD: DSM-IV-R (subtype: combined (84.5%), inattentive (15.5%)) Age: mean at time of diagnosis: 8.14, range: 6-10 years old IQ: not stated Sex: 129 males, 58 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Spain Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. DSM-IV-R diagnosis of ADHD, inattentive or combined subtype 2. Start of OROS-methylphenidate treatment at the time of ADHD diagnosis 3. Continuous OROS-methylphenidate treatment for ≥ 48 months 4. Evaluated at the Pediatric Neurology Unit of the Navarra Hospital Complex in Pamplona, Spain, between January and December 2009 *Exclusion criteria*

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Durá-Travé 2012 *(Continued)*

	1. Methylphenidate treatment stop during school holidays or summer periods
Interventions	Methylphenidate type: sustained release, osmotic release oral system Methylphenidate dose: at baseline 0.89 mg/kg/day, gradually increased to 1.31 mg/kg/day at 48 months Administration schedule: once daily Duration of intervention: 48 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Height, weight, and BMI measured at baseline (time of ADHD diagnosis and start of methylphenidate treatment), 6, 12, 18, 24, 30, 36, 42, and 48 months. Weight and height measurements were taken with patients wearing only underwear and no shoes, precision of 100 g and 0.1 cm. The growth charts and data tables of the Centro Andrea Prader (Zaragoza, Spain, 2002) were used as standard references
Notes	Sample calculation: no Any withdrawals due to adverse events: not stated Ethics approval: the study was approved by the Ethics Committee of the Navarra Hospital Complex, Pamplona, Spain Funding: the authors received no financial support for the research, authorship, and/or publication of this article Vested interests/authors' affiliations: the authors declared no potential conflicts of interest *Key conclusions of the study authors*: at the time the participants were diagnosed with ADHD, 1 out of every 3 patients was in a deficient nutritional situation (subnutrition or malnutrition). Continued treatment with OROS-methylphenidate for 30 months had a negative influence on height and weight. However, we observed a recovery of anthropometric variables from the 30th to the 48th month of OROS-methylphenidate treatment (growth-rebound); this means that the effects of stimulant drugs, and specifically methylphenidate, on the growth curve would be a transitory condition that attenuates as time passes. *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* regarding IQ requested through personal email correspondence with the study authors with no reply

Döpfner 2011a, OBSEER

Methods	The OBSEER study (Observation of Safety and Effectiveness of Equsym XL in Routine Care). A non-interventional, non-controlled, multicentre, prospective, observational, postmarketing surveillance study
Participants	Number of participants screened: 852 Number of participants included: 822 Number of participants followed up: 777 (completed all 3 planned visits) Number of withdrawals: 45 Diagnosis of ADHD: ICD-10; F90.0 430 (55.41%), F90.1 282 (36.34%), F90.8 64 (8.25%)

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Döpfner 2011a, OBSEER *(Continued)*

	Age: mean 10.04 (SD 2.47) years (range 6-17) IQ: above 70 Sex: 663 males (81.25%), 153 females (18.75%) Methylphenidate-naïve: 30.17% Ethnicity: not stated Country: Germany Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Confirmed diagnosis of ADHD according to DSM-IV-TR (314.00 or 314.01) or ICD-10 (F90.0, F90.1 or F90.8) 2. Therapy with Equasym XL already intended by the attending physician 3. Patients had to be attending school *Exclusion criteria* 1. Contraindications according to the summary of product characteristics 2. Presence of a mental handicap
Interventions	Methylphenidate type: once-daily modified-release methylphenidate, Equasym XL (30% immediate-release- and 70% modified-release methylphenidate) Methylphenidate dosage: 10 mg - 120 mg, maximum recommended daily dose (60 mg/day) exceeded in 6 patients Administration schedule: once daily Duration of intervention: 5 days to 12 months (mean 2.26 months) Treatment compliance: not stated
Outcomes	Adverse events (AEs) were evaluated by the treating physician at each study visit, and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 11.1 and classified into AEs and serious AEs (death, life-threatening conditions, hospitalisation or prolongation of hospitalisation, persistent injury/disability, incapacity for work, medically significant conditions and congenital abnormalities/birth defects) DAYAS (The Daily Profile of ADHD Symptoms) completed by teacher and parents at each visit
Notes	Sample calculation: yes Ethics approval: no approval was needed for this study Funding/vested interests/authors' affiliations: the study was funded by UCB and the article (Döpfner 2011) is part of a supplement sponsored Shire Development Inc. *Key conclusions from study authors*: this open-label, observational, post-marketing surveillance study investigates the effectiveness and safety of Equasym XL which is a combination of 30% immediate-release MPH and 70% modified-release MPH, in the treatment of ADHD in daily clinical practice. The effectiveness of Equasym XL was rated better than prior or no therapy and generally well tolerated *Comments from study authors*: limitations on the study: open-label, no control group: therefore, physicians and parents were not blinded to the study treatment or dose

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Döpfner 2011a, OBSEER *(Continued)*

	Some of the participants were previously treated with stimulants, therefore the results from this group can only be generalised to a population in which a switch to Equasym XL is planned due to suboptimal effects of the prior medication. This was an open-label study with no control group, only data on adverse events are therefore extracted *Supplemental information* regarding data were attempted to retrieve from the authors by email. Sent twice, no answer

Döpfner 2011b

Methods	A randomised, controlled, double-blind, multicentre clinical cross-over trial with 2 modified release methylphenidate interventions: 1. Medikinet Retard 2. Concerta
Participants	Number of participants screened: 122 Number of participants included: 113 Number of participants followed up: 91 Number of withdrawals: 22 Diagnosis of ADHD: ICD-10 diagnosis of hyperkinetic disorder. 61% had a subtype corresponding to DSM-IV ADHD combined subtype Age: regarding the 113 included: mean: 10.2, range 6.0-17.11 years IQ: 99.2 (SD 9.7) Sex: 86 males, 27 females Methylphenidate-naïve: 0% Ethnicity: not stated Country: Germany Comorbidity: oppositional defiant disorder or conduct disorder (36%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Children participating in this trial were aged between 6.0 and 17.11 years 2. Body weight > 20 kg 3. Diagnosis of a Hyperkinetic Disorder according to ICD-10 was confirmed in a structured clinical interview based on a German Diagnostic Checklist for ADHD (DCL-ADHD) 4. IQ > 80 in a German version of the Culture Fair Intelligence tests (CFT1 or CFT20) 5. Attending a primary, secondary, or special school for handicapped pupils 6. Have teacher(s) who were willing to participate and fill out rating scales 7. Had to be methylphenidate responders after clinical evaluation and careful titration 8. Had to take methylphenidate ≥ twice daily or a single dose of Concerta or Medikinet retard 9. Had to have received daily doses of methylphenidate of 18-36 mg before inclusion 10. Had to have had no change in the dose of methylphenidate in the previous month 11. Had to agree to eat breakfast every day during the study period

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Döpfner 2011b *(Continued)*

	12.Had to be able to swallow the capsules *Exclusion criteria* 1. Any contraindication to methylphenidate 2. Treatment with psychostimulants other than methylphenidate in the previous 4 weeks 3. Needed another ADHD treatment (e.g. behavioural therapy or immediate inpatient treatment)
Interventions	Methylphenidate type: Medikinet (equal proportions of immediate- and slow-release methylphenidate) and Concerta (immediate-release and OROS-methylphenidate) Methylphenidate dosage: participants were randomly assigned to 1 of 6 possible sequence combinations Each patient received the following treatments in a sequence: Lower doses: Medikinet Retard 20 mg (10 mg immediate release) or 10 mg (5 mg immediate release) Lower doses: Concerta: 18 mg (4 mg immediate release) High dose: Medikinet Retard: 30 mg (15 mg immediate release) or 20 mg (10 mg immediate release) High dose: Concerta 36 mg (8 mg immediate release) Administration schedule: once daily Duration of each medication condition: 1 week per treatment, 3 weeks in total Treatment compliance: the compliance was more than 99%
Outcomes	*Non-serious adverse events*: Both doctors, teacher and parents documented side effects weekly The DAY profile of ADHD Symptoms (DAYAS): potential adverse effects of ADHD medication were assessed by parents with 11 items for the whole week. Additionally, potential adverse effects of ADHD medication are assessed by teachers with 9 items for the whole week. Here the ratings from teachers and parents were obtained at the end of the week (Thursdays or Fridays) to provide a comprehensive assessment of the week and to avoid the possible impact of carry-over treatment effects Furthermore, from the final report from Medice: all AE were coded according to MedDRA. The onset of the event was significant for assignment of the AE to 1 of the treatment groups (dose group/pharmaceutical form). If an event lasted over several treatment groups it was only evaluated for the treatment group in which it first appeared Blood pressure, rated weekly by investigator Heart rate, rated weekly by investigator
Notes	Sample calculation: yes Ethics approval: yes Funding/vested interests/authors' affiliations: Manfred Döpfner is currently a consultant for Medice, Shire Pharmaceutical, and Eli Lilly; has in the last 3 years received grant funding from UCB-Pharma, Medice, and Eli Lilly; has recently served on the advisory boards of Medice, Shire Pharmaceutical, and Eli Lilly; and has spoken at events sponsored by Medice, Shire Pharmaceutical, Eli Lilly, and Janssen Cilag. Claudia Ose is CEO at Center for Clinical Studies at University Hospital Essen Germany. R. Fischer is a full-time employee of Medice. R. Ammer is Chief Executive Officer of Medice. Andre Scherag currently serves as trial statistician on a data safety and monitoring board for Boehringer Ingelheim KG. The study is funded by Medice Company. Any withdrawals due to adverse events: 4

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Döpfner 2011b *(Continued)*

Key conclusions from study authors: in summary, based on the efficacy and safety data from this trial it can be claimed that Medikinet retard with a higher IR component than Concerta and an equivalent daily dose is superior to Concerta in the morning and that children and adolescents may also be treated with a lower daily dose of Medikinet retard without resulting in a clinically relevant worse effect during school time as assessed by SKAMP-D. "Since there is no placebo group or no 'no-intervention' group in the trial, we can only use the data on adverse events. We extract data from this study as if it was an observational study

Comments from the study authors: in this study, carry-over effects are expected to be negligible because of the short half-life of methylphenidate.

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: yes, only participants who responded well to the medication were included

Supplemental information regarding final report and protocol received through personal email correspondence with the medical director from Medice in December 2013 (Roland 2013 [pers comm])

Döpfner 2011c

Methods	A cohort study of methylphenidate use for 4-6 weeks
Participants	Number of participants screened: not stated Number of participants included: 467 Number of participants followed up: 447 Number of withdrawals: 20 (excluded in intention-to-treat analysis, but included in the tolerability evaluation) Diagnosis of ADHD: 48% ICD-10 diagnosis of ADHD (subtype: not stated), 42% "hyperkinetic disorders which affected their social behavior" (subtype: not stated) Age: mean: 10.7 (2.5) years (range: 6-17) IQ: not stated, but half of the children were in primary school Sex: 361 males, 106 females Methylphenidate-naïve: 14% Ethnicity: not stated Country: Germany Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Age 6-17 2. Diagnosed with ADHD 3. Indication for treatment with Medikinet retard *Exclusion criteria* 1. Patients were excluded if they had any contraindications listed in the summary of product characteristics

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Döpfner 2011c *(Continued)*

Interventions	Methylphenidate type: Medikinet retard (extended release) Mean methylphenidate dosage: 22.6 mg (range: not stated) Administration schedule: once daily Duration of intervention: 4-6 weeks Treatment compliance: was assessed by prescribing physician. In 57% of cases there was improved compliance after the medication switch; no change was observed in 39%, and compliance deteriorated in 4%
Outcomes	*Non-serious adverse events*: 11 items in the paediatric diagnosis system KIDS assesses potential adverse events of the medication In 79 patients, adverse events were recorded by the physician, and these events were described as severe in 13 cases. The most frequent adverse events were appetite disorders, head- and stomachache and sleep disorders
Notes	Sample calculation: no Ethics approval: non-interventional study pursuant to Section 4 sentence 3 and Section 67 AMG (German Medicines Act) Funding/vested interest/authors' affiliations: Prof Döpfner is employed as a consultant to the following companies and receives research funding from these companies: Janssen-Cilag, Lilly, Medice, Novartis, Shire, UCB. Dr Fischer is an employee of Medice. Ms Ose is participating in studies which are supported by Medice and UCB Any withdrawals due to adverse events: 10 *Key conclusions of the study authors*: the overall evidence showed that Medikinet retard was well tolerated in routine clinical practice, can be used effectively to treat symptoms of ADHD, can improve compliance to medication and can contribute to a further improvement in symptoms in previously suboptimally treated patients *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: by implication, since treatment would not be indicated for non-responders *Supplemental information* regarding data requested from the authors by email in June 2014. No answer received

Efron 1997

Methods	A 4-week double-blind, cross-over study with 2 arms: 1. Methylphenidate 2. Dexamphetamine
Participants	Number of participants screened: not stated Number of participants included: 125 participants were randomly assigned to 1 of 2 possible drug condition orders (methylphenidate or dexamphetamine) Number of participants followed up: not stated Number of withdrawals: 4 due to severe adverse events (2 on methylphenidate, 2 on dexamphetamine) Diagnosis of ADHD: DSM-IV (subtype: combined (81.8%), hyperactive-impulsive (1.6%), inattentive (17.6%))

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Efron 1997 *(Continued)*

	Age: mean 104.8 (SD 27.6) months (range 60-179 months) IQ: mean 98.9 (SD 13.8) Sex: 114 males, 11 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: Australia Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. 5-15 years 2. DSM-IV criteria for ADHD 3. T-score of ≥ 1.5 SD units above the mean on the attention problems scale of the Child Behavior Checklist (CBCL) or Teacher Report Form (TRF) 4. Decision made to undertake stimulant medication trial on clinical grounds *Exclusion criteria* 1. History of intellectual disability, gross neurologic abnormality, or Tourette syndrome
Interventions	Methylphenidate dosage: 0.3 mg/kg/dose, rounded off to the nearest capsule size Administration schedule: twice a day, after breakfast and after lunch Duration of intervention: 2 weeks. 24-hour washout period between interventions Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Barkley Side Effects Rating Scale (SERS): adverse events rated on a scale from 0 (absent) to 9 (severe). The list of side effects were compiled from those commonly reported anecdotally in the literature Parent rated at baseline and the end of each 14 day period
Notes	Ethics approval: yes. The study protocol was approved by the Ethics in Human Research Committee of the Royal Children's Hospital, Melbourne, Australia, and written informed consent was obtained from parents Funding: clinical research scholarship from the Royal Children's Hospital Research Foundation Vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: nightmares, stomachaches and anxiousness decreased in frequency on methylphenidate, whereas poor appetite increased on methylphenidate. Most children with ADHD improve significantly on both methylphenidate and dexamphetamine. There was a slight advantage to methylphenidate on most measures. Many symptoms commonly attributed to stimulant medication are actually preexisting characteristics of children with ADHD and improve with stimulant treatment *Comments from the study authors*: a significantly greater number of side effects were reported as present by parents at baseline than during the methylphenidate condition. Parents motivated to have their child diagnosed with ADHD may have over-reported symptoms at baseline, including adverse events

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Efron 1997 *(Continued)*

	Supplemental information regarding adverse events received through personal email correspondence with the authors in October and December 2013 (Barker 2013 [pers comm])

El-Fiky 2014

Methods	A cohort study of methylphenidate use for 6 weeks
Participants	Number of participants screened: 31 Number of participants included: 31 Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-5 (subtype: combined (70.9%), hyperactive-impulsive (6.5%), inattentive (22.6%)) Age: females: mean 8.2 (SD 3), range 5-14 years old. Males: mean 8.4 (SD 2.2), range 6-14 years IQ: mean: females: 100.8, males: 106.5 Sex: 21 males, 10 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: Egypt Comorbidity: oppositional defiant and conduct disorders: 11 (35.4%); specific phobic disorders: 3 (9.6%); childhood depression: 2 (6.5%), multiple comorbid problems (of conduct, agoraphobia, social and specific phobias): 2 (6.5%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. No contra-indications to stimulant's therapy 2. DSM diagnosis 3. 5-15 yo 4. Both sexes 5. Consent of parents *Exclusion criteria* 1. IQ below 90 2. Chronic general medical conditions 3. Forms of pervasive developmental or tics disorder 4. Epilepsy 5. Previous poor response or intolerance to stimulants 6. Non-consenting families
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage: male: 0.75 mg/kg (SD 0.12); female: 0.76 mg/kg (SD 0.16) Administration schedule: not stated

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El-Fiky 2014 *(Continued)*

	Time points: not stated Duration of intervention: 6 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Measure method: Stimulant Drug Side Effects Rating Scale of Barkley
Notes	Sample calculation: not clear, but authors stated: "A pilot study involving 10 subjects (8 males, 2 females) was conducted to determine size and selection methods, interrater reliability and applicability of tools, and dose ranges of methylphenidate (0.4-1 mg/kg)." Ethics approval: not stated Funding/vested interests/authors' affiliations: not stated Any withdrawals due to adverse events: not clearly stated, but no mention of dropouts *Key conclusions of the study authors*: no statistically significant gender differences; females recorded less improvement and showed more 'talk less' and 'less interest' as side effects. Conclusive evidence for the role of gender in ADHD require bypassing methodological limitations as well as confounding factors. *Comments from the study authors*: since the above mentioned gender differences were less apparent than expected in the absence of gender-by-ADHD interaction, they can be attributed to many confounding factors than modification of ADHD effect by gender *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes *Supplemental information* attempted to retrieve, but no contact information for the authors found

El-Zein 2005

Methods	A 3 months cohort study following 12 children taking methylphenidate
Participants	Number of patients screened: 35 Number included: 18 Number followed up: 12 Number of withdrawals: 6 Diagnosis of ADHD: DSM-IV (subtypes: not stated) Age: 8.5 (SD 3.5) years old, range: not stated IQ: not stated Sex: 10 males, 2 females Methylphenidate-naïve: 100% Ethnicity: white: 50%, African American: 33%, Hispanic: 16% Country: USA Comorbidity: not stated Comedication: not stated

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El-Zein 2005 *(Continued)*

	Sociodemographics: not stated *Inclusion criteria* 1. ADHD diagnosis according to DSM-IV criteria
Interventions	Methylphenidate type: not stated (clinician's given choice as to what they prescribed) Methylphenidate dosage: 20 to 54 mg/day Administration schedule: not stated Duration of intervention: 3 months Treatment compliance: not stated
Outcomes	*Serious adverse events*: A 10 ml blood sample was taken before starting methylphenidate, and a second blood sample was collected after 3 months of treatment with this drug. Type of effect: 3 cytogenetic endpoints (chromosome aberrations, sister chromatid exchanges and micronuclei frequencies) measure method (peripheral blood lymphocytes obtained pre and post treatment)
Notes	Sample calculation: not stated Ethics approval: after being informed of the study, a parent or guardian signed an informed consent that was approved by the Institutional Review Board of UTMB, the child also assented, and the study participant was then enrolled Funding/vested interest/authors' affiliations: not stated *Key conclusions of the study authors*: in all participants, treatment induced a significant 3, 4.3 and 2.4-fold increase in chromosome aberrations, sister chromatid exchanges and micronuclei frequencies, respectively (PZ0.000 in all cases). These findings warrant further investigations of the possible health effects of methylphenidate in humans, especially in view of the well-documented relationship between elevated frequencies of chromosome aberrations and increased cancer risk *Comments from the review authors*: the critique of the study by Preston, Kollins et al needs to be read alongside this study as it highlights considerable methodological concerns in this small cohort/patient series

Famularo 1987

Methods	A naturalistic observational study, where the effectiveness of drug treatment (methylphenidate) were tested by a drug treatment during a grading period and no drug treatment for the next grading period
Participants	Number of patients screened: not stated Number of participants included: 13 Number of participants followed up: 10 Number of withdrawals: 3 Diagnosis of ADHD: DSM-III diagnosis of ADD (subtype: inattentive) Age: mean: 9.4, range 7-12 years old IQ: above 90

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Famularo 1987 *(Continued)*

	Sex: 4 males, 6 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: USA Comorbidity: not stated, but see exclusion criteria Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. ADD disorder according to DSM III *Exclusion criteria* 1. IQ < 90 2. Anxiety or panic disorder 3. Seizure disorder 4. Major affective disorder 5. Thought disorder 6. Post-traumatic stress syndrome, or medical or neurological disease 7. No other DSM III diagnosis
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 0.4 to 1.2 mg/kg/day Administration schedule: twice daily Duration of intervention: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: 1 child reported decreased appetite without weight loss Another child's sleep onset was 15-20 minutes later than usual after initiation of pharmacological treatment There were minimal and clinically insignificant increases in pulse
Notes	Sample calculation: not stated Any withdrawals due to adverse events: no Ethics approval: not stated Funding/vested interest/authors' affiliations: not stated *Key conclusions of the study authors*: the results of this study provide tentative support for 2 conclusions: ADD without hyperactivity appears to be a potentially stimulant-treatable condition, even though hyperactivity is specifically excluded from its symptomatology; and school grades in children with ADD without hyperactivity may be influenced by the use of stimulants *Comments from the study authors*: the fact that significant results were obtained with such a small sample reflects the consistency with which the effects of the medication were exhibited across participants. However, it cannot be argued that these 10 participants adequately represent all ADD without hyperac-

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Famularo 1987 *(Continued)*

	tivity children. In addition, the results may have been affected by factors such as teacher bias, student motivation, and parental encouragement *Supplemental information* requested through personal email correspondence with the authors in August 2013 and January 2014. No reply

Faraone 2007a

Methods	A long term, open-label, longitudinal study of methylphenidate use for up to 37 months
Participants	Number of participants screened: 268 Number of participants included: 191 Number of participants followed up: 127 Number of withdrawals: 64 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: range 6-12 years old IQ: not stated Sex: not stated Methylphenidate-naïve: not stated Ethnicity: not stated Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. 6-12 years old 2. DSM-IV diagnosis of ADHD
Interventions	Methylphenidate type: transdermal system Methylphenidate dosage: 6.25 cm^2 (0.5 mg/hour) to 50 cm^2 (3.6 mg/hour) Administration schedule: 12 hour wear time Duration of intervention: 37 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Weight, height and BMI, values were converted to age-corrected standard scores (z scores) and percentiles using the normative growth charts and transformations provided by the Centers for Disease Control and Prevention
Notes	Sample calculation: not stated Ethics approval: the study was approved by each site's local institutional review board or by a central IRB

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Faraone 2007a *(Continued)*

	Funding/vested interests: this study was supported in part by a grant from Shire Pharmaceutical Development to SF Authors' affiliations: Dr Faraone receives research support from McNeil Consumer & Specialty Pharmaceuticals, Shire US, and Eli Lilly; is on the speakers' bureaus of Eli Lilly, McNeil Consumer & Specialty Pharmaceuticals, Shire US, and Cephalon; and has had an advisory or consulting relationship with the McNeil Consumer & Specialty Pharmaceuticals, Noven Pharmaceuticals, Shire US, Cephalon, and Eli Lilly. Mr Giefer has no financial relationships to disclose *Key conclusions of the study authors*: methylphenidate transdermal system treatment is associated with growth deficits in both weight, height, and BMI, but growth deficits attenuate over time. Baseline growth influences the effect of MTS treatment on both height, weight, and BMI, whereas prior stimulant therapy, dose, and total time treated influences only weight and BMI *Comments from the study authors*: prior stimulant therapy predicted smaller weight and BMI (but not height) deficits during the course of treatment with MTS. Growth velocity analyses showed that the rates of weight and BMI increases were negative in the first year of the study but positive at later time points. These findings suggest that any adverse effects of MTS on weight or BMI occur near the commencement of treatment and show some attenuation over time *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated

Feeney 1997

Methods	A patient report of af 13-year old boy developing a tonic-clonic ictal event on sertraline and methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-III (subtype: not stated) Age: 13 years old IQ: > 70 Sex: male Ethnicity: unknown Country: USA Comorbidity: depression Comedication: sertraline Sociodemographics: unknown
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 80 mg/day (1.8 mg/kg/day) Administration schedule: not stated Duration of treatment: 10 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: No significant side effects for approximately 10 months
Notes	Funding/vested interests: not stated Authors' affiliations: Wright State University, School of Medicine, Dayton, Ohio

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Feeney 1997 *(Continued)*

	Key conclusions of the study authors: first reported seizure in a patient with combined methylphenidate and sertraline treatment *Comments from the study authors*: more research is needed *Supplemental information* regarding ADHD diagnosis and IQ received through personal email correspondence with the authors in September 2013 (Klykylo 2013 [pers comm])

Fernández-Fernández 2010

Methods	A patient series of cardiac adverse effects of methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV-R (subtype: combined) Age: 7, 8, and 10 years old IQ: > 85 Sex: 3 males Ethnicity: not stated Country: Spain Comorbidity: no cardiovascular diseases Comedication: not stated Sociodemographics: not stated
Interventions	**Case 1** Extended release osmotic release oral system methylphenidate, 36 mg/day for 18 months. Treatment compliance: not stated Extended release osmotic release oral system methylphenidate, 18 mg/day. Treatment compliance: not stated **Case 2** Extended release osmotic release oral system methylphenidate, 18 mg/day, > 9 months. Treatment compliance: not stated **Case 3** Extended release osmotic release oral system methylphenidate, 18 mg/day. Treatment period: not stated. Treatment compliance: not stated Discontinuation Re-administration of extended release osmotic release oral system methylphenidate, 18 mg/day. Treatment period: not stated. Treatment compliance: not stated
Outcomes	*Serious adverse events*: **Case 3** Re-administration of extended release osmotic release oral system methylphenidate, 18 mg/day: recurrence of episodes of tachycardia. Emergency department: supraventricular tachycardia treated with adenosine *Non-serious adverse events*:

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Fernández-Fernández 2010 *(Continued)*

	Case 1 Extended release osmotic release oral system methylphenidate, 36 mg/day, 12-18 months: elevated arterial blood pressure with 2 SDs. No other intercurrent factors or symptoms Extended release osmotic release oral system methylphenidate, 18 mg/day: normalisation of blood pressure **Case 2** Extended release osmotic release oral system methylphenidate, 18 mg/day, 6 months: repetitive episodes of self-limiting tachycardia. Duration: a few minutes. ECG: self-limiting sinus tachycardia, 150 beats/minute. Maintaining methylphenidate treatment for > 3 months: some episodes of tachycardia **Case 3** Extended release osmotic release oral system methylphenidate, 18 mg/day: several episodes of tachycardia
Notes	Funding/vested interests: not stated Authors' affiliations: Unidad de Neurologiá Pediátrica. Hospital Universitario Infantil Virgen del Rocío. Sevilla, España *Key conclusions of the study authors*: these cases should make us be cautious and investigate the possible existence of family or personal cardiovascular pathology *Comments from the study authors*: to date, our patient is the youngest one diagnosed with supraventricular tachycardia secondary to methylphenidate treatment *Supplemental information* regarding ADHD diagnostic criteria and IQ received through personal email correspondence with the authors in August 2013 (Fernández-Fernández 2013 [pers comm])

Fernández-Fernández 2011

Methods	A patient report of infantile psychosis during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV-R (subtype: combined) Age: 10 years old IQ: > 70 Sex: male Ethnicity: not stated Country: Spain Comorbidity: not stated Comedication: not stated Sociodemographics: adopted
Interventions	2 years of extended release methylphenidate, dosage: 0.7/kg/day 1 week of extended release methylphenidate, dosage: 1.2 mg/kg/day Administration schedule: once daily Treatment compliance: not stated

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Fernández-Fernández 2011 *(Continued)*

Outcomes	*Serious adverse events*: Infantile psychosis. Significant behavioural changes with emotional lability, mood changes, disruptive behaviour and aggressive behaviour towards his mother and relatives. Presence of inner voices Discontinuation of methylphenidate treatment: no disruptive behaviour, aggressive attitude, nor inner voices
Notes	Funding/vested interests: not stated Authors' affiliations: Unidad de Neurologiá Pediátrica. Hospital Universitario Infantil Virgen del Rocío. Sevilla, España *Key conclusions of the study authors*: caregivers of children treated with psychostimulants should be informed of possible side effects in order to ensure proper treatment in case of appearance. Professionals must be familiar with the adverse reactions that may occur with methylphenidate treatment. Paediatric neurologists and child psychiatrists must be agile in handling these reactions when it comes to withdrawal of the medication, treatment of the adverse reactions and prevention of misdiagnosis or the establishment of a chronic antipsychotic or stimulant treatment *Supplemental information* regarding ADHD diagnostic criteria and IQ received through personal email correspondence with the authors in April 2013 (Fernández-Fernámdez 2013b [pers comm])

Findling 1996

Methods	A patient report of an 11-year old girl who experienced transient side effects after receiving MPH
Participants	Diagnosis of ADHD: DSM-III-R (subtype: combined) Age: 11 years old IQ: > 70 Sex: female Ethnicity: not stated Country: USA Comorbidity: major depression (single episode, marked severity) Comedication: sertraline 25 mg, twice daily Sociodemographics: not stated
Interventions	Methylphenidate dosage: 5 mg twice daily Duration of intervention: the patient was still taking methylphenidate at the follow-up at 3 months. Adverse effects occurred in the initiation of the treatment Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Mild and transient anorexia, transient weight loss 2 kg observed at the initiation of methylphenidate therapy
Notes	Ethics approval: not stated Funding/vested interests/authors' affiliations: not stated

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Findling 1996 *(Continued)*

Key conclusions of study authors: these cases support previous suggestions that adjunctive treatment with psychostimulants might be a safe and effective intervention for children treated with fluoxetine or sertraline who have persistent ADHD symptoms and suggest that such combined treatment might be suitable for adults as well

Supplemental information: email sent twice to author in order to get data on BP and HR. No reply

Findling 2009

Methods	A multicentre, prospective, 12-month, open-label, flexible-dose, phase III extension of 4 previous trials. This trial consisted of 3 phases: a dose-optimisation period (4 weekly visits), a dose-maintenance period (11 monthly visits), and a 30-day follow-up period
Participants	Number of participants screened: not stated Number of participants included: 327 Number of participants followed up at 12 months: 157 Number of withdrawals: 170. Diagnosis of ADHD: DSM-IV-TR (subtype: combined (82%), hyperactive-impulsive (2.1%), inattentive (15.9%)) Age: mean 9.2 (SD 1.9), range 6-12 years old IQ: normal Sex: 212 males, 115 females Methylphenidate-naïve: 47.4%, before participation in the antecedent study Ethnicity: white (73.7%), African American (14.7%), Asian (1.5%), others (10.1%) Country: USA Comorbidity: not stated Comedication: none Sociodemographics: not stated *Inclusion criteria*: 1. DSM-IV-TR ADHD diagnosis 2. 6-12 years old 3. Previously participated and completed 1 of 4 specific methylphenidate transdermal system trials 4. Fewer than 28 days between completion of treatment in the previous study and entry into the present one *Exclusion criteria*: 1. Early termination from the aforementioned trials because of non-adherence with study-related procedures or occurrence of ≥ 1 serious adverse event(s) Female participants pregnant or lactating 2. Comorbid psychiatric diagnoses (with the exception of oppositional defiant disorder in 3 of 4 studies) 3. Seizure disorder, chronic tic disorder, Tourette syndrome, allergic disease with skin manifestations, sensitive skin-syndrome 4. Sensitivities to ingredients in soaps, lotions, cosmetics, or adhesives 5. Any skin disease or history of any chronic disease that could interfere with patch application

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Findling 2009 *(Continued)*

6. Any hypersensitivity or clinically significant intolerance to methylphenidate or any components of the study treatments
7. Considerable general medical illness (except mild stable asthma) or an unstable medical condition, disability, or other condition that the investigator felt might interfere with or prevent completion of the study
8. The use of concomitant medications (including anticonvulsants, amphetamine, clonidine, pemoline, antidepressants, antipsychotics, sedating antihistamines, investigational medications, herbal preparations, and medications that affect blood pressure, heart rate, or the central nervous system)

Interventions	The patients either continued their current optimised methylphenidate transdermal system dose (from the previous study) for 12 months or entered a 4-week stepwise dose titration phase to an optimal methylphenidate transdermal system dose, followed by an 11-month dose maintenance phase Methylphenidate transdermal system dose: 10 mg, 15 mg, 20 mg, or 30 mg Administration schedule: 7 am, patch removed after 9 hours Duration of intervention: 12 months, the median duration of exposure to methylphenidate transdermal system during the extension study was 335 (range 7-392) days Treatment compliance: not stated
Outcomes	*Serious adverse events*: There were no serious cardiovascular events (e.g. sudden death, myocardial infarction or stroke) over the 12 months of the study. 3 serious AEs were reported in 3 participants. None of these considered related to treatment *Non-serious adverse events*: Physical examinations were performed at baseline, 6 months, and the final visit Height was measured at baseline, week 4, and months 2, 4, 6, 8, 10, and 12 Weight was measured at baseline, weeks 1 through 4, and months 6, 8, 10, and 12 Participants removed their clothing and shoes and wore a gown to ensure consistency between measurements. Height was measured using a calibrated stadiometer with the participant standing on a flat surface, shoes off, and the chin parallel to the floor. Weight was measured using the same calibrated scale at each visit: Vital signs (resting systolic and diastolic blood pressure (SBP and DBP), heart rate) were measured at baseline and all subsequent visits Blood pressure and heart rate were measured in the same arm using the same cuff type in each participant after 5 minutes' rest in a seated position - Clinical laboratory tests and a 12-lead electrocardiogram (ECG) were performed at baseline, week 4, months 3 and 6, and the end of the study, and analysed by unblinded paediatric cardiologists AEs were monitored at each study visit, and coded and defined using the Medical Dictionary for Regulatory Activities version 7.0. The severity and relationship of AEs to study treatment were assessed by the study investigators. Severity was rated as mild (easily tolerated, does not interfere with usual activities), moderate (interferes with daily activities, but participant is able to function), or severe (incapacitating, participant is unable to work or complete usual activities) Current and previous patch application sites were examined and rated for skin reactions and discomfort by trained, unblinded investigators at baseline; weeks 1 through 4; months 2 through 6, 8, and 10; and the end of the study. Dermal response scale 0-7 (no reaction - strong reaction beyond site). Dermal discomfort scale: 0-3 (no discomfort - severe, intolerable discomfort) Sleep behaviour investigated by using Children's Sleep Habits Questionnaire (CSHQ, 33 items), completed by parents/caregivers at baseline; weeks 1 through 4; months 2 through 6, 8, and 10; and at the

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Findling 2009 *(Continued)*

end of the study. Item scores range from 1 (rarely occurring, 0-1 times/wk) to 3 (usually occurring, 5-7 times/wk), with total scores ranging from 33-99

1 month after the last dose of study drug, participants' parents or legally authorised caregivers were contacted by telephone regarding ongoing or new AEs.

2 participants who had received MTS in the earlier studies had 1 AE each (tachycardia (154 beats/min) and worsening weight loss (6.6 kg)) that began before receipt of MTS in the present study. These AEs persisted and led to the participants' withdrawal after ˜1 and 4 months of treatment, respectively: blood pressure and pulse

The highest mean increase from baseline in SBP (5.8 mm Hg) across dose levels was recorded with the 30-mg dose at month 10. The highest mean increase in DBP (5.5 mm Hg) was observed with the 20-mg dose at week 2

Across dose levels, the proportion of participants with an SBP above the upper limit of normal (> 123 mmHg) ranged from 1% to 10%, whereas 1.5% had an above normal SBP at baseline. No participants had an above normal DBP (> 90 mmHg) at baseline; however, 1 participant in each MTS dose group had an above normal DBP at some time in the study

The highest mean increase in heart rate (5.6 beats/min) occurred with MTS 15 mg at month 3

ECG. There were no apparent trends toward changes in ECG indices at any MTS dose. ECG abnormalities were considered clinically significant in 4 participants and were recorded as 4 AEs. 3 of these AEs were tachycardia (123, 136, and 122 beats/min) and 1 was prolongation of the corrected QT (QTc) interval.

QTc. Another participant had a QTcB interval of 544 ms at 3 months (QTcF, 476 msec; heart rate, 133 beats/min). A repeat ECG performed ˜2 weeks later recorded a QTcB of 419 ms (QTcF, 380 ms; heart rate, 107 beats/min). Although the results of the ECG at 3 months were deemed abnormal because of the prolonged QTc interval, they were not considered clinically significant.

Laboratory analyses. No clinically significant changes from baseline or in the pattern of abnormal values on haematology, clinical chemistry, or urinalysis tests

Dermal AEs. 33 dermal AEs were reported by 28 participants. AEs occurring more than once were rash (n = 6), urticaria (n = 6), allergic dermatitis (n = 2), contact dermatitis (n = 2), eczema (n = 2), generalised pruritus (n = 2), and skin hyperpigmentation (n = 2). 1 participant receiving MTS 10 mg had a pruritic rash possibly related to study treatment. Another participant receiving MTS 10 mg discontinued due to allergic dermatitis on the waist and knees, also possibly related to MTS treatment

Mean (SD) dermal response scores at current and previous patch application sites were 1.2 (1.1) and 0.8 (1.0), respectively, across study visits, indicating minimal erythema

15 participants had 30 instances of a dermal response score of 5 at the current patch site, 4 participants had 6 instances of a dermal response score of 6, and 2 had 2 instances of a dermal response score of 7

Sleep behaviour. No apparent overall effect on sleep behaviour. Regarding insomnia, see below

Weight. 32.9 kg SD 9.9, range: (16.3-90.6 kg), **height**: 1.37 (SD 0.13), range: 1.08-1.72 m.

Weight loss in 33 participants (also in table 2), poor weight gain in 1, and increased weight in 2. Mean (SD) changes in the z scores for weight, height, and BMI at the end of the study were –0.2 (0.43), –0.0 (0.44), and –0.3 (0.72), respectively. The 95% CIs for weight change from baseline to end point were 0.70 to 2.99 for participants aged 6 to 9 years and 6.40 to 10.27 for participants aged ≥10 years

At visit 16, mean (SD) weight changes from baseline in participants receiving MTS 10 mg, 15 mg, 20 mg, and 30 mg were 2.73 (2.53), 1.62 (3.44), 2.49 (3.44), and 1.61 (3.41) kg, respectively. At visit 16, mean (SD) weight changes from baseline in participants receiving MTS 10, 15, 20, and 30 mg were 2.73 (2.53), 1.62 (3.44), 2.49 (3.44), and 1.61 (3.41) kg, respectively

Notes	Sample calculation: estimated enrollment 450

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Findling 2009 *(Continued)*

Ethics approval: the study protocol was approved by the appropriate institutional review board or independent ethics committee for each site

Funding/vested interests: Shire Development Inc. provided study medication and support for study-related care, and the company was involved in the study design, conduct, and data analysis

Authors' affiliations: all but 1 of the authors receives or have received research support from, acted as a consultant for, and/or served on a speaker's bureau for several pharmaceutical companies

Key conclusions of the study authors: long-term efficacy in paediatric patients was demonstrated by improvements in the ADHD-RS-IV, CGI-I, and PGA assessments. Most adverse events (98.3%) were mild to moderate. With the exception of application-site reactions associated with transdermal delivery of methylphenidate, adverse events were generally typical of those associated with methylphenidate

Comments from the review authors: if < 7 days had passed between the completion of the previous study and entry into the present one, baseline assessments were used from the previous study

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: yes

Supplemental information and adverse event data have not been possible to receive through personal email correspondence with the authors in October-November 2013

Findling 2010

Methods	This was a Phase IIIB, randomised, double-blind, parallel-group, placebo-controlled, multicentre, dose-optimisation study evaluating the efficacy and safety of 1. Methylphenidate transdermal system (10-, 15-, 20-, or 30-mg/9-hour patches) 2. Placebo transdermal system The study consisted of 4 experimental periods: 1. Screening and washout 2. Dose optimisation (5 weekly visits) 3. Dose maintenance (5 monthly visits) 4. A 7-day post-treatment follow-up. The follow-up was an open-label extension study for evaluating the safety and efficacy of methylphenidate transdermal system (10-, 15-, 20- or 30 mg/9-hour patches) for participants who completed all required study visits and consisted of 3 experimental periods
Participants	**For the open-label extension:** Number of participants screened: not stated Number of participants included: 163 (110 previously on MPH and 53 on PL) Number of participants followed up: 162 Number of withdrawals 1 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 14.5 (SD 1.24) years (range 13-17) IQ: ≥80 Sex: 121 males, 41 females Methylphenidate-naïve: 56% (122)

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Findling 2010 *(Continued)*

Ethnicity: white (78%), African American (17%), Asian (0.6%), others (4.4%)

Country: USA

Comorbidity: none

Comedication: not stated

Sociodemographics; not stated

Inclusion criteria

1. Male or female adolescents 13-17 years
2. Primary diagnosis of ADHD according to DSM-IV
3. IQ score of > 80
4. A total score of ≥ 26 on the ADHD-Rating Scale-IV (ADHD-RS-IV) at baseline
5. Participants were required to have electro-cardiogram (ECG) results within normal range or variants that were not clinically significant as judged by investigators in conjunction with the central laboratory
6. Blood pressure measurements within the 95th percentile for age, gender, and height
7. No current or history of skin disease or other skin problems including sensitive skin or signs of skin irritation
8. Females must have a negative urine pregnancy test at entry and agree to use acceptable contraceptives throughout the study period and for 30 days the last dose of IP
9. Participant and parent of legally authorised representative are able, willing and likely to fully comply with study procedures and restrictions
10. Regarding the 6-month open-label study: participants must have completed all required study visits or completed a 5-week dose-optimisation period without achieving an acceptable condition (i.e. . ≥ 25% decrease from baseline in a participant's ADHD-Rating Scale IV score with minimal side effects)

Exclusion criteria

1. Conduct disorder or comorbid psychiatric illnesses (such as clinically significant obsessive compulsive disorder, depressive, or anxiety disorders; posttraumatic stress disorder; psychosis; bipolar illness; or pervasive developmental disorder)
2. A history of structural cardiac abnormality, cardiomyopathy, cardiac rhythm abnormalities, or other serious cardiac problems; suicidal ideation; alcohol or other substance abuse (except caffeine or nicotine) within the last 6 months
3. Seizures during the previous 2 years and those who had a history of being non-responsive to psychostimulant treatment use of clonidine, atomoxetine, antidepressants, sedatives, antipsychotics, anxiolytics, P450 enzyme-altering agents, or other investigational medications within 30 days prior to screening
4. Female participants who are pregnant or lactating
5. Regarding the 6-month open-label study: participants were not eligible to participate in the extension study if they were discontinued from the antecedent study due to protocol violation (including noncompliance), an AE for which continued treatment would be medically contraindicated, or a serious adverse event (SAE). Participants with considerable general medical illness (except mild, stable asthma) or an unstable medical condition, disability, or other condition the investigator believed might interfere with or prevent completion if the study were also excluded

Interventions	Methylphenidate type: transdermal system Mean methylphenidate dosage at month 6: 10 mg (5.6.%), 15 mg (7.9%), 20 mg (32.6%), and 30 mg (53.9%); median exposure time: 168.0 days (range, 3-200 days) Administration schedule: single patch in the morning, once daily for 9 hours Duration of intervention: 6 months Titration period: 5 weeks of the 6 months

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Findling 2010 *(Continued)*

	Treatment compliance: 88 fulfilled the protocol
Outcomes	Regarding the 6-month open-label study: Dose optimisation (5 weekly visits) versus dose maintenance (5 monthly visits): Adverse events were monitored at each study visit and assessed by an open-ended inquiry along with specific dermatological questions asked by an investigator or qualified evaluator. AEs were considered treatment emergent if they began or worsened on or after application of the first patch and occurred before or at the same time as application of the patch. AEs coded and defined using the MedDRA, version 7.03) a 7-day post-treatment follow-up. Height: measured at month 6 visit by the investigator Weight: recorded at all 5 visits by the investigator Vital signs (systolic blood pressure, diastolic blood pressure pulse), measured at all study visits, by the investigator. 12-lead ECG performed at entry, week 4, month 3, month 6, by the investigator Blood and urine samples collected at entry, week 4, month 4, and month 6 Dermal skin reaction: measured by DRS at each study visit Sleep: measured by the non-validated Post-Sleep Questionnaire. Measured at the 6 month visit Any changes noted between evaluation data at study entry and data obtained at schedule visits deemed to be clinically significant by the investigator were considered an adverse event
Notes	Sample calculation: yes Ethics approval: yes Funding: this study was funded by Shire Development Inc., which was involved in the study design, conduct, and data analysis Vested interests/authors' affiliations: Dr Findling has received research support, acted as a consultant, and/or served on speakers' bureaus for Abbott, Addrenex, As- traZeneca, Biovail, Bristol-Myers Squibb, Forest, GlaxoSmith Kline, KemPharm, Johnson & Johnson, Eli Lilly, Lundbeck, Neuropharm, Novartis, Organon, Otsuka, Pfizer, Sanofi-Aventis, Sepracor, Schering-Plough, Shire, Solvay, Supernus Pharmaceuticals, Validus, and Wyeth. Dr Katic has received research support, acted as a consultant, and/or served on speakers' bureaus for Forest, GlaxoSmithKline, Lundbeck, Merck, Novartis, Sanofi-Aventis, Sepracor, Shire, Somerset, and Wyeth. Dr Rubin has received research support, acted as a consultant, and/or served on speakers' bureaus for Abbott, Addrenex, Cephalon, Eli Lilly, Johnson, Johnson, McNeal, Novartis, Shire, and UCB Celltech. Dr Moon received research support, acted as a consultant, and/or served on speakers' bureaus for Abbott, AstraZeneca, CNS Response, Eli Lilly, Johnson & Johnson, McNeil, Novartis, Pfizer, Sanofi- Aventis, Shire, Synosia Therapeutics, Takeda, and UCB Inc. Drs Civil and Li are employees of Shire Development Inc. Dr Civil is an employee of Shire Development, Inc. At the time of this study, Dr Li was an employee of Shire Development, Inc. *Key conclusions of the study authors:* regarding the 6 months open-label study: methylphenidate transdermal system was generally well tolerated, and AEs were generally typical of those associated with oral methylphenidate, with the exception of application-site reactions associated with transdermal delivery of methylphenidate *Comments from the study authors*: it is important to note that participants who failed to respond to psychostimulants in the past and those with conduct disorder and other psychiatric comorbidities were excluded from the study. Regarding the 6-month study: no clinically significant findings between laboratory evaluation parameters obtained postentry relative to screening values obtained at the antecedent study *Comments from the review authors*: as already stated, people who earlier had failed to respond to psychostimulants were not included in the study. Therefore results can only be generalised to responders. Regarding the 6-month open-label study: participants who had not reached an acceptable response by the end of week 5 were withdrawn from the study *Supplemental information* requested from the study authors and Noven Pharmaceuticals with no reply

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Gadow 1995

Methods	A randomised, placebo-controlled, double-blind, cross-over trial with 2 interventions: 1. Methylphenidate in 2-3 dosages 2. Placebo Phases: 1. Washout if medications prior to trial 2. 8 week RCT with 2 weeks in each arm 3. Open-label follow-up at 24 months
Participants	Number of participants screened: not stated Number of participants included: 34. Participants were randomly assigned to different orders of the 3 dosages Number of participants followed up: 12-months follow-up: 30; 18 months follow-up: 26; 24 months follow-up: 26 Number of withdrawals: 8 Diagnosis of ADHD: DSM-III-R (subtype: not stated) Age: mean: 8 years and 10 months, range: 6.1-11.9 years old IQ: mean: 105.9 (SD 13.7) Sex: 31 males, 3 females Methylphenidate-naïve: 71% Ethnicity: white: 85%, African American: 3%, Asian: 3%, Hispanic: 9% Country: USA Comorbidity (only data from 21 children from Gadow 1995): tics: 100%, anxiety and/or depressive disorder: 8/21 (38%), obsessive-compulsive disorder: 3/21 (14%), most of the children furthermore had either oppositional defiant disorder or conduct disorder and academic problems Comedication: not during the RCT. During the follow-up 4 children were treated with an anti-tic medication in combination with methylphenidate (neuroleptic n = 3, clonidine, n = 1) Sociodemographics: not stated *Inclusion criteria* 1. Meet DSM III-R diagnostic criteria for ADHD 2. Either chronic motor tic disorder or Tourette disorder 3. ADHD had to be a primary reason for seeking clinical services 4. In general, be above the cutoff on 2-3 parent- and teacher completed hyperactivity and/or ADHD behaviour rating scales 5. Written signed statement from the parents consenting to their child's participation *Exclusion criteria* 1. Dangerous to self or others 2. Tics as the major clinical management concern 3. Psychosis 4. IQ below 70 5. Seizure disorder, major organic brain dysfunction or major medical illness

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Gadow 1995 *(Continued)*

	6. Contraindications to medication (other than tics) 7. Pervasive developmental disorder
Interventions	Methylphenidate dosage: participants were randomly assigned to 1 of 4 possible drug condition orders of doses: 0.1 mg/kg (mean: 4.4 mg), 0.3 mg/kg (mean: 9.0 mg) and 0.5 mg/kg (mean: 14.0 mg) methylphenidate and placebo. Upper dosages limit was 20 mg. When the 0.5 mg/kg dose was not preceded by a low dose condition, the child was gradually build up to the moderate dose. The build-up days occasionally fall on scheduled school observation days.The observer were unaware of these days, and observations were conducted as usual, but these data were excluded from the analyses Administration schedule: 2-3 times daily at morning and noon, approximately 3.5 hours apart, 7 days a week Duration of each medication condition: 2 weeks Washout prior to study initiation: methylphenidate: 1 week, antipsychotic: 3 weeks, clonidine: 2 weeks Medication-free period between intervention: none Titration period: none Treatment compliance: parents and nurses were asked to return unused medication envelopes, which allowed the researchers to assess compliance. However, no further description in the paper *24 month follow-up*: total daily dose of methylphenidate, MED (minimal effective dose - after RCT): (mean 16.5 mg, range 5-40 mg); second visit (mean 28.5 mg, range 15-60 mg); third visit (mean 29.2 mg, range 10-90 mg); and fourth visit (mean 34.5 mg, range 15-92 mg)
Outcomes	*Non-serious adverse events* **During the 8-week RCT** Side Effect Checklist (SSEC), 13 items, rated by parents on Saturday and Sunday and rated by teacher twice a week Global Tic Rating Scale (GTRS), rated by parents on Saturday and Sunday and rated by teacher twice a week Motor and vocal tic category was, were observers coded presence or absence of tics in the classroom, lunchroom or playground, 4 times for each medication condition *Physician evaluations* Yale Global Tic Severity Scale (YGTSS), rated every second week Tourette Syndrome Unidentified Rating Scale, rated every second week Global Tic Rating Scale (GTRS) (only assessed in 22 patients), rated every second week Shapiro Tourette Syndrome Severity Scale (OBS! Only assessed in 22 patients), rated every second week Motor tic frequency tics; rated in 180 5-second intervals in a simulated classroom, and tics were coded as either present or not present in each interval, rated every second week Weight, assessed every second week Heart rate, assessed every second week Blood pressure, assessed every second week **During the 24-months** follow-up *Physician evaluations*

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Gadow 1995 *(Continued)*

All rated at MED (right after RCT) 6 months, 12 months, 18 months, and 24 months

Yale Global Tic Severity Scale (YGTSS)

Shapiro Tourette Syndrome Severity Scale

3 subscales from the Tourette Syndrome Unified Rating scale

Total number of tics

Number of tics observed in 2 minutes of quiet conversation with the physician

The LeWitt Disability Scale which assesses tics and the symptoms of comorbidities

The Global Tic Rating Scale (GTRS)

Blood pressure

Heart rate

Pulse

Weight

Parents' ratings

Based on the last 2 weeks and rated at MED (right after RCT) 6 months, 12 months, 18 months, and 24 months

Stimulant Side Effect Checklist (SSEC)

GTRS

Notes

Sample calculation: yes

Any withdrawals due to adverse events: no

Ethics approval: no information

Funding: supported in part by a research grant from the Tourette Syndrome Association Inc and a Public Health Service Grant from the National Institute of Mental Health

Vested interests/authors' affiliations: not stated

Key conclusions from study authors: during the course of this short-term drug evaluation, physician, teacher, and parent ratings were in uniform agreement that methylphenidate did not lead to a worsening in the severity of the children's tic disorder. Furthermore methylphenidate is an effective drug for the treatment of ADHD and oppositional and aggressive behaviour. Furthermore the follow-up study showed that long-term treatment with methylphenidate seems to be safe and effective for the management of ADHD behaviours in many (but not necessarily all) children with mild to moderate tic disorder. Nevertheless, careful clinical monitoring is mandatory to rule out the possibility of drug-induced tic exacerbation in individual patients

Comments from the study authors: the magnitude of clinical improvement associated with the 0.3 mg/kg dosage compared with 0.5 mg/kg dosage was generally trivial for many children. The 0.5 mg/kg dosage was associated with more side effects, but fortunately they were generally of limited clinical significance.The generalisability of the findings from this study are subject to several qualifications. First, our data pertain to observed treatment effects over an 8-week period and therefore cannot address the issue of tic exacerbation as a function of long-term drug exposure. Furthermore the findings pertain only to children with ADHD and with tics that are of mild to moderate severity and that occur frequently enough to be observed during 15-minute intervals

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no, children were not excluded from participation in the study if they had prior experience with stimulant drug therapy or if such a therapy purportedly had exacerbated their tics.

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Gadow 1995 *(Continued)*

	Comments from the review authors: 26 of the children received stimulant medication throughout the follow-up interval, and of these children, 1 was switched to dextroamphetamine. However, we have chosen still to use the results for the 26 in our analyses. All of the included articles are a mix of different protocols, so the total number of included participants differ from article to article *Supplemental information* regarding cross-over data requested through personal email correspondence with the authors in April 2013 (Gadow 2013 [pers comm]). No data regarding the interventions were available

Galland 2010

Methods	A cross-over trial with 2 interventions: 1. Methylphenidate 2. No medication Phases: 2 Part of a case-control study: ADHD group randomly assigned to 2 nights on and 2 nights off of methylphenidate versus non-medicated non-ADHD control group
Participants	Number of patients screened: not stated Number included: 30. Participants were randomly assigned to methylphenidate or no treatment Number followed up: 27 for cross-over RCT, 28 for observational data Number of withdrawals: 3 for RCT, 2 for observational data **RCT** Diagnosis of ADHD: DSM-IV (subtype: combined (78%/21), inattentive (22%/6)) Age: mean: 10 years 6 months, range: 6 years 7 months to 12 years 4 months IQ: above 70 Sex: 21 males, 6 females Methylphenidate-naïve: 0% Ethnicity: white: 23, Maori: 1, other: 3 Country: New Zealand Comorbidity: oppositional defiant disorder: 9 (33%), specific phobia: 1 (4%) Comedication: no Sociodemographics: mean deprivation index: 5.5 *Inclusion criteria* 1. Children aged 6-12 years 2. Diagnosis of ADHD (DSM-IV) 3. Prescribed methylphenidate 4. Full-scale IQ of ≥ 70 (Wechsler Intelligence Scale for Children, 3rd edition) *Exclusion criteria* 1. Gross sensory or motor problems

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Galland 2010 *(Continued)*

	2. Significant developmental delay, autism or psychosis
Interventions	Participants were randomly assigned to methylphenidate or no medication. Methylphenidate type: Ritalin Mean methylphenidate dosage: not stated Administration schedule: 7 children had standard methylphenidate formulation once daily, 9 twice daily and 2-3 times daily; 4 children had slow release alone, 4 in combination with once daily standard and 1 in combination with twice daily standard formulation Duration of intervention: 2 nights Washout prior to study initiation: none Medication-free period between interventions: not clear, there was 5 to 7 days between medication and non-medication phases Titration period: none, participants had been treated with methylphenidate for a median of 3 years 9 months (range 3 months to 6 years 8 months). ADHD children were randomised to either the first night as a medication- and caffeine-free night for 48 hours prior to each study night, or a medication night where they maintained their methylphenidate dosage regimen 48 hours prior to each study night, but remained caffeine-free Treatment compliance: urinary methylphenidate was reported as detected/or not detected. No control children returned a positive test on either night
Outcomes	*Non-serious adverse events*: Standard polysomnographic (PSG) recordings on the second night of 48 hours on or off MPH Sleep questionnaire (28-item), completed by the parent (predominantly mother) over that week General adverse events, parent rated, observational data
Notes	Sample calculation: not reported Ethics approval: yes, Otago Ethics Committee approved the study Funding/vested interests/authors affiliations: the project was supported by a grant from the Health Research Council of New Zealand *Key conclusions from study authors*: findings suggest that methylphenidate reduces sleep quantity but does not alter sleep architecture in children diagnosed with ADHD *Comments from the study authors*: 1. It is possible that the longer sleep duration and shorter sleep latency on the off- compared to on-medication night could be interpreted as purely rebound, or that the on-medication night reflects a truer baseline and the off-medication night reflects a medication withdrawal effect 2. The dosages and formulations of methylphenidate were not standardised 3. Only 1 PSG recording was conducted for each condition, which means the information collected could be subject to a first-night effect *Comments from the review authors*: we considered this a RCT study even though the authors describe it as a case-control study, because the ADHD children were randomly assigned to on- or off-methylphenidate. Only observational data on adverse events is used here *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated

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Galland 2010 *(Continued)*

	Supplemental information received through personal email correspondence with the authors in August 2014 (Galland 2014 [pers comm])

Garg 2014

Methods	An open-label randomised parallel group clinical trial of methylphenidate and atomoxetine use for 8 weeks
Participants	**Methylphenidate group** Number of participants screened: not stated Number of participants included: 33 Number of participants followed up: 26 Number of withdrawals: 7 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (66.7%), hyperactive-impulsive (6.1%), inattentive (27.3%)) Age: mean: 8.47 (SD 2.22), range: 6-14 years old IQ: > 70 Sex: 27 males (81.1%), 6 females (18.2%) Methylphenidate-naïve: 100% Ethnicity: not stated Country: India Comorbidity: oppositional defiant disorder (15/45.5%), conduct disorder (1/3%) Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. 6-14 years old 2. Diagnosed with ADHD according to DSM-IV-TR 3. Having moderate to severe illness as assessed by Clinical Global Impressions Severity Scale (CGI-S) *Exclusion criteria* 1. Patients with history of non-response or adverse reactions to methylphenidate in the past 2. Those who had taken any medication for ADHD in the past month 3. Those with history of heart disease, seizures, pervasive developmental disorder, substance abuse, mental retardation or tic disorder were excluded
Interventions	Methylphenidate type: immediate release Mean methylphenidate dosage: 11.59 (2.83) mg/day, at conclusion of the study: 17.35 (7.52) mg/day (or 0.62 mg/kg/day) Administration schedule: once or twice daily Duration of intervention: 8 weeks

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Garg 2014 *(Continued)*

	Treatment compliance: not stated
Outcomes	The various side effects were noted on each assessment on the Adverse Events Checklist prepared for the study. It was a semi-structured check list enlisting all the common side effects of methylphenidate and atomoxetine. The parents were asked to rate the severity of each side effects produced in their children as mild, moderate and severe. Those who reported mild side effects were continued on the same dose. For those who developed moderate severity of side effects, dose was reduced. Those who rated any adverse effect to be severe were taken out of the study after stopping the medication *Non-serious adverse events*: 18 (55%) patients developed side effects during the course of the study The commonest reported adverse effect was reduced appetite
Notes	Sample calculation: not stated Ethics approval: clearance was obtained from the ethics committee of the Government Medical College and Hospital, Chandigarh Funding/vested interest: none *Key conclusions of the study authors*: methylphenidate and atomoxetine are efficacious in Indian children with ADHD at lesser doses than previously used. Their efficacy and tolerability are comparable *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes, exclusion of non-responders *Supplemental information* received through personal email correspondence with author in July 2016 (Arneja 2016 [pers comm])

Gau 2006

Methods	An open, randomised, parallel, active-controlled equivalent 28 day trial with 1. Immediate release methylphenidate 2. Osmotic release oral system (OROS) methylphenidate
Participants	Number of participants screened: not stated Number of participants included: 64 Number randomised to immediate release methylphenidate: 32, and to OROS methylphenidate: 32 Number followed up in each arm: immediate release methylphenidate: 32, OROS methylphenidate: 32 Number of withdrawals in each arm: 0 Diagnosis of ADHD: DSM-IV/ICD-10 (combined 50 (78.1%), hyperactive-impulsive 2 (3.1%), inattentive 12 (18.9%)) Age: mean: 10.5, range: 6-15 years old IQ: > 80 Sex: 58 males, 6 females Methylphenidate-naïve: 0 Ethnicity: Asian 100% Country: Taiwan Comorbidity: no

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Gau 2006 *(Continued)*

	Comedication: no Sociodemographics: parents education: college: 55%, high school: 30%, junior high school: 10%, other: 5% *Inclusion criteria* 1. Been taking methylphenidate 10-40 mg for the past 3 months 2. Able to comply with the study visit schedules 3. Their mothers and teacher were willing and able to complete the weekly assessments *Exclusion criteria* 1. Significant gastrointestinal problems 2. A history of hypertension 3. Known hypersensitivity to methylphenidate 4. Co-existing medical condition 5. Concurrent medication (such as monoamine oxidase inhibitors, and medicines used to treat depression, prevent seizure, or prevent blood clots) likely to interfere with the safe administration of methylphenidate 6. Glaucoma, Tourette syndrome, active seizure disorder or psychotic disorder 7. Girls who had reached menarche
Interventions	Methylphenidate type: immediate release and osmotic release oral system methylphenidate Mean methylphenidate dosage: OROS: 27.7 mg/day (SD 13.5); immediate release: 26.7 mg/day (SD 7.6) Administration schedule: OROS: once daily; immediate release: 3 times daily Duration of intervention: 28 days Treatment compliance: parents were required to record the time of drug administration on an adherence sheet. Pill counting was performed for each participant. Days forgetting to take medication: immediate release group 8.6 (SD 5.7); OROS group 2.0 (SD 3.9)
Outcomes	*Non-serious adverse events*: Barkley's Side Effects Questionnaire at baseline, on day 14 and day 28 Vital signs. At baseline, on day 14 and day 28
Notes	Sample calculation: no Ethics approval: IRB of National Taiwan University Hospital Funding/vested interest/authors' affiliations: the study was supported by Janssen-Cilag, Taiwan. Drs. Susan S.F. Gau and Wei-Tsuen Soong have conducted clinical trials on behalf of Janssen-Cilag, Taiwan and Eli Lilly and Company, Taiwan. They have also been speakers for Janssen-Cilag, Taiwan and Eli Lilly and Company, Taiwan Any withdrawals due to adverse events: no *Key conclusions of the study authors*: OROS methylphenidate has similar efficacy to immediate release methylphenidate, with less severity of decreased appetite. OROS methylphenidate is superior over immediate release methylphenidate in treating ADHD children and adolescents in the context of Chinese culture *Comments from the study authors*: the short study period limits our understanding regarding long-term efficacy of methylphenidate and the possible side effects on appetite, cardiovascular functioning, and so on in the Chinese population

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Gau 2006 *(Continued)*

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: yes

Supplemental information regarding IQ and diagnostic criteria received through personal email correspondence with the authors in October 2013 (Gau 2013 [pers comm])

Gau 2008

Methods	An observational national survey where all the children with bad adherence were switched to other medications among those OROS methylphenidate
Participants	*Cross-sectional study, phase 1*: Number of participants screened: not stated Number of participants included: 607 Diagnosis of ADHD: DSM-IV (subtype: combined (59.6%), hyperactive-impulsive (11.2%), inattentive (29.2%)) Age: mean 9.5 (SD 2.4), range 5-16 years old IQ: 89.5% had an IQ > 70 Sex: 504 males, 103 females Ethnicity: not stated Country: Taiwan Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Age 5-16 years old 2. Clinical diagnosis of ADHD based on DSM-IV criteria 3. Immediate release methylphenidate treatment for ≥ 3 of the preceding 6 months 4. Immediate release methylphenidate for the last month without severe adverse events or possible contraindications 5. Patients whose parent or guardian has signed and dated an informed consent to participate in the survey of drug compliance 6. Patients who are still in school *Exclusion criteria* 1. Systemic disease or clinically significant gastrointestinal problem, including narrowing (pathologic or iatrogenic) 2. Comorbid psychiatric disorders, except for conduct disorder and oppositional defiant disorder. *Cohort study, phase 2*: (Patients from phase 1 with bad adherence) Number of participants screened: 604 Number of participants included: 137

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Gau 2008 *(Continued)*

	Number followed up: 124 Number of withdrawals: 13 **The following d**ata are**on all patients from phase 2, n = 240.** Diagnosis of ADHD: DSM-IV (combined (60.8%), hyperactive-impulsive (8.3%), inattentive (30.8%)). Age: mean: 10.9 (SD 2.8), range: 5-16 years old IQ: 95% > 70% Sex: 198 males, 42 females Methylphenidate-naïve: none
Interventions	**Phase 1:** Methylphenidate type: immediate release Methylphenidate dosage: 18 mg Administration schedule: 3 times daily (n = 83), twice daily (n = 308), once daily (n = 162) Duration of intervention: st least 3 of the preceding 6 months Treatment compliance: poor adherence was defined as missing ≥ 1 doses on a school day on ≥ 2 days per week for 4 weeks. 240 patients defined as poor adherents **Phase 2** Methylphenidate type: osmotic release oral system Methylphenidate dosage: 24.9 mg Administration schedule: once daily Duration of intervention: 3 weeks or more Treatment compliance: not stated Patients who took IR-MPH 5 mg once, twice or thrice daily and IR-MPH 10 mg once, twice or thrice daily were switched to OROS-MPH 18 mg and 36 mg per day, respectively
Outcomes	Safety measures assessed by the investigators were decreased appetite, dizziness/headache, gastrointestinal disturbance, poor sleep quality, and other side effects *Non-serious adverse events*: 18.8% had poor adherence due to side effects
Notes	Sample calculation: no Ethics approval: approved by the Joint Institute Review Board, Taiwan, and the institutional review boards of each study site Funding/vested interest/authors' affiliations: the national health research institute.The work was supported by Janssen-Cilag, Taipai, Taiwan *Key conclusions of the study authors*: poor adherence to medication may be an important reason for suboptimal outcome in ADHD treatment, physicians should ensure adherence with therapy before adjusting dosage or switching medication *Comments from the study authors*: the investigator's judgement with respect to adherence was based on patient and parent reports of missed doses without pill count, therefore, overestimate of adherence

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Gau 2008 *(Continued)*

	is very likely. *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes, excluded children with previous experience of adverse events

Germinario 2013

Methods	A cohort study of 6- to 17-year-olds registered on the Italian ADHD National Registry from 2007 to June 2010 before beginning treatment with methylphenidate or atomoxetine (ATX) with follow-up to 24 months
Participants	**Patients with outcomes on cardiovascular measures** Number of participants screened: 840 Number of participants included: 351 Number of participants followed up: 214 at 6 months, 190 at 12 months, 77 at 24 months Nnumber of withdrawals: 137 at 6 months, 161 at 12 months, 274 at 24 months Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 10.41, range 6-17 years old IQ: not stated Sex: 305 males, 346 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Italy Comorbidity: not stated for methylphenidate subgroup Comedication: not stated Sociodemographics: not stated **Patients with outcomes on weight** Number of participants screened: 840 Number of participants included: 840 Number of participants followed up: 296 at 6 months, 184 at 12 months, 55 at 24 months Nnumber of withdrawals: 137 at 6 months, 161 at 12 months, 274 at 24 months Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 10.41, range 6-17 years old IQ: not stated Sex: 305 males, 346 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Italy Comorbidity: not stated for methylphenidate subgroup

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Germinario 2013 *(Continued)*

	Comedication: not stated Sociodemographics: not stated Number of patients screened: 840, number included: 840 followed up: 296 at 6 months, 184 at 12 months, 55 at 24 months number of withdrawals: 544 at 6 months, 656 at 12 months, 785 at 24 months The rest of the demographic data regarding the sample were described together with the atomoxetine group, and therefore this data are not extracted **Patients with outcomes on height** Number of participants screened: 840 Number included: 840, number followed up: 288 at 6 months, 167 at 12 months, 55 at 24 months, number of withdrawals: 552 at 6 months, 673 at 12 months, 785 at 24 months The rest of the demographic data regarding the sample were described together with the atomoxetine group, and therefore this data are not extracted. All met DSM-IV diagnostic criteria for ADHD **Patients from the Campania Region** Number of patients screened: 8, number included: 8, number followed up: 5, number of withdrawals:3 The rest of the demographic data regarding the sample were described together with the atomoxetine group, and therefore this data are not extracted **Patients from the Lombardy Region** The national ADHD Registry contained data on 1733 patients treated with MPH or atomoxetine between June 2007 and May 2010. Number included: 229 were enrolled from 15 regional centres, 130 of these were drug-naïve. Regarding the 130 drug naïve, 34 of these received MPH Number included: 34 number followed up: 34, number of withdrawals: 10 DSM-4 diagnosis of ADHD: combined (79.4%), hyperactive-impulsive (8.8%), inattentive (11.8%). Age (mean, 10.7 years). IQ: 2 participants had mental retardation. Sex (m: 28, f: 6), MPH-naïve (100%). Ethnicity: not stated. Country: Italy. Comorbidity (type: % learning disorders 14, ODD 14, language disorder 5, mental retardation 2), comedication: 7 patients, sociodemographics: 2 were adopted, 11 only child **Article on adverse events** Number of patients screened: not stated, number included: 1098 followed up: 931 number of withdrawals: 167 Subtype: (combined, n = 941, inattentive = 124, hyperactivity, n = 32) *Inclusion criteria*: Patients aged 6 to 17 years with ADHD treated with atomoxetine or MPH who were registered with the Italian ADHD National Registry from 2007 onwards To be diagnosed with ADHD, participants had to present with significant functional impairment and symptoms had to be present before 7 years of age, persist for ≥ 6 months, be present in more than one setting *Exclusion criteria*: Other mental or spectrum disorder; altered baseline ECG or no ECG assessment; or no information on drug therapy, only 1 follow-up, or follow-up of < 6 months
Interventions	902/1758 were treated with oral MPH chlorohydrate (Ritalin) 10 mg tablet at a dose of 0.3-0.6 mg/kg/dose/day. The total daily dose (mean 18.4 mg) could be administered in 2-3 doses per day at the discretion of the child's neuropsychiatrist. Duration of intervention: see under 'Description of participants'. A

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Germinario 2013 *(Continued)*

	methylphenidate test dose of 0.3 mg/kg was administered first and the dosage increased up to 0.6 mg/kg/dose depending on clinical response and tolerability Treatment compliance: adherence to treatment was not evaluated. But participants with compliance problems were excluded Regarding the sample from the Lombardy Region MPH dosage: mean MPH dosage: 39.9 mg. Administration schedule: both stated. Duration of intervention: treatment compliance: daily dose of MPH ranged from 10 mg to 75 mg. All participants were drug-naïve
Outcomes	*Serious adverse events*: 11 experienced serious adverse reactions Arrhythmia *Non-serious adverse events*: BP and HR were assessed monthly ECG assessed at baseline and every 6 months. Prolongation of QTc interval was defined as any prolongation with respect to detected value at the screening before the first administration of the drug. ECG with alterations or pathological aspects were read by paediatric cardiologist Liver status assessed every sixth month at the follow-up Suicidal thoughts assessed every sixth month at the follow-up Convulsion assessed every sixth month at the follow-up BMI assessed every sixth month at the follow-up Height and weight and BMI: monitoring was recommended monthly. The mean number of height measures per participant was 6.11, ranging from 1 to 33, whereas the mean number of weight measures per participant was 6.14 ranging from 1 to 33 Any events occurring for the first time as well as a worsening of the disorder while on the study drug were defined as adverse events. Parents were requested in advance to report any adverse events during follow-up visits **Sample from the Campania region** Participants were monitored for adverse events periodically by clinicians at the reference prescription centre at 1 week, 1 month, and every 3 months for the first year, and every 6 months thereafter, monitored by trained monitors. The median follow-up period was 289 days
Notes	*Sample calculation: y*es *Ethics approval:* approved by the Ethical Committee of the ISS Funding/vested interest: this study was supported by an independent grant n. FARM5AJL82_001 Italian Medicine Agency (AIFA) Any withdrawals due to adverse events: 30 patients dropped out due to adverse events Authors' affiliations: authors declare no financial interests Key conclusions of the study authors: regular monitoring of cardiovascular parameters (anamnestic history and BP and HR measurements) is recommended for all patients, but should be considered mandatory, perhaps at more frequent intervals, for participants at high risk. Furthermore; ADHD drugs show a negative effect on linear growth in children in middle term. Such effect appears more evident for ATX than for MPH. The study also suggests that ATX is more likely to be reported as causing harm than methylphenidate

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Germinario 2013 *(Continued)*

Comments from the study authors:

Limitations: it is not clear whether the observed slowdown in growth is a transient effect or a permanent potential reduction for individual growth with respect to the final height. As our observation time was only 24 months of follow-up, we were not able to evaluate if the negative effect on growth persisted after 24 months treatment. Second we could not assess if the negative effect observed on height would persist after permanent discontinuation of drugs. Third approximately 60% of participants could not be included in the analyses

Comments from Ruggiero 2012:

Among all the ATX- or MPH-base, most occurred in patients from Campania, probably because of our intensive monitoring program. During our study period, we introduced monitors who periodically and systematically interviewed clinicians at reference prescription centres. This was an active method to enhance the identification of adverse drug reactions (ADRs) by clinicians and to solicit them to report ADRs

Comments from the review authors:

In the description of participants, we have chosen to divide them up according to outcome. Many of the participants will be found in several of the descriptions according to outcomes

Exclusion of MPH non-responders/or children who have previously experienced adverse events on MPH: no

Supplemental information regarding additional data and additional publications received through personal email correspondence with the authors in December 2013 and January 2014. Asked authors how they distinguished between serious adverse events and serious adverse reactions. Answer from authors: "We have catalogued the events reported compulsorily Italian Drug Agency as Serious adverse events. The serious adverse reactions are severe events for which reporting was not mandatory. I acknowledge that is a classification unorthodox [sic]" (Panei 2014 [pers comm])

Gerwe 2009

Methods	An 8-week, multicentre, prospective, open-label, single-arm, non-interventional trial with 2 groups: 1. Transition from immediate release methylphenidate to osmotic release oral system methylphenidate 2. Initiation of OROS methylphenidate
Participants	Number of participants screened: 313 Number of participants included: 306 Number of participants followed up: 263 Number of withdrawals: 43 (14.1%) discontinued prematurely due to adverse events (n = 37, 12.1%), and/or lack of efficacy (n = 23, 7.5%), lost to follow-up (n = 2), non-compliant (n = 2), gave other reasons (n = 8) Diagnosis of ADHD: ICD-10 (F90.0 (72.5%), F90.1 (34.3%), F90.8 (1.6%), F90.9 (3.3%), others (9.2%)). Age: 10.2 (SD 2.3), range 6-14 years old IQ: not stated Sex: 246 males (80.4%), 60 females (19.6%) Methylphenidate-naïve: 24.5% Ethnicity: not stated Country: Germany

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Gerwe 2009 *(Continued)*

	Setting: outclinic Comorbidity: 38.6%. Conduct disorder 25.5%, conduct disorder with ODD 24.2%, anxiety disorder 5.6%, OCD 1.3% Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Male or female patients 2. 6-14 years old 3. ADHD diagnosis according to ICD-10 4. OROS-methylphenidate therapy already planned by treating physician (initiation of OROS-methylphenidate therapy or transition from immediate release to OROS-methylphenidate) 5. The patients were allowed to be pre-treated with immediate release methylphenidate preparations once to thrice daily
Interventions	Methylphenidate type: osmotic release oral system Methylphenidate dosage, whole sample: 36 mg/day (median), 29.5 (SD 12.7) mg/day starting dose, 32.8 (SD 13.2) mg/day final dose, range: 18-72 mg/day. Methylphenidate dosage, switch treatment subgroup: 31.6 (SD 12.7) mg/day starting dose, 34.4 (SD 13.5) mg/day final dose Methylphenidate dosage, initial treatment subgroup: 22.8 (SD 10.0) mg/day starting dose, 27.8 (SD 10.8) mg/day final dose Administration schedule: once daily Duration of intervention: 55 (SD 17.1) days, range 6-113 days Treatment compliance: 2 patients discontinued due to lack of compliance
Outcomes	Documentation of adverse events at week 1, 2 and 8 or premature termination. Measurement of blood pressure and pulse frequency and ratings of quality of sleep and appetite on Likert scales from 1 (very good) to 5 (very bad) at baseline, week 1, 2 and 8 or premature termination. Measurement of height, weight and documentation of tics at baseline and week 8 or premature termination. All ratings were performed by the treating physician. Measuring instruments for the documentation of adverse effects and tics are not stated *Non-serious adverse events*: A total of 319 adverse events were reported by 160 (52.3%) of 306 patients. For 161 of 319 adverse events (50.5%) in 95 patients (31%) a causal relationship between the administration of OROS methylphenidate and the event was assessed as at least possible by the investigator *Serious adverse events*: 4 serious adverse events were reported in 2 patients
Notes	Sample calculation: not stated Any withdrawals due to adverse events: 37 Ethics approval: the International Ethics Committee of the University of Freiburg, Germany Funding: this study was supported by Janssen-Cilag GmbH, Germany Authors' affiliations: authors are employees of Janssen-Cilag or have received consulting fees

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Gerwe 2009 *(Continued)*

Key conclusions of the study authors: transitioning from immediate release methylphenidate or no methylphenidate-treatment to OROS-methylphenidate in patients aged 6-14 years with a diagnosis of ADHD was associated with significant improvements in daily functioning in several areas of life, severity of disease and quality of life

Comments from the study authors: no further information about dosage or dosing regimen of a prior MPH treatment. Neither standardised diagnostic procedures nor a pre-defined titration scheme were performed. No specification for transition period from MPH-IR to OROS-MPH was made. Methylphenidate-naïve patients experienced somewhat more adverse effects, especially insomnia and anorexia, which probably also led to the slightly larger mean decreases in weight and tendencies to impaired quality of appetite and sleep, compared to the switch treatment group

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no

Ghanizadeh 2008a

Methods	A patient report of decrease in appetite during treatment with methylphenidate
Participants	Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 8.5 years old IQ: about 100 to 110 Sex: male Ethnicity: not stated Country: Iran Comorbidity: oppositional defiant disorder Comedication: not stated Sociodemographics: not stated
Interventions	MPH dosage: 20 mg daily Administration schedule: not stated Duration of intervention: 1 month Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Significant decrease in appetite
Notes	Ethics approval: informed consent was obtained Funding/vested interests: not stated *Key conclusions of study authors*: this report is about a child with ADHD who experienced insomnia, night terrors, and depression associated with the long-term use of clonidine. He revealed resolution of insomnia and night terror when clonidine was removed *Comments from the review authors*: the adverse effects (decrease in appetite) occurred while the patient was only getting methylphenidate

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Ghanizadeh 2008a *(Continued)*

	Supplemental information regarding IQ was retrieved through personal email communication with the author in July 2013 (Ghanizadeh 2013 [pers comm])

Ghanizadeh 2008b

Methods	A patient report of nocturnal enuresis during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 11 years old IQ > 80 Sex: male Ethnicity: Persian Country: Iran Comorbidity: no Comedication: not stated Sociodemographics: not stated
Interventions	Methylphenidate dose: 20 mg/day, 2 months. Discontinuation of methylphenidate for 1,5 months. Re-administering of methylphenidate, 20 mg/day, 3 months Discontinuation of methylphenidate, some months. Re-administering of methylphenidate, 20 mg/day, 2 months. Discontinuation of methylphenidate Type of methylphenidate: not known Administration schedule: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Methylphenidate titrated to 20 mg/day: nocturnal enuresis Discontinuation of methylphenidate: enuresis stopped immediately Methylphenidate, when titrated to 20 mg/day: immediate re-occurence of nocturnal enuresis Discontinuation of MPH: enuresis stopped immediately Methylphenidate, when titrated to 20 mg/day: immediate re-occurence of nocturnal enuresis Discontinuation of MPH: enuresis stopped immediately
Notes	Ethics approval: not stated Funding/vested interests: not stated *Key conclusions of study authors*: clinicians should be aware of this potential side effect of methylphenidate *Comments from the study author*: although both the boy and his mother were interviewed to obtain precise information, it should be noted that the boy may be suffering from a non-standard type of enuresis or the parents may be biased to see a connection between drug and enuresis that does not exist. Future researches are necessary to study if there is any possible association

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Ghanizadeh 2008b *(Continued)*

	Supplemental information was received through personal email correspondence with the author in July 2013 (Ghanizadeh 2013 [pers comm])

Ghanizadeh 2008c

Methods	A patient report of bilateral photophobia during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (K-SADS-PL) (subtype: combined) Age: 7 years old IQ > 80 Sex: male Ethnicity: Persian Country: Iran Comorbidity: no (no history of general medical condition such as albinos or migraine headache, neither in the child nor in the parents. No positive history of head trauma, and the patient never wore contact lenses. No pathological findings on physical examination by an ophthalmologist) Comedication: no Sociodemographics: not stated
Interventions	Methylphenidate type: not known Methylphenidate dosage: 35 mg/day Administration schedule: not stated Duration of intervention: 1 year with discontinuation ≥ 3 times of 3 months each Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Photophobia, occurring a few days after initiation of methylphenidate treatment Discontinuation of methylphenidate ≥ 3 times with no symptoms of photophobia Re-administration of methylphenidate: immediate reoccurrence of photophobia
Notes	Ethics approval: not stated Funding/vested interests: not stated *Key conclusions of study authors*: to the authors' knowledge, no report of methylphenidate-related photophobia has been found. This is the first report of methylphenidate-associated photophobia. Although the underlying pathophysiology cannot be defined in a patient report, this possible side effect should be considered in patients on methylphenidate *Supplemental information* was received through personal email correspondence with the author in July 2013 (Ghanizadeh 2013 [pers comm])

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Ghanizadeh 2009

Methods	A patient report of excessive talking during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 5 years old IQ: > 70 Sex: male Ethnicity: not stated Country: Iran Comorbidity: no Comedication: no Sociodemographics: not stated
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 10 mg/day Administration schedule: not stated Duration of treatment: about 7 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Mother and nursery teacher complained about increased hypertalkativity starting about 45 minutes after taking medication. The increased hyper-talkativity continued for about 3-4 hours. They scored hypertalkativity as 7-9 on a 1-10 visual analogue scale (10 is maximum) Re-challenge was conducted more than 20 times and hyper-talking reoccurred every time he took the medication
Notes	Ethics approval: not stated Funding/vested interests: not stated *Key conclusions of study authors*: this is a report of excessive talking after taking methylphenidate in a child with ADHD. Further research is necessary to study if there is any possible association

Ghanizadeh 2012

Methods	Double-blind, placebo controlled parallel trial 1. Methylphenidate + nortriptyline 2. Methylphenidate + placebo Investigating the efficacy, tolerability, and adverse effects of nortriptyline for treating enuresis in children with ADHD. No control/no-intervention group
Participants	Number of patients screened: 45 Number included in trial: 43

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Ghanizadeh 2012 *(Continued)*

	Number included in placebo group: 16 First follow-up in placebo group: 13 Number of withdrawals in placebo group: 3 Second follow-up in placebo group: 13 Lost to final evaluation in placebo group: 1 Final evaluation in placebo group: 12 Diagnosis of ADHD: DSM-IV-TR (subtype: not stated) Age: mean: 8.9, range: 5-14 years old IQ: above 70 Sex: 34 males, 9 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: Iran Comorbidity: primary enuresis (100%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Children diagnosed with both ADHD and primary enuresis 2. 5-14 years old 3. Both genders 4. Written consent from parents *Exclusion criteria* 1. Any major psychosocial stressors 2. Urinary complaints 3. Concurrent behaviour therapy for enuresis (desmopressin or carbamazepine) 4. Enuresis alarms 5. Concurrent behaviour therapy for enuresis 6. Fluid-intake restriction during the clinical trial 7. Clinically estimated mental retardation 8. Active medical problems such as hepatic, renal, cardiac, or pulmonary dysfunction 9. Urinary tract infection in the last month 10. Urinary urgency and frequency 11. Enuresis due to an underlying condition, such as diabetes
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 20 mg/day (< 30 kg), 30 mg/day (> 30 kg) Administration schedule: not stated Duration of intervention: 45 days Treatment compliance: not stated
Outcomes	Spontaneously reported adverse events

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Ghanizadeh 2012 *(Continued)*

	Systematically reported using a checklist, at baseline and 2 weeks and 4 weeks after onset of interventions, and 2 weeks after stopping the interventions
	Bedwetting, parent rated, daily
Notes	Sample calculation: not stated
	Ethics approval: yes, Shiraz University of Medical Sciences
	Funding: the author received a grant
	Vested interest/authors' affiliations: not stated *Key conclusions from study authors*: nortriptyline decreases the frequency of enuresis in the children with ADHD and its effect disappears after the discontinuation of treatment *Comments from the study authors*: the sample size was relatively small and may result in type II errors. In addition, all children were diagnosed with ADHD and formed a clinical sample. Therefore, the results of this study cannot be generalised to other settings, such as a community sample. There was a predominantly higher number of boys than girls, and also it is not clear whether these results can be generalised to other age groups. In the literature there are contradictory reports about the relationship between enuresis and sociodemographic factors. Therefore, it is questionable whether the findings of this study can be applied to other cultures. This current trial was short-term, and the children had not received an enuresis alarm or desmopressin. Therefore, they were not therapy-resistant children.
	Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: not stated
	Supplemental information received through personal email correspondence with the authors in June 2014 (Ghanizadeh 2014 [pers comm])

Ghanizadeh 2013

Methods	An 8-week parallel trial with 2 arms: 1. Methylphenidate and folic acid 2. Methylphenidate and placebo
Participants	Number of patients screened: not stated
	Number included: 49
	Number randomised to methylphenidate + placebo: 26
	Number randomised to methylphenidate + folic acid: 23
	Number followed up in methylphenidate + placebo: 13
	Number of withdrawals in methylphenidate + placebo: 13
	Methylphenidate + placebo group
	Diagnosis of ADHD: DSM-IV (subtype: not stated)
	Age: mean 9.9, range 5-16 years old
	IQ: no estimated mental retardation
	Sex: 23 males, 3 females
	Methylphenidate-naïve: not stated
	Ethnicity: not stated

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Ghanizadeh 2013 *(Continued)*

	Country: Iran Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Diagnosis of ADHD according to DSM-IV 2. Aged 5 to 16 years 3. Children and parents providing informed consent *Exclusion criteria* 1. Self-reported allergic reaction to folic acid 2. Kidney disease, estimated mental retardation, mild pervasive developmental disorder, infection, anaemia, alcoholism or epilepsy 3. Being on dialysis 4. Taking medication such as phenytoin, methotrexate, nitrofurantoin, tetracycline, barbiturates, such as phenobarbital, and antiepileptic medication such as phenytoin or primidone 5. Diagnosed psychotic disorder or diagnosed mood disorder 6. Other conditions that preclude participation (or increase risk) in the clinical trial (Type 1 diabetes mellitus, metabolic diseases, gastro-intestinal disorders affecting nutrient absorption, cancer) 7. Extensive use of nutritional folic acid supplements within the previous 3 months 8. Behaviour therapy or any other psychotherapy in the last 3 months or during the study
Interventions	Methylphenidate type: not stated Mean MPH dosage: 10 mg/day (< 25 kg) and 20 mg/day (> 24 kg) Administration schedule: twice daily Duration of intervention: 2 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Self-reported measures upon dropout from study
Notes	Sample calculation: yes Ethics approval: approved by the Shiraz University of Medical Sciences Ethics Committee Funding/vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: considering the marked limitations of this trial, this report suggests that methylphenidate may improve ADHD symptoms and the quality of life of children with ADHD. Current evidence does not support that folic acid as an adjuvant is effective for treating ADHD symptoms or aggression, or improving quality of life of children with ADHD *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Goetz 2011

Methods	A patient report of nocturnal visual hallucinations during methylphenidate treatment

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Goetz 2011 *(Continued)*

Participants	Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 7 years old IQ: no mental retardation Sex: female Ethnicity: not stated Country: Czech Republic Comorbidity: oppositional defiant disorder Comedication: not stated Sociodemographics: not stated
Interventions	Methylphenidate type: osmotic release oral system (OROS) Methylphenidate dosage: 18 mg/day Administration schedule: once daily Duration of treatment: 2.5 months Treatment compliance: not stated
Outcomes	*Serious adverse events*: Complex nocturnal visual hallucinations that persisted for 3 hours. No recurrence of hallucinations occurred after methylphenidate was withdrawn *Non-serious adverse events*: Mild abdominal pain and decreased appetite
Notes	Ethics approval: not stated Funding/vested interest: supported by Charles University Grant GAUK 383/2010 Authors' affiliations: Dr Goetz received research support, travel support and was speaker for Janssen and Lilly (stated in a 2012 paper) *Key conclusions of study authors*: careful sleep history should be taken before treatment, and reevaluated in the course of therapy, especially when the dose is increased, or switched to long acting formulas

Goez 2012

Methods	A randomised, double-blind, cross-over study design where participants were randomly assigned to receive a single dose of either 1. Modafinil (100 mg); or 2. Methylphenidate (10 mg) Follow-up 90 minutes
Participants	Number of participants screened: not stated Number of participants included: 28 Number of participants followed up: 28

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Goez 2012 *(Continued)*

	Number of withdrawals: none Diagnosis of ADHD: DSM-IV (subtype; combined (100%)) Age: mean 10.1 years, range 6-15 years old IQ: > 70 Sex: 26 males, 2 females Country: Canada and Israel Methylphenidate-naïve: not stated Ethnicity: not stated Comorbidity: no major psychiatric conditions Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Children and adolescents aged 6 to 15 years with classic combined subtype ADHD (DSM-IV) and a score of ≥ 65 on the parent and teacher-rated Conners Rating Scale *Exclusion criteria* 1. Children and adolescents with DSM-IV major psychiatric conditions, mental retardation, autism spectrum disorder, epilepsy, heart disease, hypertension, sleep disorders, Steven Johnson syndrome or hypersensitivity to modafinil, methylphenidate or other psychostimulants
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 10 mg Administration schedule: single dose Duration of treatment: single dose Wash-out: 2 weeks for those who received modafinil first Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Patients and their families were subsequently contacted and requested to report any adverse effects that might have occurred 7 participants (25%) reported adverse events, including abdominal pain, diarrhoea, hyposomnia, and headaches. All adverse events were minimal and resolved spontaneously All appear to have been rated up to 90 minutes following administration of methylphenidate
Notes	Sample calculation: not stated Ethics approval: yes Funding: the authors received no financial support for the research, authorship, and/or publication of this article Vested interests/authors' affiliations: the authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Goez 2012 *(Continued)*

Key conclusions of the study authors: Modifinil may serve as an effective alternative treatment for ADHD in paediatric patients who do not respond well to methylphenidate or other stimulants

Comments from the study authors: adverse events for both agents were mild and self-limited. The study do not provide any information on long-term drug effects and long-term adverse effects. Furthermore, small number of participants and even smaller number of participants for whom numerical scores could be obtained.

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: participants who have had an hypersensitivity reaction to either drug were excluded

Supplemental information regarding the protocol and side effects requested from the study authors in October 2013 with no reply

Golubchik 2011

Methods	A cohort study assessing methylphenidate use for 12 weeks on symptoms of ADHD and comorbid trichotillomania
Participants	Number of patients screened: not stated Number included: 9 Number followed up: 9 Number of withdrawals: none mentioned Diagnosis of ADHD: DSM-IV-TR (subtype: not stated) Age: mean 11.6, range 6-18 years old IQ: no mental retardation Sex: 3 males, 6 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: Israel Comorbidity: trichotillomania (100%), tic disorder (n = 1) Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. DSM-IV-TR criteria for both trichotillomania and ADHD *Exclusion criteria* 1. Psychotic disorders, neurological diseases, movement disorders, autistic spectrum disorders, mental retardation, or any other severe physical disorder 2. History of moderate or severe adverse events, related to previous methylphenidate treatment
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 0.5-0.7 mg/kg

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Golubchik 2011 *(Continued)*

	Administration schedule: not stated Duration of intervention: 12 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Self-reported by patient. Not clear if it was throughout 12-week period or at specific time points Loss of appetite, headache, excessive preoccupation with one's hair, abdominal pain, motor tic exacerbation
Notes	Sample calculation: no Any withdrawals due to adverse events: no Ethics approval: yes, approved by Mental Health Center institutional review board Funding/vested interest/authors' affiliations: not stated *Key conclusions of the study authors*: some efficacy of methylphenidate treatment was shown in trichotillomania patients with low rate of stressful life events. A large scale study is mandatory to evaluate the efficacy of methylphenidate for trichotillomania in ADHD/trichotillomania patients *Comments from the study authors*: the main limitations of this study are the open-label design, the small sample size (N = 9), and the relatively short treatment duration (12 weeks) *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes, exclusion of those with history of moderate or severe adverse events to methylphenidate

Gracious 1999

Methods	A patient report of atrioventricular nodal re-entrant tachycardia during stimulant treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 13 years old IQ: > 70 Sex: female Ethnicity: African American Country: USA Comorbidity: obsessive compulsive disorder and dysthymia Comedication: 50 mg/day sertraline Sociodemographics: not stated
Interventions	**First prescription** Methylphenidate type: not stated Methylphenidate dosage: 30 mg Administration schedule: twice daily: morning and noon

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Gracious 1999 *(Continued)*

	Duration of treatment: 3 months Treatment compliance: noncompliant with the afternoon dose **Second prescription** Methylphenidate type: sustained release methylphenidate Methylphenidate dosage: 20 mg Administration schedule: once daily: morning Duration of treatment: 11 months Treatment compliance: intermittently compliant
Outcomes	**First prescription** No serious or non-serious adverse events reported **Second prescription** *Serious adverse events*: After 5 months of treatment; 2 15-minute episodes of chest pain, associated with tingling in her fingers and shortness of breath. Heart rate: 96. Blood pressure: 155/79. 1 month later chest pain, shortness of breath, sweating, and palpitations beginning during urination. Heart rate: 100 No cardiac complaints in the following 5 months
Notes	Funding/vested interests: none Authors' affiliations: Division of Child Psychiatry, Case Western Reserve University, University Hospitals of Cleveland, Cleveland, Ohio *Key conclusions of the study authors*: stimulant medication may evoke onset of atrioventricular nodal tachyarrhythmias in patients who have the potential to develop them, possibly in combination with a selective serotonergic reuptake inhibitor *Comments from the study authors*: the cardiologist consulted believed this patient had a structural vulnerability of genetic etiology for the arrhythmia which was then precipitated by the stimulant *Supplemental information* regarding ADHD diagnostic criteria and IQ received through personal email correspondence with the authors in October 2013 (Gracious 2013 [pers comm])

Grcevich 2001

Methods	This retrospective review of medical charts compares the efficacy, safety, dosing frequency, and medication switch rates of Adderall with methylphenidate in children and adolescents with ADHD treated in a private, outpatient psychiatric clinic over 1992 to 1998. Of the evaluable patients, 54 received Adderall, and 75 received methylphenidate
Participants	Number of participants screened: not stated Number of participants included: not stated Number of participants followed up: 75 Diagnosis of ADHD: DSM-IIIR or DSM-IV (without hyperactivity: 12, with hyperactivity: 62) Age: mean 10.2 years old

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Grcevich 2001 *(Continued)*

	IQ: not stated Sex: 58 males, 16 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: USA Comorbidity: disruptive behaviour: 9, depressive disorder: 7, anxiety disorder: 1, communication disorder: 4, impulse control disorder: 1, Asperger's: 1, other disorders: 7 Comedication: no additional ADHD medications Sociodemographics: not stated *Inclusion criteria* 1. Children and adolescents with ADHD receiving Adderall or methylphenidate and were treated in a private, outpatient psychiatric clinic between 1992 and 1998 *Exclusion criteria* 1. Patients presenting for initial evaluation only or receiving ADHD medications other than methylphenidate or Adderall
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage: 27 mg/day Administration schedule: not stated Duration of treatment: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Different types of non-serious adverse events
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interests: funded by Shire Redwood Inc. *Key conclusions of the study authors*: Adderall and methylphenidate provided comparable efficacy and safety in children and adolescents with ADHD *Comments from the study authors*: the population examined may be poorer responders to ADHD treatment than the general population. *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* regarding IQ received October 2013 (Grcevich 2013 [pers comm])

Green 2011

Methods	A 6-month follow-up study of participants continuing methylphenidate treatment following a 1-day, randomised parallel trial with 2 arms:

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Green 2011 *(Continued)*

	1. Immediate release methylphenidate 2. Placebo
Participants	Number of participants screened: 34 Number of participants included: 16 Number of participants followed up: 15 Number of withdrawals: 1 **Patients participating in the 1-day RCT** Diagnosis of ADHD: DSM-IV-TR (subtype: combined (33.3%), inattentive (50%), not otherwise specified (17.7%)) Age: mean 11.1 (SD 3.7) years old, range: 5-20 years old IQ: mean 81.4 Sex: 20 males, 14 females Methylphenidate-naïve: 61.8% Ethnicity: not stated Country: Israel Comorbidity: 8 (53.3%) had a psychiatric co-morbidity, including specific phobia (n = 4), ODD (n = 4), generalised anxiety disorder (n = 3), and eating disorder not otherwise specified (n = 1). Comedication: none of the participants was on any other psychotropic medication during the study period. Sociodemographics: not stated *Inclusion criteria*: not stated
Interventions	RCT: participants were randomly assigned to MPH or placebo. Mean MPH dosage: 15.7 (SD 5.6) mg (0.5 mg/kg). Administration schedule: once. Duration of intervention: 1 day. Titration period: no mention. Washout prior to study initiation: 3 days. Treatment compliance: not stated Follow-up: not stated Methylphenidate type: not stated Mean methylphenidate dosage: not stated Administration schedule: not stated Duration of treatment: 6 months Treatment compliance: 1 withdrew due to poor compliance.
Outcomes	*Non-serious adverse events*: Barkley Side Effects Rating Scale (modified Hebrew version) parent rated at 24 hours after methylphenidate administration and at 6-month follow-up The most common side effects after 6 months of treatment included poor appetite (93.7%), headache (66.6%), and stomachache (56.2%) None of the patients exhibited psychotic symptoms or manic, hypomanic exacerbation during the 6-month study period

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Green 2011 *(Continued)*

Notes	Sample calculation: not stated Any withdrawals due to adverse events: no Ethics approval: the study protocol was approved by the Institutional Review Board of Rabin Medical Center Funding/vested interests: no institutional or corporate/commercial relationships for the past 36 months that might pose a conflict of interest *Key conclusions of the study authors*: the use of methylphenidate in children with velocardiofacial syndrome (VCFS) appears to be effective and relatively safe. A comprehensive cardiovascular evaluation for children with VCFS before and during stimulant treatment is recommended *Comments from the study authors*: "we found that all participants (100%) with VCFS treated with methylphenidate exhibited ≥ 1 side effect". "The rate of all side effects immediately observed following initiation of treatment remained similarly high after 6 months of treatment". "Thus, according to our findings, it seems that in children with VCFS, tolerance did not develop to methylphenidate side effects". However, none of the children withdrew due to side effects Exclusion of MPH non-responders/or children who have previously experienced adverse events on MPH: no *Supplemental information* regarding ADHD diagnostic criteria and safety data (from the study sample excluding participants over 18 years of age or with an IQ below 70, or both), were received through personal email correspondence with the authors in November 2013 (Green 2013 [pers comm])

Greenberg 1987

Methods	A 6 week non-randomised controlled before-after study
Participants	Number of participants screened: not stated Number of participants included: 50 Number of participants followed up: 49 Number of withdrawals: 1 Diagnosis of ADHD: DSM-III (subtype: not stated) Age: mean 9.6, range 6-15 years old IQ: > 70 Sex: 32 males, 18 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: the children were predominantly from intact, middle class suburban families *Inclusion criteria* 1. DSM-III diagnosis of ADD

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Greenberg 1987 *(Continued)*

	2. Over 10 years old
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage: regarding 41 responders: 0.33 mg/kg/dose to 0.5 mg/kg/dose (mean 0.4 mg/kg) Administration schedule: twice daily Duration of intervention: 6 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Of the 50 participants, 8 experienced minor, transient side effects (appetite or sleep problems) and medication was terminated for 1 participant who experienced headaches associated with increased blood pressure and tachycardia
Notes	Sample calculation: no Ethics approval: not stated Funding/vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: not relevant *Supplemental information* has not been possible to retrieve due to lack of contact information

Greenhill 1983

Methods	A 2-night polysomnographic study of children with ADHD before and after 6 months of methylphenidate treatment
Participants	Number of participants screened: not stated Number of participants included: 9 Number of participants followed up: 7 Number of withdrawals: 2 Diagnosis of ADHD: DSM-III (subtype: not stated) Age: mean 8.6 years (range 6.7-10.7) IQ: > 70 Sex: 9 males Methylphenidate-naïve: none Ethnicity: white: 3, Black: 4, Hispanic: 0 Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: all children were living at home with one or more parents *Inclusion criteria*

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Greenhill 1983 *(Continued)*

1. ADHD diagnosis according to DSM-III
2. Parents had to rate the global severity of their child's behaviour disorder on the Conners' Parent Questionnaire (CPQ) in the moderate to severe range
3. Children had to score 1.8 or higher on hyperkinetic factor 4 of the Conners' Teacher Questionnaire (CTQ)
4. IQ > 70
5. After initial acceptance, children had to demonstrate ≥ 25 % decrease in summary score on the 10-item abbreviated Conners' Rating Scale (ACRS), during an open 2-week trial of MPH

Exclusion criteria

1. Children with seizure disorders, psychosis, endocrine abnormalities, manic depressive disorders, pervasive developmental, or major neurological disorders

Interventions	Mean methylphenidate dosage: 1.37 mg/kg/day by the end of 6 months Administration schedule: 3 times daily Duration of intervention: 6 months 2 weeks washout period off methylphenidate before entering study. Ongoing titration until satisfied dose was obtained
Outcomes	*Non-serious adverse events*: Side effect questionnaire - rated monthly by a physician Polysomnographic tests: total sleep time, sleep period time, sleep latency, sleep REM time, awake time, mean REM period length, mean REM period cycle, sleep effects All sleep parameters were recorded during a 48-hour stay in a sleep unit. The sleep parameters were recorded pre-drug (run 1) and on drug (run 2)
Notes	Sample calculation: no Ethics approval: not stated Funding: National Institute of Mental Health *Key conclusions of the study authors*: across and within (pre-post) group comparisons showed that methylphenidate therapy was associated with delayed sleep onset, lengthened sleep, and changes in certain REM sleep variables *Comment from the study authors*: certain methodological problems limit the interpretation of these data, e.g. the ADHD sample was small and completely male. Most of the children did not have to be awakened since they were up before the catheter placement, but if some of the children were awakened, the total sleep for these participants is not correct. Furthermore, methylphenidate-nonresponders and partially responders are excluded *Supplemental information* requested twice through personal email correspondence with the authors in September 2013. No reply

Gross-Tsur 2004

Methods	A patient series of 3 children with ADHD who manifested hallucinations during methylphenidate treatment at low therapeutic doses
Participants	Diagnosis of ADHD: DSM-IV-TR (subtype: combined (33.3%), not stated (66.6%)) Age: 7, 12, 7½ years old

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Gross-Tsur 2004 *(Continued)*

	IQ: > 70 Sex: male Ethnicity: not stated Country: Israel Comorbidity: ODD (33%), cerebral palsy (33%), mild learning disabilities (33%) Comedication: not stated Sociodemographics: adopted (33%)
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 0.25-0.3 mg/kg, 7.5-10 mg Administration schedule: once daily Duration of treatment: 1 for a short period, 2 for several months/1 year Treatment compliance: not stated
Outcomes	*Serious adverse events*: Complex visual and haptic hallucinations **Case 1** Methylphenidate, 1 year: visual and haptic hallucinations starting around 1 hour after drug ingestion Placebo substitution of methylphenidate: immediate cessation of hallucinations > 2 years follow-up: no psychiatric symptoms reappeared **Case 2** Methylphenidate, short period: visual and haptic hallucinations starting 2 hours after drug ingestion, continuing for almost 2 hours Discontinuation of methylphenidate: no recurrence Re-challenge with methylphenidate: immediate recurrence of hallucinations 3-year follow-up: uneventful **Case 3** Methylphenidate, several months: visual and haptic hallucinations Discontinuation of methylphenidate: hallucinations ceased 2-year follow-up: no recurrence
Notes	Funding/vested interests: the authors received a 1-year research grant in excess of USD 10,000 from Novartis in 1997 Authors' affiliations: no other affiliations to pharmaceutical companies stated *Key conclusions of the study authors*: we describe 3 children with ADHD who were treated with low doses of methylphenidate and developed complex visual and haptic hallucinations *Comments from the study authors*: the causal role of methylphenidate in the development of hallucinations was based on their appearance after ingestion of the drug, resolving after its withdrawal, and the absence of psychiatric comorbidity that could explain such phenomena. In 1 patient, the hallucina-

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Gross-Tsur 2004 *(Continued)*

	tions reappeared after an inadvertent re-challenge. Because methylphenidate is a widely used, well-studied, and safe pharmacologic agent, physicians who prescribe methylphenidate should be aware of even rare adverse manifestations occurring at therapeutic doses *Supplemental information* regarding IQ and ADHD diagnostic criteria received through personal email correspondence with the authors in October 2013 (Shalev 2013 [pers comm])

Grossman 1985

Methods	A patient report on methylphenidate and idiopathic thrombocytopenic purpura (ITP)
Participants	ICD-9 diagnosis of ADHD (subtype: not known) Age: 7 years old IQ: > 70 Sex: female Ethnicity: white Country: USA Comorbidity: none Comedication: not stated Sociodemographics: not stated
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 10 mg Administration schedule: twice daily Duration of intervention: 7 months Treatment compliance: not stated
Outcomes	*Serious adverse events*: Idiopathic thrombocytopenic purpura: physical examination at the Pediatric Outpatient Department found countless petechiae over the entire dermal surface, most concentrated over her buttocks. Numerous areas of purpura were noted, especially over her buttocks and extremities. Multiple areas of buccal mucosal and gingival bleeding with a large haematoma presented on the left lateral surface of her tongue. Clotted blood was seen in her nostrils and ear canals bilaterally. Bone marrow aspiration showed normal to increased megakaryocytes with normal red and white cell precursors. Methylphenidate was stopped and the patient was admitted. After 1 week of treatment for the condition her petechia had begun to fade. She did not start on methylphenidate again. There has been no recurrence of petechiae or bruising 1 year later
Notes	Ethics approval: not stated Funding/vested interests: not stated *Key conclusions of study authors*: it is hoped that the report of this case will stimulate others to report their experience, or lack thereof, regarding the association of methylphenidate and idiopathic thrombocytopenic purpura. Because of the importance of this drug to the management of certain children with attention deficit disorder and its widespread use in thousands of children, it seems important to justify with data the current precaution that "periodic CBC, differential and platelet counts are advised during prolonged therapy" or eliminate the precaution as a recommendation to clinicians

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Grossman 1985 *(Continued)*

	Comments from the study authors: the authors describe, that the patient had a mild upper respiratory tract infection 2 weeks prior to the symptoms of ITP. They describe, it is highly possible that in the case just presented the aetiology of the patient's idiopathic thrombocytopenic purpura may well have been her preceding upper respiratory tract infection rather than the methylphenidate, which she had taken without difficulty for 7 months prior to the onset of her haematologic disorder *Supplemental information* regarding ADHD diagnosis received through personal correspondence with the authors in July 2013 (Grossman 2013 [pers comm])

Gucuyener 2003

Methods	A cohort study assessing methylphenidate use amongst patients with ADHD and concomitant active seizures or EEG abnormalities
Participants	Number of participants screened: not stated Number of participants included: 119 (57 with epilepsy, 62 with abnormal EEG but no seizure activity) Number of participants followed up: 119 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 9.3, range 6-16 years old IQ: mean 92.3, range 79-112 Sex: 98 males, 21 females Methylpenidate-naïve: not stated Ethnicity: not stated Country: Turkey Comorbidity: epilepsy (47.9%) Comedication: antiepilepsy medication for those with epilepsy Sociodemographics: not stated *Inclusion criteria* 1. Diagnosis of ADHD according to DSM-IV criteria between June 1997 and June 2000 2. Diagnosis of epilepsy or EEG abnormalities without defined seizure
Interventions	Methylphenidate dosage: 0.3-1 mg/kg Administration schedule: initially once daily in the morning before school and titrated to twice a day (drug free on holidays) Duration of intervention: 12 months Treatment compliance: not stated
Outcomes	*Serious adverse events*: Seizure frequency, observer rated at 3 months intervals EEG findings, observer rated at 3 months intervals

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Gucuyener 2003 *(Continued)*

	No seizures were observed in any of the patients with ADHD and EEG abnormalities In the ADHD with seizures group, 1 patient's seizure type, generalised tonic clonic, changed to a complex partial seizure, but the number of seizures did not increase Only 5 patients had an increased seizure frequency in the ADHD with seizures group and none of the patients in the ADHD with EEG abnormalities group The number of abnormal EEGs with nonepileptic activity was decreased significantly at the end of the study in both groups (P = 0.05) *Adverse events*: Drug-related side effects
Notes	Sample calculation: no Ethics approval: not stated Funding/vested interests: not stated *Key conclusions of the study authors*: methylphenidate had a beneficial effect on EEG. Seizure frequency did not change from baseline. The side effects of methylphenidate were mild and transient. Methylphenidate is safe and effective in children with ADHD and concomitant active seizures or EEG abnormalities.The present data indicate that methylphenidate is a safe and effective agent in children with ADHD and active seizures of EEG abnormalities. Coadministration of methylphenidate and antiepilepsy drugs improves attention without any adverse effects on seizure threshold or EEG findings. We suggest that physicians give the combined medication to patients with ADHD and active seizures or abnormal EEG findings with close monitoring *Comments from the study authors*: EEG findings did not deteriorate when patients were on methylphenidate. There was a beneficial effect of methylphenidate of both EEG and seizure frequency. We observed these patients for only 1 year, and 57 epileptic patients were having active seizures. Therefore, the improvement in EEG and seizure frequency might not be completely attributable to maturation *Comments from the review authors*: all participants were on concomitant antiepilepsy medication *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated

Guerreiro 1996

Methods	A cohort study of methylphenidate treatment
Participants	Number of participants screened: not stated Number of participants included: 24 Number of participants followed up: 22 Number of withdrawals: 2 Diagnosis of ADHD: DSM-III diagnosis of ADHD (subtype: combined (around 80%), inattentive (around 20%)) Age: mean 9.1 years (range: 6.5-13) IQ: normal, learning appropriately in regular schools Sex: 20 males, 4 females

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Guerreiro 1996 *(Continued)*

	Methylphenidate-naïve: not stated Ethnicity: not stated Country: Brazil Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. DSM-III diagnosis of ADHD 2. Followed in a private clinic of 1 of the authors
Interventions	Initiation of immediate-release methylphenidate treatment: 5 mg once daily. Titrated if needed to a total maximum of 10 mg daily Administration schedule: once or twice daily. Treatment pause during weekends and holidays Duration of intervention: mean 12.6 months, range: 1 month - 3 years Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: The occurrence of adverse events were assessed by the family and teachers
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interests: not stated Authors' affiliations: the study was conducted at the Discipline of Child Neurology, Department of Neurology, Faculty of Medical Sciences (FCM), State University of Campinas (UNICAMP) *Key conclusions of the study authors*: the satisfactory and partial responses of methylphenidate treatment of ADHD observed in this study (79.1%) are in accordance with the literature, revealing therapeutic success in approximately 75% of the cases. We observed nausea and headache in 1 child, and only headache in another. Nausea can be controlled by lowering the dose; on the contrary, headache can be severe enough to result in cessation of treatment. Growth retardation is one of the possible side effects, which is of greater concern. Fortunately we did not observe this undesirable effect in our patients. *Comments from the study authors*: we might not have observed growth retardation in our study due to the use of low doses of methylphenidate and the recommendation of drug holidays *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* regarding ADHD subtype, IQ, and type of MPH received through personal email correspondence with the authors in December 2013 (Guerreiro 2013 [pers comm])

Gökce 2015

Methods	Case study
Participants	Number of participants screened: no data

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Gökce 2015 *(Continued)*

	Number of participants included: no data Number of participants followed up: no data Number of withdrawals: no data Diagnosis of ADHD: combined type ADHD Age: 12 IQ: no data Sex: male Methylphenidate-naïve: no data Ethnicity: no data Country: no data Comorbidity: no data Comedication: no data Sociodemographics: no data *Inclusion criteria*: no data *Exclusion criteria*: no data
Interventions	Methylphenidate type: extended release MPH Methylphenidate dosage: 27 mg from 10 years of age. Suicide attempt: 10 tablets of 36 mg ER-MPH Administration schedule: not stated Duration of intervention: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Physical examination: tachycardia and mildly increased blood pressure, respiration and heart rate had been determined Psychiatric examination: his mood was depressed, and tendency to sleep Laboratory tests, blood glucose level, blood urea nitrogen, creatinine, potassium (K), sodium (Na) and chloride (CL) were revealed normal The electrocardiography (ECG) parameters such as QRS duration, QT interval, R wave and PR interval were normal; however, the heart rate was elevated There was no central nervous system finding except irritability and agitation
Notes	No data

Haertling 2015

Methods	A prospective, multicentre, observational cohort study of long-acting methylphenidate use for 12 weeks
Participants	Number of participants screened: not stated

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Haertling 2015 *(Continued)*

	Number of participants included: 262 Number of participants followed up: not stated Number of withdrawals: 23 Diagnosis of ADHD: ICD-10 (subtype: combined (58%), hyperactive-impulsive (34%), inattentive (8%)) Age: mean 10.9 (SD 2.5) years old (range: 11-18) IQ: not stated Sex: 197 males, 63 females, 2 unknown Methylphenidate-naïve: 19.1% Ethnicity: not stated Country: Germany Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Definite ADHD diagnosis (DSM-IV criteria) 2. ADHD symptoms for ≥ 6 months having caused clinically significant impairment in ≥ 2 settings 3. Informed consent by parents and patients 4. Age: 11-18 years 5. Sufficient ability to read, write, communicate and understand the study procedures *Exclusion criteria* 1. Contraindications for methylphenidate
Interventions	Methylphenidate type: long-acting methylphenidate Methylphenidate dosage: start with 20 mg once daily and to adjust in weekly 10 mg increments to a maximum of 60 mg/day Administration schedule: once in the morning Duration of intervention: 12 weeks Treatment compliance: not stated
Outcomes	Measure method/instrument: AEs according to the Medical Dictionary for Regulatory Activities (MedDRA), version 13 A total of 63 AEs were reported in 36 (13.7%) patients. Severity was mild in 30.2%, moderate in 39.7%, and severe in 22.2% of AEs; 7.9% of data were missing. 28 patients had AEs believed to be treatment related (10.7%). By the end of the study, more than half of the AEs had resolved completely The most frequent AEs were loss of appetite, abdominal pain, and nausea. The most frequently affected System Organ Classes were metabolism and nutritional as well as psychiatric and nervous system disorders The number of AE per patient sums up to 4 adverse reactions in 1 patient throughout the whole treatment course (50.79% of all AEs) the outcome was 'resolved'. In 20 AE-cases (31.75%) the outcome was 'not yet resolved'. In 1 patient the outcome of the AE was not known *Serious adverse events*

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Haertling 2015 *(Continued)*

	3 (hospitalisation) (0.4% of patients) *Non-serious adverse events*: 60
Notes	Sample calculation: not stated Ethics approval: ethics committee approval Funding/vested interest: this study was initiated and sponsored by Novartis Pharma Germany. B Mueller is a full-time employee of Novartis Pharma GmbH, the market authorisation holder of Ritalin LA. F Haertling received honorariums during the participation of this study. O Bilke-Hentsch received honorariums as principle investigator of this study Authors' affiliations: Novartis Pharma *Key conclusions of the study authors*: Ritalin LA improved CGI and quality of life in children with ADHD under routine practice conditions *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated; however, children with poor response to previous treatment plans are included *Supplemental information* regarding IQ, comedication, comorbidity and additional AE tables requested through personal email correspondence with the authors in June 2016 (Mueller 2016 [pers comm]). The authors were not able to supply the information

Halevy 2009

Methods	A patient report of complex visual hallucinations during methylphenidate treatment
Participants	DSM-IV-R diagnosis of ADHD, combined type Age: 15 years old IQ: normal intelligence Sex: male Ethnicity: not stated Country: Israel Comorbidity: no (no past experience with drugs, smoking habit, or alcohol consumption. Normal physical and neurological examinations. Normal visual acuity. Electroencephalography (EEG) during a symptomatic state revealed no abnormalities and no evidence of epileptic activity) Comedication: not stated Sociodemographics: not stated
Interventions	**At 8 years of age:** Methylphenidate type: Ritalin Methylphenidate dose: 10 mg daily (0.3 mg/kg) Administration schedule: not stated Treatment compliance: not stated Discontinuation

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Halevy 2009 *(Continued)*

	Reintroduction of methylphenidate 7**years later** Methylphenidate type: not stated Methylphenidate dose: 0.15 mg/kg daily Administration schedule: not stated Treatment compliance: not stated
Outcomes	*Serious adverse events*: Hallucinations Several days after initiation of treatment: visual hallucinations of rats, accompanied by some tactile hallucinations. Only present during the time the patient was under the influence of methylphenidate and disappeared thereafter. Discontinuation: immediate complete resolution Reintroduction of methylphenidate treatment. After 2 days: same complex visual hallucinations. Discontinuation: immediate complete resolution
Notes	Funding/vested interest: the authors have no conflicts of interest to disclose with regard to this article *Key conclusions of the study authors*: the occurrence of hallucinations after a very low dose of methylphenidate on 2 occasions may suggest an idiosyncratic reaction. The phenomenon might also be explained by a drug-induced dysfunction of the monoamine transmitters *Comments from the study authors*: given the wide use of methylphenidate, clinicians should be aware of this possible side effect *Supplemental information* regarding IQ and diagnostic criteria received through personal email correspondence with the authors in August 2013 (Halevy 2013 [pers comm])

Hammerness 2009

Methods	An open-label, prospective, long-term study of osmotic release oral system methylphenidate for smoking prevention in adolescents with ADHD for 24 months
Participants	Number of participants screened: 203 Number of participants included: 154 Number of participants followed up: 30 Number of withdrawals: 124 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 15.3 years (range 12-18) IQ: > 75 Sex: 114 males, 40 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: USA Comorbidity: none Comedication: not stated

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Hammerness 2009 *(Continued)*

Sociodemographics: not stated

Supplementary data from a 6 months period during the main study

Number of participants screened: 152

Number of participants included: 114

Number of participants followed up: 57

Number of withdrawals: 57

Age: mean 14.1 years (range 12-18)

Sex: 83 males, 31 females

Inclusion criteria

1. Adolescent outpatients between 12 to 17 years of age
2. Participants with the DSM-IV diagnosis of ADHD, as manifested in the clinical evaluation and confirmed by structured interview, supplemented with structured diagnostic psychiatric interview using the Schedule for Affective Disorders and Schizophrenia for School Aged Children (KSADS-E)
3. Participants with sufficient current ADHD symptoms to warrant treatment, as measured by a Clinical Global Impression Severity Scale (CGI-S) score of greater than or equal to 4 (moderately ill); OR participants already on Concerta who are judged to be responders (CGI of 1-2) and who tolerate treatment well

Exclusion criteria

1. Any serious or unstable medical illness including hepatic, renal, gastroenterologic, respiratory, cardiovascular (including ischaemic heart disease, hypertension), endocrinologic, neurologic, immunologic, or haematologic disease
2. Clinically significant abnormal baseline laboratory values
3. History of seizures
4. Active tic disorder
5. Pregnant or nursing females
6. Mental retardation (IQ < 75)
7. Organic brain disorder
8. Eating disorders, psychosis, current episode of bipolar disorder, current depression > mild (CGI-S > 3), or current anxiety > mild (CGI-S > 3)
9. Substance abuse or dependence within the past 2 months
10. Recent change in non-monoamine oxidase inhibitor (MAOI) antidepressants (< 3 months)
11. Recent change in benzodiazepines (< 3 months)
12. Concerta non-responder
13. History of cardiovascular disease, including structural cardiac abnormalities

Participants were dropped from the study if in the investigator's opinion there was lack of efficacy, intolerable adverse events, and/or clinically significant laboratory values, pregnancy, clinical worsening, or noncompliance with the study protocol

Interventions	Methylphenidate type: osmotic release oral system Mean methylphenidate dosage: 63.1 mg at week 6 and 67.2 mg after 6 months Administration schedule: morning Duration of intervention: 24 months Treatment compliance: not stated
Outcomes	*Serious adverse events*:

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Hammerness 2009 *(Continued)*

	Adverse events were systematically recorded at each visit. Adverse events were assessed according to a general query by the treating physician, monitoring emergent and/or ongoing subjective complaints. Adverse effects were followed to resolution There were no serious adverse events or serious cardiovascular adverse events (AEs) in the first 6 months 10 of 114 participants reported ≥ 1 cardiovascular complaint Vital signs were collected as a single, first reading, typically 7 to 10 h after morning administration of medication, during after school office visits Participants with systolic blood pressure (SBP) or diastolic BP (DBP) readings (or both) at or above the 95th percentile for sex, age and height on ≥ 3 consecutive appointments were defined as hypertensive Participants with SBP and/or DBP readings above the 90th percentile for sex, age, and height on ≥ 3 consecutive appointments were defines as prehypertensive During OROS methylphenidate treatment 8% (n = 9/114) of the sample met our defined criteria for pre-hypertension and 6% (n = 7/114) of the sample met criteria for hypertension It seems the denominator being used for calculation of adverse event proportions below 154 came from the 2-year study on smoking. Incorporates 50 more participants than those studied in the present work *Non-serious adverse events* Different types of adverse outcomes
Notes	Sample calculation: no Ethics approval: approved by the Massachusetts General Hospital Institutional Review board. Funding: not stated Vested interests/authors' affiliations: the authors have several affiliations to the medical industry both as researchers, speakers, consultants, etc. *Key conclusions of the study authors*: treatment with relatively high doses of OROS methylphenidate was associated with small but statistically significant mean increases in BP and HR, primarily during the first 6 weeks of treatment, without clinically meaningful changes in ECG. These observations are consistent with previous reports using lower doses *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes

Hammerness 2012

Methods	A longitudinal treatment study, receiving daily doses of osmotic release oral system for 6 weeks
Participants	Number of participants screened: 27 Number of participants included: 20 Number of participants followed up: 10 Number of withdrawals: 10 Diagnosis of ADHD: DSM-IV-TR Age: mean 14.2, range 12-17 years old

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Hammerness 2012 *(Continued)*

IQ: > 75

Sex: not stated (majority males)

Methylphenidate-naïve: 10%

Ethnicity: not stated

Country: USA

Comorbidity: medically healthy

Comedication: no

Sociodemographics: not stated

Inclusion criteria

1. Male or female. 12-17 years of age
2. ADHD participants must meet the study criteria for the 'Prevention of Cigarette Smoking in ADHD Youth with CONCERTA Protocol'
3. Each participant and his/her authorised legal representative must understand the nature of this proposed study, and must sign informed consent and informed assent documents
4. Participant and parents must have a level of understanding sufficient to communicate intelligently with the investigator and study coordinator, and to cooperate with study procedures

Exclusion criteria

1. Clinically significant chronic medical condition including hepatic, renal, gastroenterologic, respiratory, cardiovascular (including ischaemic heart disease), endocrinologic, neurologic, immunologic, or haematologic disease
2. Organic brain disorders or mental retardation (IQ < 75)
3. Contraindication to MRI including presence of metal or surgical devices (plates, implants, braces or other items)
4. Pregnancy; women of child bearing potential must be using a medically approved method of birth control. Women of child bearing potential will receive a urinary pregnancy test prior to each MR scanning session
5. Severe phobia of being in small, enclosed spaces
6. Investigator and his/her immediate family; defined as the investigator's spouse, parent, child, grandparent, or grandchild will not be eligible to participate in the treatment arm of the study
7. Participants with active, clinically significant psychiatric comorbidity
8. Participants were dropped from the study if in the investigators' opinion there was lack of efficacy, intolerable adverse events and/or clinically significant laboratory values, pregnancy, clinical worsening, or noncompliance with the study protocol

Interventions	Methylphenidate type: osmotic release oral system Mean methylphenidate dosage: 54 mg/day (0.90 mg/kg/day). Doses were clinically adjusted up to a maximal dose of 1.5 mg/kg/day, according to tolerability and symptoms, until the participant achieved an ADHD-specific Clinical Global Impression Scale-Improvement score of 1-2 Administration schedule: daily Duration of intervention: 6 weeks Treatment compliance: not stated Wash out period prior to study: prior medication for ADHD participants was discontinued 1-4 weeks prior to the initial study scan
Outcomes	*Non-serious adverse events*:

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Hammerness 2012 *(Continued)*

	Adverse events were systematically collected
Notes	Sample calculation: no Ethics approval: yes, approved by the Massachusetts General Hospital and McLean Hospital Institutional Review boards Funding: this work was supported in part by the Pediatric Psychopharmacology Council Fund and by McNeil Pharmaceuticals Vested interest/authors' affiliations: the authors have several affiliations to the medical industry both as researchers, speakers, consultants, etc. *Key conclusions of the study authors*: these preliminary findings suggest the presence of glutamatergic abnormalities in adolescents with ADHD, which may normalise with methylphenidate treatment. Documented clinical improvement and endpoint symptomatology by and ADHD-specific rating scale *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes

Haubold 2010

Methods	A retrospective cohort study of medical treatment of ADHD in a child and adolescent psychiatric practice, Germany, 1997-2007
Participants	NB: the following characteristics include patients treated with methylphenidate, atomoxetine and amphetamine Number of participants screened: 152 Number of participants included: 103 Number of participants followed up: 103 Number of withdrawals: 0 Diagnosis of ADHD: ICD-10 (aubtype: predominantly inattentive (31.1%), predominantly hyperactive (68.9%)) Age: mean: 9.5 years (range: 4-18) IQ: not stated, however only 4 patients had comorbid mental retardation Sex: 92 males (89.3%), 11 females (10.7%) Methylphenidate-naïve: not stated Ethnicity: not stated Country: Germany Comorbidity: disruptive behaviour disorder: 68%, learning disorders: 29.1%, motor developmental disorder: 4.9%, autism spectrum disorders: 20.4%, adjustment disorder: 18.3%, emotional disorder: 6.8%, tics: 6.8%, anxiety disorder: 2.9%, Tourette syndrome: 2.9%, OCD: 1%, enuresis (plus partial encopresis): 6.8%, mental retardation: 3.9%, sleeping disorder: 1.9%, epilepsy: 1.9%, attachment disorder with disinhibition: 1.0%, adiposity: 1.0%, stutter: 1.0%, nail biting: 1.0%, harmful alcohol use: 1.0%, articulation disorder: 1%, no comorbidities: 9.7% Comedication: not stated Sociodemographics: not stated *Inclusion criteria*

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Haubold 2010 *(Continued)*

1. Confirmed ADHD diagnosis
2. Patients who had received medical treatment during the period 2005-2007

Exclusion criteria

1. Children and adolescents without a confirmed ADHD diagnosis
2. Children and adolescents diagnosed with ADHD without medication or with medical treatment, which does not include the 2005-2007 period

Interventions	Methylphenidate type: immediate-release methylphenidate (Ritalin, Medikinet, Equasym), extended-release methylphenidate (Ritalin SR and Ritalin LA) and IR-MPH + ER-MPH. A change of type of medication took place when adverse events occurred or the effect on the core symptoms of ADHD was not satisfactory Mean of medication changes: 4 (SD 2.9) times (range: 0-13) Methylphenidate dosage per day: 0.6 mg/kg (IR-MPH), ER-MPH (0.8 mg/kg), IR-MPH + ER-MPH (0.2 mg/kg + 0.7 mg/kg) Administration schedule: not stated Mean duration of intervention: 3.4 SD 2.10 years (range 2-9.9) Drug holidays were permitted, and the cumulative dose of drug over the entire treatment duration of the children was calculated Treatment compliance: not stated
Outcomes	*Serious adverse events*: Not stated *Non-serious adverse events*: It was assumed that during an office visit, the doctor paid attention to all of the adverse events listed below and, if present, these have been logged. Timing, severity or duration of the occurrence of adverse events have not been described in the medical records with sufficient consistency and could therefore not be included in the evaluation No/any adverse event: trouble falling asleep or sleeping problems, loss of appetite, tic disorder, headache, abdominal pain, anxiety disorder, OCD, nausea BMI: BMI values of children in this study were compared with age and gender reference values (Appendix, Table 1 and Table 2) based on a sample of over 34,000 German children and adolescents of all ages and sexes
Notes	Sample calculation: not stated Any withdrawals due to adverse events: not stated Ethics approval: not stated Funding/vested interests: not stated Authors' affiliations: Faculty of Medicine, Eberhard Karls University, Tübingen, Germany. Other affiliations not stated *Key conclusions of the study authors*: the study shows that immediate-release methylphenidate and the combination of immediate- with extended-release methylphenidate should be first choice for ADHD drug treatment. For extended-release methylphenidate as single treatment regimen and for atomoxetine and immediate-release methylphenidate as combination treatment regimens, the benefit/risk ratio should be thoroughly weighed for each individual patient

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Haubold 2010 *(Continued)*

	Exclusion of MPH non-responders/children who have previously experienced adverse events on MPH: no

Hazell 2003

Methods	A 6-week, double-blind, randomised, parallel study comparing clonidine vs placebo in methylphenidate-treated children diagnosed with ADHD
Participants	Number of participants screened: not stated Number of participants included: 29 Number of participants followed up: 25 Number of withdrawals: 4 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 125.4 months (range: 6-14 years old) IQ: > 70 Sex: 25 males, 4 females Methylphenidate-naïve: none Ethnicity: white Country: Australia Comorbidity: borderline intellectual functioning: 12%, anxiety: 6%, pervasive developmental disorder: 1.5% Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. 6 to 14 years 2. DSM-IV diagnosis of ADHD and comorbid ODD or CD treated for a minimum of 3 months with either methylphenidate or dexamphetamine 3. Attended psychiatric or paediatric clinics supervised by the authors 4. T-scores for attention problems and aggressive behaviour on the Child Behavior Checklist of ≥ 70, placing them in the 'clinically significant' range *Exclusion criteria* 1. Obsessional symptoms, movement disorders, or psychosis 2. Mental retardation (IQ < 70) 3. History as determined by a physician of cardiac anomalies or other medical contraindications to the prescription of clonidine
Interventions	Mean methylphenidate dosage: 0.67 mg/kg/day Administration schedule: not stated Duration of intervention: 6 weeks Treatment compliance: not stated

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Hazell 2003 *(Continued)*

Outcomes	*Non-serious adverse events*:
	Parent and self-report side effects checklists (Barkley)
	Pulse rate, and lying and standing blood pressure. Obtained at baseline and at weekly intervals for 6 weeks
	Height and weight assessed at baseline and at week 6
Notes	Sample calculation: yes
	Any withdrawals due to adverse events: no
	Ethics approval: approved by the Hunter Area Health Research Ethics Committee and the University of Newcastle Human Research Ethics Committee
	Funding/vested interests: supported by the Australian Rotary Health Research Fund
	Authors' affiliations: none declared
	Key conclusions of the study authors: the findings support the continued use of clonidine in combination with psychostimulant medication to reduce conduct symptoms associated with attention-deficit/hyperactivity disorder. Treatment is well tolerated and unwanted effects are transient
	Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no. But patients had to have been treated with methylphenidate for a minimum of 3 months

Hechtman 2011

Methods	A patient report about a boy, who gets very emotional, with frequent crying, marked irritability and many tantrums when treated with methylphenidate. MPH use for around a year
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined)
	Age: 5 years old
	IQ: > 70
	Sex: male
	Ethnicity: not stated
	Country: Canada
	Comorbidity: oppositional defiant disorder and substantial learning disability in expressive and receptive language
	Comedication: not stated
	Sociodemographics: not stated
Interventions	OROS MPH dosage: 54 mg (the dosage was titrated from 36 mg to 54 mg)
	Administration schedule: once daily
	Duration of intervention: 1-2 months
	Treatment compliance: not stated
Outcomes	*Non-serious adverse events*:

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Hechtman 2011 *(Continued)*

	In late afternoon and early evening he became very emotional, with frequent crying, marked irritability and many tantrums. The emotional side effects subsided after he discontinued methylphenidate treatment
Notes	Funding/vested interests: Dr Hechtman declares having sat on the advisory boards/been a consultant for Eli Lilly, GlaxoSmithKline, Ortho Janssen, Purdue Pharma, and Shire Canada *Comments from the study authors*: children with ADHD often have other comorbid conditions that need to be addressed and treated, as stimulant medication is not likely to correct everything It is still unclear what predicts preferential response to 1 or the other stimulant. This preferential response should be kept in mind, so when children don't respond well to methylphenidate, the first change in medication should be to amphetamines *Supplemental information* regarding diagnostic criteria, type of ADHD and intervention period received through personal correspondence with the author in August 2013 (Hechtman 2013 [pers comm])

Hemmer 2001

Methods	Comparative cohort study on seizure development during MPH treatment
Participants	Number of participants screened: not stated Number of participants included: 234 (stimulant: 205, control: 29) Number followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-III, DSM-III-R or DSM-IV (subtype: not stated) Age: range: 3-20 years old IQ: not stated Sex: 179 males, 55 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Meeting diagnostic criteria for ADHD according to DSM-III (ADD with or without hyperactivity), DSM-III-R, or DSM-IV (primarily inattentive, primarily hyperactive/impulsive, or combined subtypes) 2. Having received an EEG in the clinic 3. Follow-up either by office visit or by telephone in 1999
Interventions	Methylphenidate dosage: 0.3-1 mg/kg/day Administration schedule: not stated Duration of intervention: not stated

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Hemmer 2001 *(Continued)*

	Treatment compliance: not stated
Outcomes	*Serious adverse events*: Patient 1: first seizure occurred 6 weeks after initiation of MPH treatment. She experienced 2 episodes several hours apart characterised by unresponsiveness, chewing movements, and tonic eye deviation. Stimulants were not reintroduced. She had an initial normal EEG before MPH treatment Patient 2: she was treated uneventfully with MPH for 12 months, and experienced an unprovoked 4-minute generalised tonic-clonic seizure 2 months after discontinuation of methylphenidate. Her EEG prior to stimulant treatment revealed generalised epileptiform discharge Patient 3: experienced a 2-minute generalised tonic-clonic seizure with focal onset (tonic rightward head deviation) 3 years after initiation of MPH. Carbamazepine was initiated, and later replaced by phenytoin. MPH was reinitiated and there were no further seizures for the subsequent 14 months. EEG prior to stimulant treatment revealed focal epileptiform discharge Patient 4: episode 10 months after MPH initiation. He was heard to fall and was found unresponsive with upward eye deviation for approximately 2 minutes. EEG prior to stimulant treatment revealed focal epileptiform discharge
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interest: supported by the Crown Family Authors' affiliations: no affiliations to pharmaceutical companies stated *Key conclusions of the study authors*: our data suggest that a normal EEG can be used to assign children to a category of 'minimal risk' for seizure. In contrast, an epileptiform EEG in neurologically normal children with ADHD predicts considerable risk for the eventual occurrence of seizure. The risk, however, is not necessarily attributable to stimulant use

Hollis 2007

Methods	A patient report of acute and transient dyskinesia occurring within hours of taking modified release methylphenidate
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined/hyperactive-impulsive/inattentive) Age: 7 years old IQ: Wechsler Abbreviated Scale of Intelligence language skills in the average/high-average range, and nonverbal skills in the high-average/superior range Sex: male Ethnicity: white British Country: UK Comorbidity: conduct disorder (with predominant aggression) Comedication: on both occasions, treatment with methylphenidate was temporally associated with a recent withdrawal of risperidone. Sociodemographics: parents separated before he was born. He has an older brother and 3 older half-sisters, none of whom have had behaviour problems. His mother has fibromyalgia. There is no history of mental or movement disorders in the family
Interventions	Methylphenidate type: modified release methylphenidate (Concerta XL)

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Hollis 2007 *(Continued)*

	Trial 1: 36 mg, 12 hours after abruptly stopping daily risperidone (1.5 mg) Trial 2: 18 mg, after a reducing course of risperidone over 4 weeks, with 6 risperidone-free days before treatment
Outcomes	*Non-serious adverse events*: Trial 1: dyskinesia, marked overactivity, distress, headache, fatigue, and vomiting within 8 hours of treatment Trial 2: dyskinesia, increased aggression, difficulty sleeping within 8 hours of treatment
Notes	*Key conclusions of the study authors*: This report is the first of a dyskinesia occurring after a single first dose of methylphenidate in a previously stimulant-naïve patient after neuroleptic withdrawal. It is also the first to link this effect with modified-release methylphenidate. The dyskinesia described here consisted of both brief tic-like movements and more sustained dystonic movements and posturing *Supplemental information* regarding diagnostic criteria received through personal email correspondence with the authors in October 2013 (Hollis 2013 [pers comm])

Holtkamp 2002

Methods	A patient report of growth impairment during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 7.6 years old IQ: normal Sex: male Ethnicity: not stated Country: Germany Comorbidity: bronchial asthma Comedication: inhaled corticosteroids Sociodemographics: not stated
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 0.75-0.8 mg/kg/day Administration schedule: morning and noon Duration of treatment: 19 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Appetite loss (only in the first weeks of medicine) Growth impairment
Notes	Funding/vested interests: not stated

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Holtkamp 2002 *(Continued)*

	Key conclusions of the study authors: one may conclude that some children are at risk of serious growth decrement when treated with methylphenidate. The growth of children should thus be monitored carefully, even if there are no alarming gastrointestinal side effects from methylphenidate. We found that the determination of growth velocity was a sensitive marker for the evaluation of growth impairment in our patient

Hong 2012

Methods	An 8-week open-label trial to investigate the independent and interaction effects of DAT1, DRD4,ADRA2A and NET1 on treatment response to methylphenidate in ADHD
Participants	Number of participants screened: not stated Number of participants included: 112 Number of participants followed up: 103 Number of withdrawals: 9 Diagnosis of ADHD: DSM-IV (subtype: combined (69, 61.6%), hyperactive-impulsive (6, 5.4%), inattentive (29, 25.9%), not otherwise specified (8, 7.1%)) Age: mean 9.1 (SD 2.1) years IQ: 107.4 SD 13.7 Sex: not stated Methylphenidate-naïve: 100% Ethnicity: Asian Country: South Korea Comorbidity: ODD (15, 13.4%), anxiety disorder (12, 10.7%), enuresis (5, 4.5%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Children diagnosed with ADHD according to DSM-IV criteria 2. Stimulant-naïve *Exclusion criteria* 1. IQ < 70 2. Currently diagnosed with tic disorder, OCD, language disorder, learning disorder, convulsive disorder 3. Past and/or ongoing history of pervasive developmental disorder, schizophrenia, bipolar disorder, brain damage
Interventions	Methylphenidate type: immediate release and extended release Mean methylphenidate dosage: 19.8 SD 8.2 mg/day (initial dose) and 29.1 SD 11.6 mg/day (final dose) Administration schedule: not stated Duration of intervention: 8 weeks Treatment compliance: 1 participant's parents were anxious about their child taking psychiatric medication, this participant discontinued prematurely

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Hong 2012 *(Continued)*

Outcomes	ADHD-RS (ADHD Rating Scale-IV) which consists of 18 items, each item is rated from 0 (never or rarely) to 3 (very often). Rated by parents before and after 8 weeks of treatment The study design did not include collection of side-effect profiles, so possible reasons for dropping out were not systematically assessed *Non-serious adverse events*: 2 of the 9 dropouts experienced loss of appetite after methylphenidate medication, and 1 also complained about insufficient effect. Another participant was documented to experience insomnia, and described to be hyperactive at the last visit before dropping out. The remaining dropouts are not accounted for
Notes	Sample calculation: none Ethics approval: institutional review board for human subjects at the Seoul National University Hospital Funding: Supported by the Jun Sang-Bae Child and Adolescent Psychiatry Research Fund of the Korean Neuropsychiatric Association in 2009 Vested interests/authors' affiliations: no conflicts of interest or financial ties *Key conclusions of the study authors*: genetic determinants of methylphenidate response consist of both the dopaminergic and noradrenergic gene polymorphisms, and efforts to predict response to methylphenidate should cover these 2 catecholaminergic systems and their multifaceted aspects of their interactions as well *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: all participants were methylphenidate-naïve

Hulvershorn 2012

Methods	A 4-week before-after study
Participants	Number of participants screened: not stated Number of participants included: 25 Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV-TR (subtype: not stated) Age: range 10-14 years old IQ: above 80 Sex: not stated Methylphenidate-naïve: not stated Ethnicity: not stated Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria*

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Hulvershorn 2012 *(Continued)*

	1. ADHD diagnosis 2. Frequent, severe temper outbursts and chronic irritability 3. Medication-free 4. Right-handed
Interventions	Methylphenidate type: osmotic release oral system Methylphenidate dosage: titrated to a therapeutic dose over 4 weeks Administration schedule: morning Duration of intervention: 4 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Intermittent 'hot' feeling: n = 1 Decreased appetite: n = 6 Upset stomach: n = 4 Felt jittery: n = 1 Intermittent headaches: n = 1 Headache: n = 1
Notes	Sample calculation: not stated Ethics approval: not stated Funding: Klingenstein Third Generation Foundation, Brain Behavior Research Trust (NARSAD), Indiana University Health Values Fund Authors' affiliations: not stated *Key conclusions of the study authors*: we present preliminary data on corticolimbic functional connectivity (FC) abnormalities seen in highly irritable youth with ADHD. Open-label methylphenidate was well tolerated and resulted in parent-rated improvements in ER. Methylphenidate appears to impact FC between the amygdala, visual/insular cortices and pallidum *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* regarding ADHD diagnostic criteria, IQ and adverse effect data received through personal email correspondence with the authors in August 2013 (Hulvershorn 2013 [pers comm])

Ilgenli 2007

Methods	A 4 hours before-after study of methylphenidate acute effect on QT intervals
Participants	Number of participants screened: not stated Number of participants included: 25 Number of participants followed up: 22 Number of withdrawals: 3

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Ilgenli 2007 *(Continued)*

	Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 9.4, range 7-15 years old IQ: no intellectual disability Sex: 11 males, 11 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Turkey Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Age between 7 and 15 years 2. ADHD based on DSM-IV. Only symptoms rated as 'often' or 'very often' were counted toward the diagnosis 3. No history of intellectual disability, gross neurologic abnormality or Tourette syndrome 4. Patient decision to participate in a stimulant medication trial on clinical grounds
Interventions	Methylphenidate type: not stated Methylphenidate dosage:10 mg Administration schedule: not stated Duration of intervention: 2 hours Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: ECG were taken 2 hours before and 2 hours after administration of methylphenidate QT dispersion was measured as the difference between maximum and minimum QT intervals QTc was calculated with the use of Bazett's formula
Notes	Sample calculation: not stated Ethics approval: yes, approved by the institutional ethical committee Funding/vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: this study reveals that methylphenidate reduces QT dispersion during the acute period, shortly after its administration. Data support the reliability of this drug in terms of early arrhythmia *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* received through personal email correspondence with the authors in November 2013 (Ilgenli 2013 [pers comm])

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Irmak 2014

Methods	A patient report of phobias and visual hallucinations during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 9 years old IQ: WİSC-R: performance IQ: 78, verbal IQ: 87 Sex: male Ethnicity: not stated Country: Turkey Comorbidity: Moebius syndrome Comedication: none Sociodemographics: not stated
Interventions	Methylphenidate type: osmotic release oral system (OROS) Methylphenidate dosage: gradually titrated up to 1 mg/kg Administration schedule: not stated Duration of treatment: not stated Treatment compliance: not stated
Outcomes	*Serious adverse events*: Methylphenidate prescribed at initial ADHD diagnosis, then withdrawn following the onset of phobias and visual hallucinations as well as lack of improvement in attention problems
Notes	*Key conclusions of the study authors*: dramatic occurrence of adverse effects in our patients suggests that there is an increased vulnerability to adverse effects of methylphenidate in patients with syndromes when compared to other ADHD patients *Supplemental information* regarding ADHD diagnosis, IQ and comedication received through personal email correspondence with the authors in June 2016 (Irmak 2016 [pers comm])

Işeri 2007

Methods	30-day prospective cohort study of methylphenidate
Participants	Number of participants screened: 428 Number of participants included: 20 Number of participants followed up: 20 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype: combined 100%) Age: mean 9.27 (SD 1.59), range: 6-12 years old IQ: normal Sex: 20 males

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Işeri 2007 *(Continued)*

	Methylphenidate-naïve: 100% Ethnicity: not stated Country: Turkey Comorbidity: ODD 35% Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. Pre-pubertal children aged 6-12 years old 2. ADHD DSM-IV diagnosis 3. No previous methylphenidate treatment 4. No history or current co-morbid psychiatric condition apart from ODD 5. Male *Exclusion criteria* 1. Intellectual disability or developmental delay 2. History of head injury 3. Any other neurological, metabolic or infectious disorder 4. Liver or kidney dysfunction 5. Routine use of any drugs
Interventions	Methylphenidate type: short-acting Methylphenidate dosage: 0.6 mg/kg/day Administration schedule: not stated Duration of intervention: 30 days Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Severity (0: not a problem, 1: mild, 2: moderate, 3: severe) of 13 possible side effects rated by mothers Appetite status (0: not a problem, 1: mild, 2: moderate, 3: severe) rated by mothers before and after medication Height and weight were measured before and after treatment and BMI was calculated. The patients were instructed not to change diet or physical activity during the study
Notes	Sample calculation: not stated Ethics approval: approved by the institutional ethical committee Funding: Gazi University Scientific Project Fund *Key conclusions of the study authors*: short-acting methylphenidate does not affect leptin appetite at 0.6 mg/kg/day dose. Did not show significant difference between pre- and postleptin levels *Comments from the study authors*: limitations of the study: small sample size, short duration of the study, only 1 dose of methylphenidate *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: all participants were methylphenidate-naïve

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Işeri 2007 *(Continued)*

	Supplemental data regarding the vomiting and skin eruptions have not been possible to receive from the authors. We have tried to get in contact with them twice without success

Jafarinia 2012

Methods	A 6-week randomised, double-blind, parallel group study with 2 arms: 1. Bupropion 2. Methylphenidate
Participants	Number of participants screened: 55 Number of participants included: 44 Number of participants randomised to methylphenidate: 22 Number of participants followed up: 19 Number of withdrawals: 3 Diagnosis of ADHD: DSM-IV-TR (subtype: not stated) Age: mean 9.7 (1.9) years (range 6-17) Sex: 14 males, 6 females Methylphenidate-naïve: 100% Ethnicity: 100% Persian Comorbidity: none Comedication: not stated IQ: above 70 Sociodemographics: not stated *Inclusion criteria* 1. 6-17 years old 2. DSM-IV-TR diagnostic criteria for ADHD confirmed by a child and adolescent psychiatrist 3. Total or subscale scores (or both) of ≥ 1.5 SDs above norms for patient's age and gender on Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) - School Version 4. The children and their parents had to be willing to comply with all requirements of the trial *Exclusion criteria* 1. Psychiatric comorbidities (excluding oppositional defiant disorder) 2. High risk of suicide 3. Mental retardation (IQ < 70) 4. Clinically important chronic medical condition (such as epilepsy and organic brain disorders) 5. Drug abuse or dependence in the last 6 months 6. Hypertension or hypotension 7. History of allergy to bupropion or methylphenidate 8. Abnormal electrocardiogram 9. Psychotropic medication use in the last 14 days
Interventions	Participants were randomly assigned to methylphenidate or bupropion

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Jafarinia 2012 *(Continued)*

	Methylphenidate dosage range: 20-30 mg/day depending on weight (20 mg/day for 30 kg and below and 30 mg/day for above 30 kg) Methylphenidate mean dosage at week 6: 25.5 mg/day Administration schedule: not stated Duration of intervention: 6 weeks Titration period: 3 weeks initiated after randomisation Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Side effects measured in both groups. 11 side effects were recorded during the course of the study
Notes	Sample calculation: yes Any withdrawals due to adverse events: not stated Ethics approval: yes Funding/vested interests: public funding *Key conclusions of study authors*: bupropion has a comparable safety and efficacy profile with methylphenidate in children and adolescents with ADHD *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: all participants were methylphenidate-naïve *Supplemental information* requested from the authors twice in August 2013 with no answer

Jensen 1999 (MTA)

Methods	The Multimodal Treatment Study of Children With ADHD (MTA) is a 14-month multicentre, randomised, parallel clinical trial with 4 arms 1. Medication Management (MGT) 2. Behavioural Treatment (BEH) 3. Combined Treatment (medication management + behavioural treatment) (COMB) 4. Community Care (the control group) (CC) Phases: for the 2 groups receiving medication there was initially a 28-day titration period. This titration phase was carried out as a randomised, double-blind, placebo-controlled, cross-over trial with daily switching of MPH doses (placebo, low, middle, and high). Once the delivery of randomly assigned treatments by MTA staff stopped at 14 months, the MTA became an observational study in which participants and families were free to choose their own treatment but in the context of availability and barriers to care existing in their communities. The following follow-up assessments took place after the RCT 10 months follow-up (24 months after randomisation), 3-year follow-up, 8-year follow-up, 10-year follow-up In our review we will compare combined treatment with behavioural treatment (RCT) according to our protocol, and look at the medication treatment group as a cohort (observational)
Participants	**Titration period (Greenhill 2001)** The 28 day RCT (COMB + MGT group) N = 289 (MGT: n = 144, COMB: n = 145), N completed = 256 N not finishing titration = 33. Out of the completers, 198 were assigned to an individually best dose of MPH for the 14-month trial, the rest on other medication or no medication **Main study (Jensen 1999):**

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Jensen 1999 (MTA) *(Continued)*

Number of patients screened: 4541, N included = 579, N randomised to MPH + behavioural treatment (COMB) = 145, MPH: 144, behavioural treatment (BEH): 144, N followed up in each arm: combined treatment (COMB): 142; MPH: 136; behavioural treatment (BEH): 141, number of withdrawals/dropouts in each arm: combined treatment: 3; MPH: 8; behavioural treatment: 3

All the demographic data below is for the COMB, BEH, and MGT group:

DSM-IV diagnosis of ADHD (combined (100%))

Age: mean: 8.4 years (range: 7-9.9).

IQ: mean 100.4

Sex: m: 346, f: 87

MPH-naïve (177/2)

Ethnicity: white: 60.3%, African American: 20.6%, Hispanic: 8.8%, others: 10.4%

Country: USA and Canada

Comorbidity: anxiety disorder 35.1%, conduct disorder 14.1%, oppositional-defiant disorder 38.8%, affective disorder 3.5%, tic disorder 10.2%, mania/hypomania 3%)

Comedication (not stated)

Sociodemographics (130 families on welfare. The population range widely in SES). There were no significant differences in baseline demographics between the 3 groups

10-month follow-up (MTA Group 2004)

Number of patients followed up in each arm: MGT: 128, COMB: 138, BEH: 139

Age: mean: 8.4 years

Sex: m: 322, f: 83

There were no difference from the demographic characteristics of the originally randomised 579 MTA participants and the participants who were assessed in the 10-month follow-up. The only statistically significant difference among treatment groups was a trivial difference in age (MHT was 0.3 years older that BEH)

3-year follow-up (Jensen 2007)

Number of patients followed up in each arm: MPH: 115, combined: 127

Age: mean: 11.7 years (range: 10-13)

Sex: m: 291, f: 78

There were no significant differences in baseline characteristics between participants in the 36-month assessment and those who were unable to follow

8-year follow-up (Molina 2008)

Number of patients followed up in each arm: MGT: 101, COMB: 119. 32.5% of the MTA sample were medicated over 50% if days in the past year

Age: mean: 16.8 years (range: 13-16). At the 8-year assessment, 55 MTA participants had turned 18 years. Only 30% of the sample still fulfilled an ADHD diagnosis. Participants lost to the 8-year follow-up, compared with those retained, were more often male, had younger mothers, had less educated parents, had lower parent income, and were more likely to have been on welfare at baseline

10-year follow-up, blood pressure (Vitiello 2012)

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Jensen 1999 (MTA) *(Continued)*

Number of participants followed up in each arm: MGT: 77, COMB: 93. A comparison of patients who were retained through year 10 (n = 346) and those who were not (n = 233) showed a lower proportion of males in the retained group. Furthermore the participants were divided into groups based on the following criteria: never medicated, currently medicated, previously medicated. For the currently medicated group, the number of participants were respectively 184, 184, 108, 50, and 12 for 24 months, 36 months, 72 months, 96 months and 120 months follow-up. Medication use during the previous 30 days was the criterion for positive medication status)

Growth studies: at 24 months assessment (Jensen 2004)

For both growth outcomes on the originally assigned, randomised, treatment groups were collected, and furthermore naturalistic subgroups had been made. The naturalistic subgroups consisted of those who had been medicated at all the assessment points up to 24 months (medication use during the previous 30 days was the criterion for positive medication status) and those who had not been medicated at the assessment points. Patients with consistent use of medication (med/med): 255, patients with no use of medication (NoMed/NoMed): 139 COMB: n = 135 mGT, n = 120

Growth studies: up to 36-month assessment (Swanson 2007)

Naturalistic subgroups were established based on the patterns of treatment with stimulant medication. If medication was used within a 30-day period before the assessment medication status was positive (med) and otherwise negative (no med). If an individual's medication status changed at any assessment point, then they were placed in the inconsistently medicated group. Patients with Med, n = 70. At the baseline at 14-, 24-, 36-month assessment points, respectively, the percentages of medicated children taking methylphenidate were the following: 85.4%, 79.7%, 76.8%, 73.5%. The naturalistic subgroups did not differ on initial size at birth (birth weight), age, parent or teacher ratings of ADHD symptoms, sex, expected adult size (mid-parent size), welfare status, or maternal smoking

Inclusion criteria:

1. Boys and girls between ages of 7-9.9 years
2. In grades 1 through 4
3. In residence with the same primary caretaker(s) for the last 6 months or longer
4. Meeting the DSM-IV criteria for ADHD combined type

Exclusion criteria:

1. Child currently in hospital
2. Child currently in another study
3. Below 80 on all WISC-III scales and on SIBBipolar disorder, psychosis, or personality disorder
4. Chronic serious tics or Tourette syndrome
5. OCD serious enough to require separate treatment
6. Neuroleptic medication in previous 6 months
7. Major neurological or medical illness
8. History of intolerance to MTA medications
9. Ongoing or previously unreported abuse
10. Missed 1/4 of school days in previous 2 months
11. Same classroom as child already in MTA study
12. Parental stimulant abuse in previous 2 years
13. Non-English speaking primary caretaker
14. Another child in same household in MTA study
15. No telephone
16. Suicidal or homicidal

Interventions	**Titration period (Greenhill 2001)** Mean MPH dose during titration period: COMB: 32.1 mg/d MGT: 28.9 mg/d. Medication management started with a 4-day single-blind, safety lead-in period, during which participants were exposed to 3 progressively higher daily MPH doses given 3 times daily. This was followed by a 28-day, double-blind,

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Jensen 1999 (MTA) *(Continued)*

daily, switch titration of methylphenidate hydrochloride, using 5 randomly ordered repeats each of placebo, 5 mg, 10 mg, and 15 mg or 20 mg. Cross-site teams of experienced clinicians blindly reviewed graphs portraying parent and teacher ratings of responses to each of the 4 doses and by consensus selected each child's best dose Compliance: not stated. 29 of the 32 placebo responders had to go back to taking MPH during the maintenance period

Main study (Jensen 1999)

Participants were randomly assigned to MGT, COMB, or BEH. Mean MPH dosage during the main study: COMB 31.2 mg/d, MGT: 37.8 mg/d. Administration schedule: 3 times a day; breakfast, lunch and in the afternoon. Duration of intervention: 14 months. Treatment compliance: monthly pill counts, intermittent saliva measurements to monitor taking methylphenidate, and encouragement of families to make up missed visits. "the study achieved a high degree of adherence to protocol." NB: for participants not obtaining an adequate response to MPH during titration, alternate medications were titrated openly in the following order until a satisfactory one was found: dextroamphetamine, pemoline, imipramine, and if necessary, others approved by a cross-site panel. Thus 256 participants successfully completed titration; of these, 198 of 289 participants were assigned to an individually titrated best dose of MPH. 26 were titrated to dextroamphetamine, 32 given no medication because of a robust placebo response

10 months follow-up (MTA Group 2004)

Duration of intervention: 24 months (10 months follow-up from the 14 months RCT)

Treatment compliance: not stated. From end of treatment to the first follow-up, the percentage of participants on medication decreased for COMB (87% vs 70%) and MPH (93% vs 72%) but increased for behavioural (23% to 38%)

3-year follow-up (Jensen 2007)

Duration of intervention: 3 years (36 months follow-up from the 14 months RCT). Treatment compliance: not stated. At 36 months the percentage of participants on medication were 70% for the combined group, 72% for the MPH group and 45% for the behavioural intervention group

8-year follow-up (Molina 2009)

Duration of intervention: 8 years. Mean MPH dose: 44.93 mg

10-year follow-up (Vitello 2012)

Duration of intervention: 10 years. Treatment compliance: not stated. Mean MPH dosage: 54.3 mg

Outcomes

Titration period (Greenhill 2001)

- CLAM (with inattention/overactive (I/O),
- Aggressive/defiant (A/D) and mixed (I/O + A/D) subscales). Sssessed daily by parents and teachers
- SKAMP (with attention and deportment subscales) rated daily by parents and teachers)

Main study (Jensen 1999)

- SNAP Inattention and hyperactivity-impulsivity subscale, both parent and teacher. Assessed at baseline, 3, 9, and 14 months
- SNAP oppositional-defiant disorder subscale, both parent and teacher rated. Assessed at baseline, 3, 9, and 14 months
- Abikoff Classroom Observational System (ADHD and oppositional/aggressive symptoms), blind ratings by blind observer

Serious adverse events:

Main study (Jensen 1999)

- 6 of 11 reported severe side effects could have been due to non-medication factors
- 3 deaths were recorded among the ADHD participants during the 10 years of observation: a suicide at age 14 (the patient was on MPH), a fatal car accident at age 17 (the patient was the driver and was on

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Jensen 1999 (MTA) *(Continued)*

MPH), and a sudden unexplained death at age 17 (the patient was found dead in bed; no specific cause of death could be determined; he had been previously treated with MPH and had been off medication for more than 1 year when he died

Non-serious adverse events

Main study (Jensen 1999)

Participants had up to 8 additional sessions provided when needed to address clinical emergencies or instances of possible study attrition

- Pittsburgh Side Effects Rating Scale, monitored monthly, reviewed by the pharmacotherapist
- Internalising symptoms (anxiety and depression) were measured with an internalising subscale from parent- and teacher-completed SSRS, measured at baseline, 3, 9, and 14 months
- Children's self-ratings on the Multidimensional Anxiety Scale for Children (MASC). Assessed at baseline, 3, 9, and 14 months

Titration period (Greenhill 2001)

- Pittsburgh Side Effect Rating Scale (10 adverse events commonly associated with MPH were rated)

3-year follow-up (Molina 2007)

- Substance abuse; substance use was assessed at 24 and 36 months using a child-reported substance use questionnaire (Molina and Pelham, 2003) adapted for the MTA. The measure included items for lifetime and current (past 6 months) use of licit substances (alcohol, cigarettes, chewing tobacco) and illicit drugs (marijuana and other street drugs). Also included were items for inappropriate or non-prescribed use of medications, including stimulants
- Delinquency; assessed by the Self-Reported Antisocial Behavior Questionnaire through the 24-month assessment and the
- Self-reported delinquency questionnaire at the 36-month assessment. Delinquency was coded along an ordinal scale based on the most serious act committed during the past 6 months: 0 = no delinquency; 1 = minor delinquency only at home (e.g. theft of less than USD 5 or vandalism); 2 = minor delinquency outside of the home (e.g. vandalism, cheating someone, shoplifting less than USD 5); 3 = moderately serious delinquency (e.g. vandalism, theft of ≥ USD 5, weapon carrying); 4 = serious delinquency (e.g. breaking and entering, drug selling, attacking someone with the intent to seriously hurt or kill, rape); and 5 = engagement in ≥ 2 different level 4 offenses. Because only a small number of MTA children were coded 5 (n = 14 at baseline, n = 4Y5 between 14 and 36 months), we grouped codes 4 and 5 for data analyses, making a 5-level ordinal scale of 0 to 4

8-year follow-up (Molina 2009)

- Delinquent behaviour coded on a 5-point ordinal scale using parent and youth report across several measures
- Number of contact with police and arrests using the Services for Children and Adolescents-Parent Interview (SCAPI), parent reported
- Depression rated with the Children's Depression Inventory, self-rated
- Anxiety rated with the Multidimensional Anxiety Scale for children, self-rated
- Psychiatric hospitalisation by 8 year, parent reported

8-year follow-up, substance abuse (Molina 2009)

The substance use outcomes were measured at all interviews beginning with the 24-month assessment

- Substance use: substance use was assessed with a child/adolescents-reported questionnaire adapted for the MTA

For the analysis of stimulant treatment duration in relation to substance use at the 8-year follow-up, the primary outcome was number of substances used in the past 6 months, to ensure that most stimulant treatment received would have preceded substance use. Component variables included the following: 'drunk' once or more or drank alcohol 3 to 4 times or more, ≥ 1 cigarettes/day in the past month (time frame exception specific to tobacco); marijuana ≥ 2 times, and any other illicit drug use or pre-

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Jensen 1999 (MTA) *(Continued)*

scription medication misuse. Secondary analyses explored each class of substances separately. Substance Abuse or Dependence (SUD). For the analysis of stimulant treatment exposure over time in relation to substance use at the 8-year follow-up, the primary outcome variable was SUD in the past year for any substance (excluding tobacco). Secondary analyses explored alcohol and marijuana/other drug use disorders separately

10-year follow-up (Vitello 2012)

- Blood pressure and heart rate monitoring, measured after participants had been sitting for 5 minutes, adjusted for age and sex
- Height and weight
- Hospitalisation measured at each assessment point
- No symptomatic cardiovascular events leading to medical attention were reported during the period of observation, and no stimulant treatment discontinuation consequent to cardiovascular adverse effects occurred during the 10-year period

Growth (Jensen 2004, Swanson 2007)

- Height in cm and weight kg, assessed at baseline, 14 months, 24 months, and 36 months

Notes

Sample calculation: yes power analysis, 576 participants were required

Ethics approval: yes, approved by both local institutional review boards and the National Institutes of Health Office for Protection From Research Risk

Exclusion of MPH non-responders/children who have previously experienced adverse events on MPH: no

Any dropouts due to adverse events: 4 patients were removed during the lead-in (titration period) because of prohibitive side effects. 1 child with buccal movements, another with skin picking; a third with depression, crying, sleep delay, and appetite loss, and a fourth who was anorexic, listless, and emotionally constricted
Comments from the study authors:

Main Study (Jensen 1999)

Recruitment, screening, and selection procedures aimed to collect a carefully diagnosed sample of impaired children with ADHD and a wide range of comorbid conditions and demographics characteristics representative of patients seen in clinical practice. The design did not include a no-treatment or placebo group. More than 3/4 of participants given behavioural treatment were successfully maintained without medication throughout the study. Consequently, it should not be concluded that behavioural treatment interventions did not work. Combined treatment and medication management treatments were clinically and statistically superior to behavioural treatment and community care in reducing children's ADHD symptoms. For other areas of function (oppositional/aggressive behaviours, internalising symptoms, social skills, parent-child relations, and academic achievement), few differences among our treatments were noted, and when found, were generally of smaller magnitude. The significantly lower total daily dose of methylphenidate in the combined treatment arm are noteworthy but not unforeseen. The importance of this finding is unclear, and a rigorous test of the question would likely require a different design

Titration period (Greenhill 2001)

Its short 28-day duration also limited its generalisability to long-term treatment. Rates of response to MPH ran between 70% to 80% within the expected range.The MTA titration study showed a steeper dose-response curve for younger and lighter ADHD children. When ratings were collected under placebo-controlled, double-blind conditions, parents reported more adverse events than did teachers. For this reason, clinicians would be wise to collect MPH side effect ratings from parents in the afternoon and evenings

10-month follow-up (Group 2004)

At follow-up, MGT participants' dose levels (in methylphenidate equivalents) were significantly higher than COMB participants. There interesting results suggest the possibility that early COMB interventions

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Jensen 1999 (MTA) *(Continued)*

might allow reducing overall medication requirements during later periods, consistent with findings that other have reported

3-year follow-up (Jensen 2007)

By 36 months, none of the randomly assigned treatment groups differed significantly on any of the 5 clinical and functional outcomes. However, despite no significant group differences at the 36-month assessment, substantial improvement was manifested by all of the groups. Because there were no untreated control groups and because all of the treatment groups were improved in terms of relevant symptomatology at 36 months compared to baseline, it is possible that all of the treatments worked, but at different rates of different time periods. It is interesting that both medication and educational services for 24 to 36 months were markers for poorer outcome at 36 months, suggesting that those who are doing poorly get more treatment yet still do not do as well as those for whom treatment is not considered essential

Vitiello 2001

Comorbid anxiety, oppositional defiant disorder, or conduct disorder was not associated with statistically significant differences in MPH dose at end of titration or maintenance, number of medication changes, or time to first change. A short-term response to placebo occurred in 32 children (of 256 who completed the double-blind titration) but was maintained in only 3 patients in the long term.

Conners 2001

It is clear that the treatment effect in the study depends on the choice of endpoint measure. The results highlight the fact that there is no 'one true outcome' for a randomised clinical trial because different measures may be sensitive to different forms of treatment

8-year follow-up (Molina 2008)

Across time (to the 8-year follow-up) 17.2% of the children were medicated at every assessment beginning with 14-months reports

10-year follow-up, (Vitiello 2012)

This clinical trial was not specifically designed to evaluate cardiovascular function. The blood pressure and heart measurements were not conducted under double-blind conditions, and the measurement methods varied across the clinical sites. Abnormal blood pressure values were not systematically confirmed over 3 separate assessments as required for a diagnosis of prehypertension or hypertension. The time of the day when measurements were made was variable

I**mplications and applications for primary care providers** (Jensen 2001)

Behavioural treatments may help families actively cope with their child's disorder and make the necessary life accommodations to optimise family functioning, even when such treatments are not as effective as medication in reducing children's ADHD symptoms. Findings suggest that high quality treatments may have considerable impact on restoring AHDH children to normal or near-normal functioning at home and in the classroom. Because essentially none of the ADHD children met the normal criteria that were met by 88% of comparison children drawn from the same classrooms at the study outset, the notion that ADHD is just normal behaviour labelled by uninformed parents or overwhelmed teachers appears not only implausible, but preposterous

Pelham 1999

The 2 major treatment modalities - behavioural and pharmacological - were assessed at different time points relative to the intensive phase of treatment. Specifically, the effects of the pharmacological treatments were assessed at post-treatment while participants were actively medicated; in contrast, the effects of BEH were assessed following fading of therapist involvement. The intensive period of BEH ended in late December or early January, and endpoint measures were typically taken 4-6 months later - usually several months after the last planned, face-to-face therapeutic contact. This design aspect has numerous implications for interpretation of the findings. For example, we cannot state that the medication (MPH for the vast majority) had long-term effects. Rather, the results simply demonstrate that effects of MPH given steadily for 14 months are the same at the end of the time as the beginning (indeed the correlations between drug effects at these 2 points of the study are very high). When dif-

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Jensen 1999 (MTA) *(Continued)*

ferences in outcome between these groups (e.g. BEH and MGT) are analysed, it is likely that combined treatment for children whose parents and teachers continued the behavioural interventions they had been taught will have an outcome superior to MGT, while combined treatment, for those whose parents and teachers did not continue BEH will be equivalent to MGT alone (which would not be surprising, as functionally that would be what they were receiving)

Growth 24-month outcomes (Jensen 2004)

The growth suppression effects could be related to a medication effect, with the continuously treated subgroup having slower growth than the untreated subgroup. Alternatively, the 'continuously treated subgroup', defined by unknown self-selection factors, could have had a slower growth rate before the start of the study, which continued during the treatment and follow-up phases on the MTA. Our data cannot make a determination of the validity of these alternative interpretations. At this first follow-up, our observations were of the children in the MTA when they were between the ages of 9 and 11 years, which is before expected phase of accelerated growth in adolescence and before the expected age when growth slows and final height is approximated. The rate of growth as well as the length of the growth phase together determines ultimate (adult) height, and it is possible that the consistent treatment with medication may reduce the rate but lengthen the duration of growth, so final height would be delayed but not reduced. It is possible that the never-medicated group was pared down to good responders and the medicated groups enriched with poor behavioural responders. In the analysis of 14- to 24-month change scores, the 'Medication status' was significant for both height ($Chi^2 = 16.16$, $P < 0.001$) and weight ($Chi^2 = 13.32$, $P < 0.004$)

Growth 36 months assessment (Swanson 2007)

We did not document a decrease in relative size in the group of participants with a history of treatment before entry into the MTA protocol during subsequent treatment with stimulant medication over 3 years. However, this group (the consistently medicated naturalistic subgroup) was smaller than the stimulant-naïve group (the newly medicated naturalistic subgroup at entry, suggesting that early treatment of children (before the ages of 7-9 years) with stimulant medication may have produced a reduction of growth rate before entry into the MTA protocol

Key conclusions of the study authors:

Main study (Jensen 1999)

For ADHD symptoms, our carefully crafted medication management was superior to behavioural treatment and to routine community care that included medication. Our combined treatment did not yield significantly greater benefits than medications management for core ADHD symptoms but may have provided modest advantages for non-ADHD symptom and positive functioning outcomes

Vitiello 2001

For most children, initial titration found a dose of MPH in the general range of the effective maintenance dose but did not prevent the need for subsequent maintenance adjustments. For optimal pharmacological treatment of ADHD, both careful initial titration and ongoing medication management are needed

Titration period (Greenhill 2001)

The MTA titration protocol validated the efficacy of weekend MPH dosing and established a total daily dose limit of 35 mg of MPH for children weighing less than 25 kg. It replicated previously reported MPH response rates (77%), distribution of best doses (10-50 mg/day) across participants, effect sizes on impairment and deportment, as well as dose-related adverse events. With 3 times daily dosing, the MTA titration trial showed that significant stimulant medication effects on ADHD symptom reduction and drug-related adverse events could be detected by parents and teachers using daily ratings under controlled conditions

10-month follow-up (MTA Group 2004)

The benefits of intensive medical intervention for ADHD extend 10 months beyond the intensive treatment phase only in symptom domains and diminish over time.

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Jensen 1999 (MTA) *(Continued)*

3-year follow-up (Jensen 2007)

By 36 months the earlier advantage of having had 14 months of the medication algorithm was no longer apparent, possibly due to age-related decline in ADHD symptoms, changes in medication management intensity, starting or stopping medications altogether, or other factors not yet evaluated.

24- and 36-month assessment of delinquency and substance abuse (Molina 2007)

Cause-and-effect relationships between medication treatment and delinquency are unclear; the absence of associations between medication treatment and substance use need to be re-evaluated at older ages. Findings underscore the need for continuous monitoring of these outcomes as children with attention deficit/hyperactivity disorder enter adolescence. There were no statistically significant effects at the $P < 0.05$ level of randomly assigned treatment on individuals rate of change in delinquency between baseline and 36 months. Result suggests the possibility that increasing delinquency between 24 and 36 months was associated with an increase in substance use in the same time period. We did not find evidence of protective or adverse effects of medication treatment for ADHD in either study.

8-year follow-up (Molina 2009)

Type or intensity of 14 months of treatment for ADHD in childhood (at age 7-9.9 years) does not predict functioning 6 to 8 years later. Rather, early ADHD symptom trajectory regardless of treatment type is prognostic. This finding implies that children with behavioural and sociodemographic advantage, with the best response to any treatment, will have the best long-term prognosis. As a group, however, despite initial symptom improvement during treatment that is largely maintained after treatment, children with combined-type ADHD exhibit significant impairment in adolescence. Innovative treatment approaches targeting specific areas of adolescent impairment are needed

10-year follow-up blood pressure (Vitiello 2012)

Stimulant treatment did not increase the risk for prehypertension or hypertension over the 10-year period of observation. However, stimulant had a persistent adrenergic effect on heart rate during treatment

Growth studies, 24-month follow-up (Jensen 2004)

In the MTA follow-up, exploratory naturalistic analyses suggest that consistent use of stimulant medication was associated with maintenance of effectiveness but continued mild growth suppression

Growth studies, 3-year follow-up (Swanson 2007)

Children with combined type attention-deficit/hyperactivity disorder were, as a group, larger than expected from norms before treatment but showed stimulant-related decreases in growth rates after initiation of treatment, which appeared symptomatic within 3 years without evidence of growth rebound

Pelham 1999

1. Active medication for ADHD is better than withdrawn BT (on some but not most measures).
2. Combined treatment adds modestly to active medication but is superior to behaviour management alone.
3. Study treatments that include active medication are better than community treatments that include medication, while BT is comparable to medication as delivered in the community.
4. Concurrent BT results in ≥ 20% lower and non-increasing medication dosages relative to treatment with medication alone.

Comorbidity (Jensen 2001**)**

Our findings suggest that ADHD children with and without ODD/CD and ANX differed on many baseline characteristics, outcomes, and response to treatment. Children with ANX tended to be more treatment-responsive than ADHD + ODD/CD and even ADHD-only participants

Anxiety (March 2000)

Contravening earlier studies, no adverse effects of anxiety on medication response for core ADHD or other outcomes in anxious or non-anxious ADHD children was demonstrated. When treating ADHD, it

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Jensen 1999 (MTA) *(Continued)*

is important to search for comorbid anxiety and negative affectivity and to adjust treatment strategies accordingly

Swanson 2007

Long-term benefits from consistent treatment were not documented; selection bias was not shown to account for the loss of relative superiority of medication over time; there was no evidence for 'catch-up' growth; early treatment with medication did not protect against later adverse outcomes. We expect that these challenges to the field's views will contribute to future controversies about the long-term outcomes in the MTA

Substance use (Molina 2012)

Our findings did not provide any evidence that ADHD medication protects from, or increases risk for, adolescent substance use or SUD. This finding held for recent medication and for days cumulatively treated with stimulants. Unmeasured confounders may have been operating because of the naturalistic follow-up study design and we did not statistically control for psychopathology and functioning at the follow-up assessment. The observed lack of associations between stimulant exposure over time and adolescent substance use/SUD do not discount the possibility that brain-based changes in neural mechanisms underlying addiction vulnerability are occurring as a function of prolonged stimulant treatment. The substance use/SUD outcomes for the MTA should be considered in the context of several unique study features and limitations. All of the children in the MTA were diagnosed with the combined type of DSM-IV ADHD, and generalisation of study results should generally not extend beyond this subtype. Our follow-up assessments, which relied on self-report and often with 2-year windows, may have missed episodes of substance use, and rates may be underestimated

Pelham 2000
75% of the children in the behavioural treatment group were maintained without medication for 14 months, and 64% did not meet diagnostic criteria for ADHD at 14 months based on the DISC interview (MTA Cooperative Group, 1999a, 1999b). Such findings highlight the fact that intensive behavioural treatments are a viable alternative to medication in treatment of ADHD

Comments from the review authors:

The authors from the MTA study have written more than 70 articles describing different outcomes and challenges of the study. We have only included those found in our comprehensive literature search or others we found relevant to include looking through the articles reference lists. We have discussed whether to include the MTA study or not since not all of the patients randomised to medication (COMB + MGT group) received MPH. Those who did not have an adequate response to MPH were given other medication (e.g. dextroamphetamine, pemoline, imipramine, or no medication). Furthermore, some of the participants in the BEH group were also medicated during the 14-month randomisation phase. For all other studies in the review, we have only included those with pure MPH receivers. Furthermore lots of the participants did not have an ADHD diagnosis at the follow-up assessment. At 8-year follow-up only 30% of the remaining participants still had a diagnosis of ADHD. However, we have chosen to use the data from MTA since it is such a large and well-known study. All of the MTA analyses will be part of the review as sensitivity analyses

Regarding Molina 2012 (substance use): we have included/asked for additional data for this article, even though that the group that were medicated in the more group were only medicated for mean 2071.10 (SD 728.87) days out of the 8 years the follow-up took place.
The following articles from the MTA study have only been assessed by one review author: Pelham 2000, Carey 2000, Swanson and Hinshaw 2007, Galanter 2003, Hinshaw 1999, Molina 2013

We sent several emails to the MTA group in order to get additional information and furthermore spoke orally to some of the authors. We did not get additional data

Johnson 2013

Methods	A cohort stud of methylphenidate use for 6 weeks

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Johnson 2013 *(Continued)*

Participants	Number of participants screened: not stated Number of participants included: 96 Number of participants followed up: 77 Number of withdrawals: 9 Diagnosis of ADHD: DSM-IV (subtype: combined (82%), hyperactive-impulsive (9%), inattentive (9%)) Age: mean 8 (SD 2.6) years (range 4-15) IQ: mean 92.7 (SD 15.9) Sex: 66 males, 11 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Ireland Comorbidity: oppositional defiant disorder: 60%, conduct disorder: 16% Comedication: paracetamol, salbutamol and steroid inhalers for asthma and ampicillin antibiotics Sociodemographics: not stated *Inclusion criteria*: 1. Between 4 and 15 years of age 2. Meet DSM-IV criteria for ADHD 3. Be stimulant naïve 4. Be willing to provide a blood or saliva sample for genetic analysis *Exclusion criteria*: 1. IQ < 70 2. Epilepsy, fragile X syndrome, fetal alcohol syndrome, maternal drug abuse during pregnancy, primary diagnosis of pervasive developmental disorder or bipolar disorder 3. Current treatment with non-stimulant psychotropic medications
Interventions	Methylphenidate type: 45 participants took short-acting methylphenidate. Otherwise not stated Methylphenidate dosage: mean 0.57 mg/kg/day (SD 0.19) Administration schedule: not stated Time points: not stated Duration of intervention: 1 year, however only data up to 6 weeks were reported here Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Barkley's Side Effect Rating Scale at 6 weeks, parent rated - included decreased appetite, weight loss, headache, abdominal pain, irritability, sadness, insomnia, and tics
Notes	Sample calculation: not stated Any withdrawals due to adverse events: not stated Ethics approval: granted by 8 local research ethics committees

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Johnson 2013 *(Continued)*

	Funding/vested interests: this study was funded by the Irish Health Research Board, Dublin Authors stated that there were no competing financial interests *Key conclusions of the study authors*: the study found an association between 2 CES1 SNP markers and sadness as a side effect of short-acting methylphenidate *Comments from the study authors*: limitations: not cross-over design; serum measures of methylphenidate were not obtained; study did not consider environmental factors impacting on CES1A1 function *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Jung 2007

Methods	A open-label cohort study of osmotic release oral system (OROS) methylphenidate use for 4 weeks
Participants	Number of participants screened: not stated Number of participants included: 91 Number of participants followed up: 83 Number of withdrawals: 8 Diagnosis of ADHD: DSM-IV (subtype: 100% combined) Age: mean 8.46, range: 6-12 years old IQ: mean 96 (SD 15.17). All above 70 Sex: 75 males, (90.4%), 8 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: Korea Comorbidity: not stated Sociodemographics: not stated *Inclusion criteria* 1. ADHD combined subtype 2. Maternal report of development history consistent with ADHD *Exclusion criteria* 1. IQ below 70 2. Gross neurological, sensory or motor impairment as determined by paediatric examinations 3. Comorbid diagnosis as: seizure, psychosis, Tourette's syndrome, mental retardation, cardiovascular disorder, thyroid disorder, drug abuse history, intestinal obstruction 4. ADHD treatment drugs, herbs, antidepressants, antipsychotics within 1 month of the study 5. Taking OROS methylphenidate less than 2 days a week during study period
Interventions	Methylphenidate type: osmotic release oral system (extended release)

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Jung 2007 *(Continued)*

	Methylphenidate dosage: start dosage was 18 or 36 mg based on the clinician's judgment and dosage was adjusted at each visit if necessary Administration schedule: once per day in the morning before 8:30 Duration of intervention: 4 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: 79.5% showed ≥ 1 harmful effects of medication with most being mild. Not mentioned how these were measured
Notes	Sample calculation: no Ethics approval: yes Funding/vested interests: Janssen Korea Pharmaceuticals LTD *Key conclusions of the study authors*: OROS methylphenidate improves performance on common tests of cognitive function. A further long-term follow-up study of these effects in ADHD is warranted *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Karabekiroglu 2008

Methods	A retrospective cohort of methylphenidate use for 6 months
Participants	Number of participants screened: not stated Number of participants included: 90 Diagnosis of ADHD: DSM-IV diagnosis (subtype: not stated) Age: mean: 9.0, range: 5-16 years old) IQ: above 70 Sex: 59 males, 14 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Turkey Comorbidity: conduct disorder (16.7%); tics (23.3%); Tourette syndrome (10.5%); obsessive compulsive disorder (16.3%); pervasive developmental disorder (8.1%); learning disorder (26.7%); depression (9.2%) Comedication: none Sociodemographics: not stated *Inclusion criteria*: 1. In a clinical sample 2. In a period of 6 months, all methylphenidate-naïve patients with attention deficit hyperactivity disorder, whose parents accepted to participate in the study with an informed consent, were included

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Karabekiroglu 2008 *(Continued)*

	Exclusion criteria: 1. Mental retardation
Interventions	Methylphenidate type: immediate release Methylphenidate dosage: 10-30 mg/day Mean methylphenidate dosage: 17.6 (SD 4.95) mg/day Administration schedule: 2-3 times/day Duration of intervention: 6 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Parents completed the Barkley Stimulant Side Effects Rating Scale (BSSERS) at baseline and on the 3rd, 7th, and 15th days of the medication
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interest: "This research had a naturalistic design. Therefore, a limited financial support, which was supplied by the authors, was needed." *Key conclusions of the study authors*: authors found significant decrease in appetite, and they suppose that some of the Barkley SES may represent both ADHD symptoms and methylphenidate adverse events *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: all participants were methylphenidate-naïve *Supplemental information* regarding the IQ of the participants received through personal email correspondence with the authors in June 2016 (Karabekiroglu 2016 [pers comm])

Karaman 2010

Methods	A patient report of a 15-year old boy with ADHD who developed pulmonary arterial hypertension (PAH) during OROS methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 15 years old IQ: intellectual capacity within normal limits Sex: male Ethnicity: not stated Country: Turkey Comorbidity: no Comedication: none MPH-naïve: yes Sociodemographics: not stated
Interventions	Methylphenidate type: osmotic release oral system (OROS)

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Karaman 2010 *(Continued)*

	Methylphenidate dosage: 54 mg/day Administration schedule: once daily, morning Duration of intervention: 18 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: On the 4th day of treatment: the patient began to experience occasional episodes of slight shortness of breath. Continued over several months. Not associated with either exercise or anxiety At the 18th month of treatment: fainting. Normal weight. No sign of allergy, hypersensitivity, or sleep apnea. Mean pulmonary arterial pressure of 40 mmHg at rest, otherwise no pathological findings from extensive testing (Examination: clear lungs, no murmurs, rubs, or gallops, and otherwise unremarkable. Laboratory tests, including C-reactive protein, thyroid and liver function tests, electrolytes. Blood gases, antinuclear antibodies, D-dimers, chest X-ray, ventilation-perfusion scintigraphy, electrocardiography, respiratory function tests. Echography. Transthoracic echocardiogram: normal except for the mean pulmonary arterial pressure) No use of any other drug. No history of alcohol and substance use and no symptoms or signs of methylphenidate misuse (intravenous (IV) injection). The personal and family histories were also negative for pulmonary or cardiovascular diseases Discontinuation of OROS-methylphenidate, 1 month: free of symptoms. Mean pulmonary arterial pressure of 28 mmHg
Notes	Funding/vested interests/affiliations: no conflict of interests or financial ties to disclose. *Key conclusions of study authors*: this case shows that pulmonary arterial hypertension should be considered in patients who present with dyspnoea and a reduced exertion tolerance and who are known to use methylphenidate *Comments from the study authors*: using the Naranjo algorithm, the likelihood that OROS methylphenidate was responsible for precipitating pulmonary arterial hypertension in our patient was judged probable

Karapinar 2014

Methods	A patient report of sudden hearing loss associated with methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 8 years old IQ: > 70 Sex: female Ethnicity: not stated Country: Turkey Comorbidity: none Comedication: none Sociodemographics: not stated

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Karapinar 2014 *(Continued)*

Interventions	Methylphenidate type: Ritalin Methylphenidate dosage: 10 mg/day Administration schedule: 5 mg twice daily Duration of treatment: 4-5 days Treatment compliance: yes
Outcomes	*Serious adverse events*: About 24 hours after taking methylphenidate the patient began feeling loss of balance, nausea, vomiting. She was kept on the medication. After third dose, her symptoms became more severe. Clinical findings suggested sensorineural hearing loss associated with drug ototoxicity in the left ear. Methylphenidate treatment was discontinued, and the hearing loss treated. At the end of the 2-month follow-up period, her hearing in the affected ear showed no significant improvement.
Notes	*Key conclusions of the study authors*: sensorineural hearing loss that occurred after the introduction of methylphenidate is a serious complication of the treatment, without resolution after discontinuation of the drug and administration of several treatments. The possibility of the development of irreversible sudden hearing loss should be borne in mind when patients are undergoing medical treatment of ADHD with methylphenidate

Kazanci 2015

Methods	2 patient reports of dyskinesia following a single dose of methylphenidate
Participants	**Case 1** Diagnosis of ADHD: DSM 5 Age: 8 years old IQ: normal Sex: male Ethnicity: not stated Country: Turkey Comorbidity: none Comedication: none Sociodemographics: uneventful pregnancy and delivery history. Born from healthy, non-consanguineous parents without any history of any psychiatric diseases, movement or muscle disorders **Case 2** Diagnosis of ADHD: DSM 5 Age: 6 years old IQ: normal Sex: male Ethnicity: not stated Country: Turkey

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Kazanci 2015 *(Continued)*

	Comorbidity: none Comedication: none Sociodemographics: uneventful pregnancy and delivery history. Born from healthy, non-consanguineous parents without any history of any psychiatric diseases, movement or muscle disorders
Interventions	**Case 1** Methylphenidate type and dosage: methylphenidate IR 10 mg/day Methylphenidate dosage: 5 mg twice daily Duration of treatment: 3 hours Treatment compliance: yes **Case 2** Methylphenidate type and dosage: OROS methylphenidate 18 mg/day Administration schedule: not stated Duration of treatment: 2 hours Treatment compliance: yes
Outcomes	**Case 1** *Non-serious adverse events*: 3 hours after first dose of methylphenidate IR 5 mg: repetitive facial contortions and abnormal neck movement. The abnormal movements decreased during the following hours. Continuation of 5 mg methylphenidate immediate release twice daily. After 2 months further increase to 10 mg twice a day and no repetition of dyskinesia **Case 2** *Non-serious adverse events*: 2 hours after a single dose of OROS-methylphenidate 18 mg: repetitive facial grimaces, lip smacking and protrusion of tongue. 2 hours later all symptoms have resolved. No treatment required. Continuation of 18 mg OROS-methylphenidate. After 3 months, further increase to 27 mg OROS-methylphenidate and no repetition of dyskinesia in the 8-month follow-up period
Notes	Funding/vested interest: the authors report no conflicts of interest related to this article *Key conclusions of the study authors*: these side effects are assumed to occur due to individual drug sensitivities. Continuation of the methylphenidate treatment, despite dyskinetic side effects, may not cause any recurrent dyskinetic movements

Kemner 2005 (FOCUS)

Methods	A 3-week, prospective, open-label, community-based, multicentre, randomised, parallel study with 2 arms: 1. Osmotic release oral system methylphenidate 2. Atomoxetine
Participants	Number of participants screened: not stated Number of participants included: 1323 Number of participants randomised to OROS-MPH: 850 Number of participants followed up: not stated

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Kemner 2005 (FOCUS) *(Continued)*

Number of withdrawals: not stated

Diagnosis of ADHD: DSM-IV-TR (subtype: combined (72%%), hyperactive-impulsive (13%), inattentive (15%))

Regarding the OROS-MPH group:

Age: mean 8.77, range 6-12 years old

IQ: above 70

Sex: 630 males, 219 females

Methylphenidate-naïve: 57.97%

Ethnicity: white: 75.12%, African American: 14.74%, Asian: 0.71%, Hispanic: 6.72%, American Indian: 0.24%, others: 2.48%

Country: USA

Comorbidity: not stated

Comedication: not stated

Sociodemographics: not stated

Inclusion criteria:

1. 6-13 years old
2. ADHD, any subtype
3. DSM-IV-TR
4. Investigator-rated ADHD-RS score of at least 24 points and a Clinical Global Impression-Severity of Illness scale (CGI-S) rating as 'moderately ill' or worse at screening
5. ADHD medication treatment naïve or previously treated with ADHD medication with suboptimal response (judged by the clinician in conjunction with the parents)

Exclusion criteria:

1. Eating disorders
2. Substance use disorders
3. Comorbid psychiatric conditions other than oppositional defiant disorder
4. History of seizure, tic disorder, mental retardation, or severe developmental disorder
5. Personal or family history of Tourette syndrome
6. Previous diagnosis of hyperthyroidism or glaucoma
7. Use of medications contraindicated for coadministration with OROS methylphenidate or atomoxetine
8. Known non-response to treatments indicated for ADHD
9. Occurrence of menarche in girls

Interventions	Methylphenidate type: osmotic release oral system Washout: more than 3 days or 5 half-lives Investigators were allowed to select starting doses Mean OROS-MPH starting dose: 21.57 mg Titration: 2 weeks, after randomisation Mean OROS-MPH dose at week 3: 32.7 mg (12.1) / 1.01 mg/kg (0.45) Mean OROS-MPH dose at week 3 for the African American patients: 32.8 mg (10.9) Mean OROS-MPH dose at week 3 for the non-African American patients: 32.7 mg (12.2)

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Kemner 2005 (FOCUS) *(Continued)*

	Administration schedule: once daily, in the morning Duration of intervention: 3 weeks Treatment compliance: 92% or higher
Outcomes	*Non-serious adverse events*: Blood pressure, heart rate, height and weight were recorded at baseline, week 2 and 3 Spontaneously reported adverse effects by patients, parents or investigators
Notes	The FOCUS study: the Formal Observation of Concerta versUs Strattera, Phase IV study Sample calculation: no Ethics approval: yes Funding/vested interests: supported by funding from McNeil Consumer & Specialty Pharmaceuticals *Key conclusions of the study authors*: these results suggest greater ADHD symptom improvement with osmotic release oral system methylphenidate compared with atomoxetine *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes, known methylphenidate non-responders and methylphenidate-optimal-responders are excluded *Supplemental information* requested from the authors and YODA-team in March and June 2014. No reply

Khajehpiri 2014

Methods	A cohort study of methylphenidate use for 6 months
Participants	Number of participants screened: not stated Number of participants included: 71 Number of participants followed up: 71 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 8.23, range: 4-15 years old IQ: not stated Sex: 46 males (64.8%), 25 females (35.2%) Methylphenidate-naïve: not stated Ethnicity: not stated Country: Iran Comorbidity: epilepsy 11.2%, neonatal jaundice 25.4%, seizure 4.2%, respiratory disease 2.82%, Down syndrome 2.82%, urinary tract infection 1.41% Comedication: methylphenidate plus risperidone: 23 (32.4%), methylphenidate plus other medications: 8 (11.3%) Sociodemographics: not stated

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Khajehpiri 2014 *(Continued)*

	Inclusion criteria All children under methylphenidate treatment alone or with other agents attending a university-affiliated psychology clinic were screened regarding all subjective and objective adverse drug reactions (ADRs) of methylphenidate No specific inclusion-exclusion criteria regarding duration of methylphenidate treatment course, methylphenidate dose, and probable co-administered medications for management of ADHD were used for patient selection
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage/day: 20.5 (SD 9.6) mg (range 5-40) Administration schedule: not stated Duration of intervention: < 1 month (2.8%) to ≥ 6 months (63.1%) Treatment compliance: 63.1% received methylphenidate for ≥ 6 months; 2.8% less than a month
Outcomes	Type of adverse event/reaction/effect: ADRs Measure method/instrument: face-to-face interview with patients or his/her parents at regular follow-up office visits through a checklist of methylphenidate adverse reactions in relevant scientific literature and reviewing their brief office charts *Serious adverse events*: The WHO definition of a serious adverse reaction was used i.e. any adverse reaction resulting in death, life-threatening situation, persistent or significant disability/incapacity, hospital admission, or prolonged hospital stay
Notes	Sample calculation: no Ethics approval: Tehran University Medical Ethics committee Funding/vested interest: not stated *Key conclusions of the study authors*: our data suggested that although methylphenidate related adverse reactions were common in children with ADHD, they were mainly mild and non-serious *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Khodadust 2012

Methods	A 6-week randomised, double-blind, parallel group study with 2 arms: 1. Methylphenidate (Ritalin) 2. Methylphenidate (Stimdate) No control/no-intervention group
Participants	Number of participants screened: not stated Number of participants included: 30 Number of participants randomised to Ritalin: 15 and Stimdate: 15 Number followed up in each arm: Ritalin: 14 and Stimdate: 14 Number of withdrawals in each arm: Ritalin: 1 and Stimdate: 1

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Khodadust 2012 *(Continued)*

	Diagnosis of ADHD: DSM-IV-TR (subtype: combined 100%) Age: Ritalin: 9.2 (0.5); Stimdate: 8.33 (0.5) IQ: above 70 Sex: Ritalin: 12 males, 3 females; Stimdate: 15 females Methylphenidate-naïve: none Ethnicity: 100% Persian Comorbidity: none Comedication: none Sociodemographics: not stated *Inclusion criteria*: 1. 6-16 years old 2. Meeting the DSM-IV diagnostic criteria for ADHD 3. No psychological or medical treatment received in the last 4 weeks before the study 4. Having informed written consent signed by parents for participating in the study 5. Not having comorbid conditions including conduct disorder, pervasive developmental disorder, mood disorders, Tourette disorder, and psychotic disorders 6. The ability to comply with the study's visits schedule *Exclusion criteria*: 1. The presence of clinically significant gastrointestinal problems, cardiovascular diseases, glaucoma, and seizure disorder 2. Suspicion or confirmation of substance abuse by patients or a family member 3. Presence of mental retardation according to educational history or, having an IQ score less than 70 4. Allergy to stimulants 5. Having to receive any psychiatric or somatic medication (except Ritalin or Stimdate) during the study
Interventions	Participants were randomly assigned to 2 methylphenidate preparations: Ritalin or Stimdate Final mean methylphenidate dose: Ritalin (29.2 (SD 9.1) mg), Stimdate (31.4 (SD 8.6) mg) Administration schedule: morning and noon Duration of intervention: 6 weeks Titration period: 4 weeks initiated after randomisation Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Nonserious adverse events checklist and telephone interviews asking about drug side effects were performed
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interests: none declared *Key conclusions of the study authors*: we recommend clinicians choose Ritalin or Stimdate according to the patient's preferences, sustained accessibility, primary response to treatment, and possible side ef-

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Khodadust 2012 *(Continued)*

	fects encountered in course of treatment. This means that neither of these drugs has been proven to be superior to the other one *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes. See exclusion criteria 4 *Supplemental information* requested twice through email correspondence with the authors in June 2013. No reply

Kim 2010

Methods	Single-site, 6-week, prospective, open-label, flexible-dose trial with osmotic release oral system methylphenidate (Concerta) monotherapy to examine OROS-MPH effect on sleep in children with AD-HD. Examination by physician at baseline, participants were seen at the first, second, fourth, and sixth weeks for repeated clinical evaluation and dosage titration
Participants	Number of participants screened: not stated Number of participants included: 27 Number of participants followed up: 24 Number of withdrawals: 3 Diagnosis of ADHD: DSM-IV (subtype: combined (66.7%), hyperactive-impulsive (4.2%), inattentive (29.2%)) Age: mean 8.2 (SD 1.4) years IQ: mean 105 (SD 11.5) Sex: 22 males, 2 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: South Korea Comorbidity: ODD: 2 (9.1%) Comedication: no medications that might influence clinical status or sleep characteristics were permitted Sociodemographics: family history of ADHD: 4, 16.7% *Inclusion criteria*: 1. Age 6-12 years 2. DSM-IV diagnosis of ADHD 3. Clinical Global Impression-Severity (CGI-S) scale rating ≥ 4 ('moderately ill' or greater severity) 4. Normal medical history screening and physical examination 5. Patients and parents who were informed and voluntarily provided consent *Exclusion criteria*: 1. Earlier exposure to a central nervous system stimulant within the previous 3 months. 2. Hypersensitivity to methylphenidate 3. IQ < 80 on the Korean Educational Developmental Institute's Wechsler Intelligence Scale for Children 4. Presence of comorbid psychiatric disorders except for oppositional defiant disorder (ODD). 5. Past and/or current history of developmental disorder, including autism spectrum disorder

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Kim 2010 *(Continued)*

	6. Presence of seizure disorder 7. Presence of significant comorbid medical illness. 8. No medications that might influence clinical status or sleep characteristics were permitted
Interventions	Methylphenidate type: osmotic release oral system (OROS) Methylphenidate dosage: the mean daily dose at week 6 was 29 (SD 6.8, range 18-45) mg or 1.08 (SD 0.24) mg/kg Administration schedule: once daily Duration of intervention: 6 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Children's Depression Inventory, rated by parents State Trait Anxiety Inventory (STAI), rated by parents Yale Global Tic Severity Scale, rated by parents Barkley Side Effect Rating Scale, rated at 1st, 2nd, 4th and 6th week by parents Questions to parents about adverse events at each follow-up visit (1st, 2nd, 4th and 6th week) Children's Sleep Habits Questionnaire (CSHQ), measured at week 6 Height measured at week 1st, 2nd, 4th and 6th week Weight measured at week 1st, 2nd, 4th and 6th week Blood pressure measured at week 1st, 2nd, 4th and 6th week Heart rate measured at week 1st, 2nd, 4th and 6th week EKG measured at week 6 Overnight polysomnography measured at week 6 Apnea and hypopnea, scored according to the recommended criteria of the American Academy of Sleep Medicine at week 6. Apnea was defined as an absence of oronasal airflow with minimal interval of 2 respiratory cycles. Hypopnea was defined as 50% air flow reduction or more for ≥ 2 respiratory cycles resulting in EEG arousals or oxygen desaturation (Z3%)
Notes	Sample calculation: not stated Ethics approval: yes Funding/vested interests: sponsored by Janssen Korea *Key conclusions of the study authors*: these results suggest that OROS MPH in open-label treatment does not appear to impair sleep on either qualitative measures of sleep or sleep architecture and may improve some aspects (including sleep quality) *Comments from the study authors*: no significant effects were found on any laboratory tests and EKG. Another important finding indicated that children who experienced subjective sleep difficulties showed increased sleep onset latency, sleep onset delay, and bedtime resistance compared with those without sleep complaints during treatment *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no. All participants were methylphenidate-naïve

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Kim 2010 *(Continued)*

	Supplemental information regarding outcome measures requested in February 2014. No reply

Kim 2011

Methods	A 4-week multicentre, open-label before-after study
Participants	Number of participants screened: not stated Number of participants included: 102 Number of participants followed up: 97 Number of withdrawals: 5 Diagnosis of ADHD: DSM-IV (subtype: combined (71.3%), hyperactive-impulsive (5.9%), inattentive (23.8%)) Age: mean 9.4 years (range 6-12) IQ: above 75 Sex: 94 males, 8 females Methylphenidate-naïve: none Ethnicity: not stated Country: Korea Comorbidity: oppositional defiant disorder (17.6%), anxiety disorder (17.6%), depression (9.8%), conduct disorder (2.9%), learning disorder (17.6%), others (5.9%) Comedication: none Sociodemographics: not stated *Inclusion criteria*: 1. ADHD based on the DSM-IV criteria. Symptoms sufficiently severe to require medication with methylphenidate upon entry into the study 2. Been on a daily dose of MPH-IR for ≥ 4 weeks and has been receiving a stable dose for ≥ 3 weeks before beginning the study *Exclusion criteria*: 1. Presence of any medical condition that will contraindicate the use of stimulant medication 2. Presence of hypersensitivity to methylphenidate 3. IQ below 75 (determined by WISC) 4. Use of any additional medication (other than MPH) for ADHD 5. Use of any medication having CNS effects (monoamine oxidase inhibitors, clonidine, tricyclic antidepressants, SSRIs, theophylline, coumarin or anticonvulsants, and antipsychotics) or any investigational medications 6. Having reached menarche 7. Having a high risk of being pregnant 8. The presence of clinically significant gastrointestinal problems, cystic fibrosis, glaucoma, seizure disorders, Tourette syndrome, cardiovascular disease, hyperthyroidism, clinical depression, suicide risk, and substance abuse
Interventions	Prior to the study stabilised on immediate release methylphenidate (IR-MPH) with a mean dose of 25 mg daily

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Kim 2011 *(Continued)*

	Then osmotic release oral system methylphenidate (OROS-MPH) dosage: 18 mg, 36 mg, or 54 mg The participants were assigned to 1 of 3 OROS-MPH doses based on their pre-study dose of IR-MPH. Participants receiving 5 mg of MPH-IR 2-3 times daily were assigned to the 18 mg once daily group; participants receiving 10 mg of MPH-IR 2-3 times daily were assigned to the 36 mg once daily group; and participants receiving 15 mg of MPH-IR 2-3 times daily or a total daily dose > 45-60 mg were assigned to the OROS-MPH 54 mg once daily group. Doses could be adjusted among these 3 levels at study visit 1 and 2 on days 7 and 14 The dose of methylphenidate before entering the study was 10-60 mg/day (mean 25.26 mg, the mean final doses of OROS-MPH was 27.67 mg/day Administration schedule: once, morning Duration of intervention: 28 days Treatment compliance: 94.3% completed the 28 day study
Outcomes	*Non-serious adverse events*: All participants received a screening physical examination at baseline and on day 28. The participants' height and weight were also measured Adverse events were documented at each visit by recording spontaneous reports of adverse events and asking parents/caregivers about the quality of their child's sleep, their children's appetite during the past week, and whether their children had experienced tics during the past week No serious adverse events were reported during the study
Notes	Sample calculation: no Ethics approval: approved by the Institutional Review Board for human participants at Seoul National University Hospital Funding: supported by Korean Jassen Pharmaceutical Company Vested interest/authors' affiliations: none *Key conclusions of the study authors*: the results of this study indicated that an IR-MPH regimen can be successfully changed to a once-daily OROS-MPH regimen without any serious adverse effects. The changes in parent/caregiver IOWA Conners ratings suggested that OROS-MPH improved the control of symptoms after school, a finding that is consistent with the 12-h duration of action of this medication. Because the therapeutic effect of OROS-MPH is sufficiently longer than that of a twice daily dose of IR-MPH, OROS-MPH had significant positive effects on oppositional/defiant behaviour in addition to its effects on the core symptoms of ADHD. No significant differences between the 2 drugs were noted related to appetite loss and sleep disturbances. Tic symptoms significantly decreased after switching from IR-MPH to OROS-MPH *Comments from the study authors*: the investigators and participants were not blind to the treatment conditions *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes. The study excludes all patients who are hypersensitive to methylphenidate *Supplemental information* requested from the study authors in January 2014. No reply

Kim 2014a

Methods	A review of the medical records of children and adolescents receiving MPH for ADHD between 2004 and 2011

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Kim 2014a *(Continued)*

Participants	Number of participants screened: not stated Number of participants included: 157 Number of participants followed up: 157 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype: combined (71.3%), hyperactive-impulsive (0.6%), inattentive (28.0%)) Age: mean 8.9, range 5-14 years old IQ: 104.5 (SD 15.3), range 71-143 Sex: 134 males, 23 females Methylphenidate-naïve: none Ethnicity: not stated Country: Korea Comorbidity: ODD 30.6%, tic 17.8%, anxiety 11.5%, depressive disorder:4.5%, elimination disorder 2.5% Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Between 5 and 14 years at the start of treatment 2. DSM-IV diagnosis of ADHD 3. Receiving methylphenidate for ≥ 1 year 4. A baseline weight and height z score > −2.0 relative to the general Korean population *Exclusion criteria* 1. Prior exposure to a central nervous system stimulant or atomoxetine 2. Having initiated MPH treatment before the age of 5 years 3. IQ < 70 on the Korean Educational Developmental Institute's Wechsler Intelligence Scale for Children 4. Past and/or current history of developmental disorder, including autism spectrum disorder 5. Past and/or current history of schizophrenia, bipolar disorder, or other psychosis 6. Current seizure disorder 7. Mean compliance for the whole treatment period < 80% 8. Taking an adjunct medication that could affect growth 9. Past and/or current medical illness that could induce growth suppression
Interventions	Methylphenidate type: OROS-MPH 52.2%, ER-MPH 26.1%, combination 27.1% Mean methylphenidate dosage: 35.0 (SD 12.4 mg); 0.98 (SD 0.27) mg/kg/day Administration schedule: not stated Duration of intervention: ≥ 1 year; mean 28.8 months (SD 16.1); range 12-88 months Treatment compliance: ≥ 80%
Outcomes	*Non-serious adverse events*: Weight and height Z score measured during the first and second year of MPH treatment

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Kim 2014a *(Continued)*

Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interests: funded by the Korean Ministry of Education, Science and Technology *Key conclusions of the study authors*: these results suggest that methylphenidate could be related to weight and height deficit in Korean children and adolescents, although the effects were minor, and disappeared after the 1st year *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Kim 2014b

Methods	A naturalistic cohort study of methylphenidate use for 8 weeks
Participants	Number of participants screened: not stated Number of participants included: 75 Number of participants followed up: 57 Number of withdrawals: 18 Diagnosis of ADHD: DSM-IV (subtype: combined (48%), hyperactive-impulsive (12%), inattentive (24%), not specified (16%)) Age: mean 9.7 (SD 2.8), range 6-16 years old IQ: not stated Sex: 61 males, 14 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: Korea Comorbidity: 4 had oppositional defiant disorder, 5 had conduct disorder, 6 had anxiety disorder, 6 had learning disorder, 10 had depressive disorder, and 10 had mild to moderate intellectual disabilities Comedication: not stated Sociodemographics: yearly household income > USD 4000 = 23 (30.7%), USD 2000-4000 = 20 (26.7%),< USD 2000 = 12 (16.0%), unknown = 20 (26.7%) *Inclusion criteria*: Children and adolescents aged 6-16 with a DSM-IV diagnosis of ADHD, with no baseline physical or laboratory abnormalities; were able to comply with the study visitation schedule and express a voluntary wish to withdraw from the trial
Interventions	Methylphenidate type: osmotic release oral system (OROS) Mean methylphenidate dosage: 36.3 (SD 15.5) mg/day Administration schedule: not stated Duration of intervention: not stated

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Kim 2014b *(Continued)*

	Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Children who withdrew from the study because of adverse events
Notes	Sample calculation: no Ethics approval: not stated Funding/vested interests: the authors declare that they have no conflict of interest, and the organisation that sponsored the research had no part in the writing of the manuscript *Key conclusions of the study authors*: methylphenidate treatment for ADHD was associated with both symptom alleviation in children with ADHD and improvement in parental depressive mood and quality of life, suggesting that the effects of treatment could go beyond symptom improvement in ADHD *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Kim 2015a

Methods	A cohort study of methylphenidate use for 12 weeks
Participants	Number of participants screened: not stated Number of participants included: 86 Number of participants followed up: 37 Number of withdrawals: 49 Diagnosis of ADHD: DSM-IV (subtype: inattentive, hyperactive-impulsive or both) Age: mean 8 IQ: > 70 Sex: 34 males, 3 females Methylphenidate-naïve: 2-month washout period prior to study Ethnicity: not stated Country: Korea Comorbidity: none Comedication: none Sociodemographics: none *Inclusion criteria* 1. Patients diagnosed at the Korea University Medical Centre between August 2007-December 2010 attending outpatient clinic 2. Showing signs and symptoms of either inattention or hyperactivity-impulsivity or both according to DSM-IV-TR criteria for ADHD *Exclusion criteria*

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Kim 2015a *(Continued)*

	1. Medical problems requiring special attention such as cardiovascular disorders, learning disabilities and mental retardation 2. Other psychiatric comorbidities
Interventions	Methylphenidate type: immediate release or extended release Mean methylphenidate dosage: 22.23 (SD 8.93) mg/0.70 (SD 0.20) mg/kg Administration schedule: not stated Duration of intervention: 12 weeks Treatment compliance: 43% completed 12 week programme
Outcomes	*Non-serious adverse events*: All participants were evaluated for adverse events during each visit, and an interview with their care providers was conducted
Notes	Sample calculation: no Ethics approval: study approved by Institutional Review Board of Guro Hospital, Korea University Medical Center Funding/vested interests: financial support from Jun Sang-Bae Child and Adolescent Psychiatry Research Grant from the Korean Foundation of Neuropsychiatric Research *Key conclusions of the study authors*: HF and RMSSD suggested that parasympathetic dominance in ADHD can be changed by methylphenidate treatment *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* requested twice from the study authors in May and June 2016 with no reply

Kim 2015b

Methods	A prospective, multicentre, open-label cohort study of 116 children with ADHD treated with OROS methylphenidate for 12 weeks
Participants	Number of participants screened: not stated Number of participants included: 143 Number of participants followed up: 116 Number of withdrawals: 27 Diagnosis of ADHD: DSM-IV (subtype: combined (36.2%), hyperactive-impulsive (5.2%), inattentive (33.6%), NOS (25%)) Age: mean 9.4, range: 6-18 years old IQ: mean 108.9 (SD 16.0) Sex: 100 males, 16 females Methylphenidate-naïve: 89.7% Ethnicity: not stated Country: Korea

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Kim 2015b *(Continued)*

	Comorbidity: depression (5.2%), anxiety (7.7%), tic disorder (7.7%), ODD (10.3%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. ADHD diagnosis (any subtype) according to DSM-IV *Exclusion criteria* 1. Patients with an IQ less than 70 (as assessed by the K-Wechsler Intelligence Scale for Children, Third Edition) 2. Seizure disorders, brain injuries, psychotic disorders, pervasive developmental disorders, or serious medical or neurologic conditions 3. Children who were taking SSRIs or antipsychotics within 4 weeks prior to study
Interventions	Methylphenidate type: osmotic release oral system (OROS) Mean methylphenidate dosage: average daily dose increased from 19.20 (SD 3.11) mg/d (0.64 (SD 0.18) mg/kg per day) at week 1 to 34.13 (SD 13.80) mg/d (1.03 (SD 0.3318) mg/kg per day) at the end of 12 weeks of dosing Administration schedule: not stated Duration of intervention: 12 weeks Treatment compliance: 12 patients dropped out because of medication non-compliance
Outcomes	8 participants dropped out because of adverse events (29.6%)
Notes	Sample calculation: no Ethics approval: yes Funding: this study has been sponsored by Janssen, Korea Vested interests/authors' affiliations: the authors have no conflicts of interest to declare. *Key conclusions of the study authors*: treatment with OROS-MPH was associated with symptomatic functional changes that were moderately correlated; therefore, symptomatic functional outcomes appear to be partially overlapped but distinct domains. Consequently, functional measures should be incorporated as important outcome measures in future treatment studies; the importance of treatments targeting functional improvement should be emphasised in the treatment of children with ADHD *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* regarding adverse events requested through personal email correspondence with the authors in June 2016 with no reply

Klein 2004

Methods	Randomised controlled trial parallel study comparing: 1. Methylphenidate alone (MPH) 2. Methylphenidate and multimodal psychosocial treatment (MPH + MPT) 3. Methylphenidate and attention control treatment (MPH + ACT)
Participants	Number of participants screened: 332

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Klein 2004 *(Continued)*

Number of participants included: 129

Number of participants randomised to each arm: MPH = 34; MPH + MPT = 34; MPH + ACT = 35

Number of withdrawals in each arm: MPH: 10; MPH + MPT: 6; MPH + ACT: 6

Diagnosis of ADHD: DSM-III-R

Age: mean 8.2 (SD 0.8) years (range: 7.0-9.9)

IQ: mean WISC IQs were full scale, 109.5 (SD 14.5); verbal, 108.5 (SD 4.0); and performance, 108.7 (SD 15.0)

Sex: 93% males, 7% females

Methylphenidate-naïve: 79.6%

Ethnicity: 84% white, 13% African American, 2% Hispanic, and 1% other

Country: USA and Canada

Comorbidity: 55 (53.4%) ODD, 31 (30%) had 1-2 symptoms of CD. 17 (16.5%) had an anxiety disorder (simple phobia, overanxious disorder, separation anxiety disorder), 4 (3.9%) had major depression

Comedication: not stated

Sociodemographics: 84 (81.2%) children lived with both parents, 13 (12.6%) with 1 parent (in all but one instance, the mother), and 6 (5.8%) with their mother and stepfather. Mean socioeconomic status was 2.5 SD 0.9 (range 1-5) (Myers 1968). There were no significant difference in baseline demographics between the 2 groups

Inclusion criteria

1. Children had to have a diagnosis of ADHD based on a parent interview with the Diagnostic Interview Schedule for Children (DISC-P2) (Shaffer 1996) conducted by clinical psychologists confirmed by a child psychiatrist based on a comprehensive clinical interview with the child and parent and teacher reports
2. On 2 separate occasions, children had to receive a mean teacher rating of ≥ 1.5 on the Hyperactivity Factor or Hyperkinesis Index of the Conners Teachers Rating Scale (CTRS) (Goyette 1978)
3. Children had to be medication free for ≥ 2 weeks before evaluation
4. Normal IQs (i.e. WISC-R ≥ 85)
5. Living with ≥ 1 parent
6. Have telephone access
7. Children had to derive meaningful benefit from the treatment without significant side effects
8. Methylphenidate treatment must not incur cognitive decrement in the children

Exclusion criteria

1. Diagnosable neurological disorders
2. Psychosis
3. Significant medical illness
4. Current physical or sexual abuse
5. Chronic tic disorder or Tourette disorder
6. A DSM-III-R developmental reading or arithmetic disorder, defined as a standard score in reading or mathematics on the Kaufmann Test of Educational Achievement of 85 or less (i.e. ≥ 1 SD below the population mean) and ≥ 15 points (1 SD) below full-scale IQ (Halperin 1984)
7. A diagnosis of conduct disorder

Interventions	Participants were randomly assigned to methylphenidate (MPH), methylphenidate and multimodal psychosocial treatment (MPH + MPT) or methylphenidate and attention control psychosocial treatment (MPH + ACT). Participants were balanced for ethnicity, sex, IQ, and oppositional defiant disorder. Assignment was done in blocks of 4 to enable group treatment components

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Klein 2004 *(Continued)*

	Mean methylphenidate dosage: year 1: MPH = 35.8 (SD 8.5) mg, MPH + MPT = 35.6 (SD 9.4) mg, MPH + ACT = 38.4 (SD 8.5) mg. Year 2: MPH = 38.0 (SD 12.6) mg, MPH + MPT = 41.0 (SD 11.2) mg, MPH + ACT = 38.4 (SD 8.3) mg Administration schedule: 8 am, noon, 4 pm Duration of intervention: 2 years Titration period: 5 weeks duration before randomisation Treatment compliance: the percentage of positive Ritalin acid assays was 87%, without differences between groups. Medication compliance was addressed by counting returned pills
Outcomes	*Non-serious adverse events*: Children's Depression Inventory (CDI) (Kovacs 1992) Piers-Harris Children's Self-Concept Scale (Amato 1984) Before every visit, teachers were called to obtain information about the child's school performance. The sessions were used to assess vital signs (weight, height, pulse, blood pressure), side effects (reported by parent and child), and the child's overall condition
Notes	Sample calculation: not stated Ethics approval: not stated Funding: supported by NIMH grants RO1 MH44848 (H.A.) and RO1 MH44842 (L.H.). Vested interests: Dr Klein is a member of the ADHD Advisory Board of Shire Pharmaceutical Co. *Key conclusions of the study authors*: in stimulant-responsive young children with ADHD without learning and conduct disorders, there is no support for academic assistance and psychotherapy to enhance academic achievement or emotional adjustment. Significant short-term improvements were maintained over 2 years *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes

Kordon 2011

Methods	A prospective, open-label, single arm, non-interventional cohort study of osmotic release oral system (OROS) methylphenidate use for 12 weeks after abrupt switching from immediate release (IR) methylphenidate
Participants	Number of participants screened: 616 Number of participants included: 598 (ITT population) Number of participants followed up: 579 Number of withdrawals: 110 (18.4%) Diagnosis of ADHD: ICD-10 (subtype: F90.0 (63.5%), F90.1 (37%), F90.8 (2%), F90.9 (2.8%), F98.8 (9.9%)). Age: mean 10.9, range 6-17 years old IQ: not stated Sex: 507 males, 91 females Methylphenidate-naïve: 8.8% Ethnicity: not stated

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Kordon 2011 *(Continued)*

	Country: Germany Comorbidity: 33.3% (subtype: conduct disorder (23.4%), oppositional defiant disorder (16.6%), anxiety disorder (3.8%), obsessive compulsive disorder (1.5%), substance abuse (0.8%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Confirmed diagnosis of ADHD (ICD-10) 2. Medically indicated switch from IR MPH to OROS MPH due to insufficient efficacy and/or tolerability, and planned by treating physician 3. Age 6-18 years old
Interventions	Methylphenidate type: osmotic release oral system (OROS) Methylphenidate starting dose: 29.5 SD 12 mg/day (range: 18-108 mg/day, median 36 mg/day) Methylphenidate final dose: 33.5 SD 13.2 mg/day (range: 18-108 mg/day, median 36 mg/day) Administration schedule: once daily Duration of intervention: 12 weeks Treatment compliance: 0.8% of ITT non compliant
Outcomes	3 visits in clinic: baseline, after 1 month of treatment, after 3 months of treatment, or on premature termination Adverse events: World Health Organization - Adverse Reactions Terminology (WHO-ART). Rated throughout the study. Spontaneous reporting. ITT safety population included only those who had ≥ 1 post-baseline efficacy measurement Sleep quality and appetite: rated at each visit using a 5-point scale (1 = very good, 5 = very bad) Vital signs: blood pressure and heart rate. Measured at every visit Body weight: measured at baseline and after 3 months of treatment
Notes	Sample calculation: no Ethics approval: independent ethics committee (Freiburg, Germany) Funding/vested interests: editorial assistance funded by Janssen-Cilag Authors' affiliations: BS is employed by Janssen-Cilag, KR is a consultant working for GEM, and paid by Janssen-Cilag *Key conclusions of the study authors*: in this naturalistic setting, transitioning from IR-MPH to OROS-MPH, in patients who showed previously insufficient response and/or poor tolerability, was successful. OROS methylphenidate was generally safe and well tolerated. Children/adolescents with ADHD who were switched from IR methylphenidate to OROS methylphenidate experienced clinically relevant improvements in symptoms, HRQoL and social functioning *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: unclear *Supplemental information* requested from the study authors twice in July 2014 with no reply

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Kratochvil 2002

Methods	A randomised, open-label, parallel, cohort study of 1. Atomoxetine 2. Methylphenidate
Participants	Number of participants screened: 319 Number of participants included: 228 Number randomised to methylphenidate: 44 Number followed up: 25 Number of withdrawals: 19 Diagnosis of ADHD: DSM-IV (subtype: combined (77.3%), inattentive (22.7%)) Age: mean 10.4 (SD 2.1) years old IQ: > 70 Sex: 44 males Methylphenidate-naïve: not stated Ethnicity: white: 81.8%, others: 18.2% Country: USA and Canada Comorbidity: ODD 59.1%, major depressive disorder 13.6%, elimination disorder 11.4% Comedication: not stated, but other psychoactive medication not permitted Sociodemographics: not stated *Inclusion criteria* 1. DSM-IV diagnosis of ADHD 2. Severity score of ≥ 1.5 SD above age and gender norms on the ADHD-IV Rating Scale-Parent Version: investigator Administered (ADHD RS) 3. Age 7-15 *Exclusion criteria* 1. History of bipolar or psychotic disorders 2. Motor tics 3. Family history of Tourette syndrome 4. Substance abuse 5. Methylphenidate non-responders (from a previous trial of methylphenidate of ≥ 2 weeks of treatment with at least 1.2 mg/kg per day) 6. Serious medical illness
Interventions	Methylphenidate type: not stated Methylphenidate dosage: initial dose 5 mg 1-3 times daily with an ascending dose titration based on the investigator's assessment of clinical response and tolerability Mean methylphenidate dosage: 0.85 SD 0.53 mg/kg pr day, or 31.3 SD 18.7 mg/day Median dose: 0.74 mg/kg/day or 27.5 mg/day. Total daily dose was not to exceed 60 mg Administration schedule: 1-3 times daily, based on clinical response and tolerability

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Kratochvil 2002 *(Continued)*

	Duration of intervention: 10 weeks Treatment compliance: not stated Washout period prior to treatment - duration not specified
Outcomes	*Non-serious adverse events* At weekly visits: ECG, liver function, blood count, urinalysis, open-ended questions
Notes	Sample calculation: yes, but sample size and power computations were performed to answer questions specific to the relapse-prevention portion of the study which followed the open-label period described in this paper Ethics approval: yes Funding/vested interest: study funded by Eli Lilly and Co Authors' affiliations: the authors are either employees or paid consultants and/or investigators of Eli Lilly. The employees are also shareholders *Key conclusions of the study authors*: the results of this study provide preliminary evidence that the magnitude and profile of symptom reduction associated with atomoxetine administration and its tolerability are comparable to that observed with methylphenidate *Comments from the study authors*: in our trial, investigators had latitude in the frequency and timing of methylphenidate dosing, and methylphenidate outcomes might have been different had all methylphenidate-treated patients been required to receive fixed dosing on a thrice-daily basis. A relatively large proportion of patients in both groups withdrew from the study early. No single reason appears to have accounted for this, but this could limit the interpretability of the results. The groups were not well matched for gender. *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes *Supplemental information* regarding IQ received through personal email correspondence with the authors in June 2014 (Kratochvil 2014 [pers comm])

Kraut 2013

Methods	A database study of methylphenidate use
Participants	Number of participants screened: not stated Number of participants included: 2,150,362 Diagnosis of ADHD: ICD-10 German Modification (subtype: not stated) Mean age: not stated, range: 3-17 IQ: not stated Sex: not stated Ethnicity: not stated Country: Germany Comorbidity: yes Comedication: not stated

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Kraut 2013 *(Continued)*

	Sociodemographics: not stated *Inclusion criteria* 1. Valid information on year of birth and sex 2. Age between 3 and 17 years in the respective year 3. Residence in Germany
Interventions	Methylphenidate type: not stated Methylphenidate dosage: not stated Administration schedule: not stated Duration of intervention: not stated Treatment compliance: not stated
Outcomes	8 participants dropped out due to adverse events
Notes	Sample calculation: not stated Ethics approval: yes Funding/vested interests/authors' affiliations: AAK received funding from Sanofi Pasteur MSD for the annual conference of the German Society of Epidemiology in 2010. The present work is unrelated to the funding mentioned. TB served in an advisory or consultancy role for Bristol Myers-Sqibb, Develco Pharma, Lilly, Medice, Novartis, Shire, Viforpharma; YES-Pharma. He received conference attendance support and conference support or received speaker's fee by Lilly, Janssen McNeil,Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Lilly and Shire. The present work is unrelated to the above grants and relationships. RTM received research funding from Sanofi PasteurMSD and Bayer-Pharma. The mentioned funding is unrelated to the present work. EG is running a department that occasionally performs studies for pharmaceutical industries with the full freedom to publish. The companies include Mundipharma, Bayer-Pharma, Stada, Sanofi-Aventis, Sanofi-Pasteur, Novartis, Celgene and GSK. In the past, EG has been consultant to Bayer-Schering, Nycomed, Teva and Novartis. The present work is unrelated to the stated relationships. IL, CL, UP, and FP declare no competing interests *Key conclusions of the study authors*: children starting methylphenidate treatment had a high prevalence of pre-existing psychiatric comorbidities which may affect methylphenidate prescribing. Cardiovascular and other comorbidities were generally rare, but require attention as they were more common among those who received methylphenidate than in the control group *Supplemental information* requested through personal email correspondence with the authors in June 2016. Data were not available

Lahat 2000

Methods	A cohort study of bone density in children with ADHD treated with methylphenidate for a mean of 13 (SD 4) months with a mean daily dose of 10 mg (SD 2.5) mg
Participants	Number of participants screened: 20 Number of participants included in the methylphenidate group: 10 Number of participants followed up: 9 Number of withdrawals: 1 Diagnosis of ADHD: DSM-IV (subtype: not stated)

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Lahat 2000 *(Continued)*

	Age: mean 8.9 (SD 1.6) years old IQ: not stated Sex: 20 males Methylphenidate-naïve: not stated Ethnicity: not stated Country: Israel Comorbidity: not stated Comedication: none Sociodemographics: not stated There were no significant difference in baseline demographics between the 2 groups except for the use of methylphenidate *Inclusion criteria* 1. DSM-IV diagnosis of ADHD 2. None on any other treatment 3. All treated with methylphenidate *Exclusion criteria* 1. No bone disease 2. No metabolic disease
Interventions	Methylphenidate type: immediate release Methylphenidate dosage: 0.5 mg/kg Mean methylphenidate dosage: 10 (SD 2.5) mg, range 7.5-12.5 mg Administration schedule: not stated Duration of intervention: 12-24 months, mean 13 (SD 4) months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Abnormal levels of: • Serum calcium • Serum phosphorous • Bone mineral density measured by dual photon absorptiometry at the lumbar spine or femoral neck • Bone turnover measured by serum bone-specific alkaline phosphatase and urinary deoxypyridinoline excretion rate Weight and height measured
Notes	Sample calculation: not stated Ethics approval: approved by the ethics committee of our medical centre. Funding/vested interests/authors' affiliations: not stated. On a more recent publication by Lahat, he was listed as working for Teva Pharmaceutical Industries Ltd., Teva Israel, Netanya, Israel

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Lahat 2000 *(Continued)*

	Key conclusions of the study authors: in conclusion, our data do not support a significant effect of methylphenidate on bone mineral density turnover in children when used for 1-2 years. *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* from the study authors requested twice with no reply

Lakic 2012

Methods	A cohort study of the influence of methylphenidate treatment on the occurrence of tics and exacerbation of pre-existing tics
Participants	Number of participants screened: not stated Number of participants included: 68 Diagnosis of ADHD: DSM-TR-IV (subtype: not stated) Age: range 7-15 years old IQ: > 70 Sex: not stated Methylphenidate-naïve: not stated Ethnicity: not stated Country: Serbia Comorbidity: tic disorder 9.7% Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. DSM-TR-IV diagnosis of ADHD 2. Currently or recently treated with methylphenidate sustained release *Exclusion criteria*: 1. Mental retardation
Interventions	Methylphenidate type: sustained-release Methylphenidate dose range: 18-36 mg/day (individualised dose) Administration schedule: not stated Duration of intervention: > 6 weeks, up to 6 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Assessment of the occurrence of tics at the time of diagnosis, start of therapy and during methylphenidate treatment. Furthermore, monitoring (type, intensity, duration) of pre-existing tics during methylphenidate treatment

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Lakic 2012 *(Continued)*

Notes	Sample calculation: not stated Ethics approval: not stated Funding: no funding Authors' affiliations: not stated *Key conclusions of the study authors*: tics as a side effect of sustained-release methylphenidate treatment in our patients was predominantly motor, of mild intensity and transient in nature, and did not require cessation of therapy *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental outcome data and information* about IQ and funding were received through personal email correspondence with the authors in October 2013 (Lakic 2013 [pers comm])

Lamberti 2015

Methods	An observational prospective study of immediate-release methylphenidate and cardiovascular effects
Participants	Number of participants screened: not stated Number of participants included: 54 Number of participants followed up: 54 Number of withdrawals: 0 Diagnosis of ADHD: DSM-5 (subtype: not stated) Age: mean 12.14 (SD 2.6) years (range 6-19) IQ: not stated Sex: 51 males, 3 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Italy Comorbidity: no cardiovascular, pulmonary, or endocrine disorders Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Drug naïve ADHD outpatient 2. ADHD diagnosis according to DSM-5 criteria 3. Attending the Unit of Child Neurology and Psychiatry of the University Polyclinic of Messina between September 2013 and March 2014 4. New user of immediate-release methylphenidate
Interventions	Methylphenidate: immediate release (IR-MPH) Methylphenidate dosage: 10-60 mg according to the participant's weight

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Lamberti 2015 *(Continued)*

	Mean methylphenidate dosage: 18.5 mg/day Administration schedule: each treatment condition was administered 7 days, 2-3 times daily, at breakfast (approximately 7:30 am), at lunch (approximately 12:30 pm), and in some cases, early afternoon (approximately 3:30 pm) Duration of intervention: 4 weeks Treatment compliance: 100%
Outcomes	For each patient, 2 standard 12-lead ECGs were obtained at a paper speed of 25 mm/second with the same instrument (Cardioline delta 3 plus), on the same day and under similar conditions. The first (predose) ECG examination was performed before the administration of the first daily dose of IR-MPH; the second (postdose) ECG was executed 2 hours after drug intake, simultaneously with the serum peak of methylphenidate *Non-serious adverse events* Treatment with immediate-release methylphenidate was associated with a slight increase of systolic and diastolic BP
Notes	Sample calculation: not stated Ethics approval: the study was approved by the local ethics committee Funding/vested interests: none *Key conclusions of the study authors*: this study underlines the relative cardiac safety of IR-MPH in childhood, even if stimulants may exert a cardiovascular effect on BP and HR. However, particular caution should be exercised by physicians in prescribing these drugs to patients with a genetic predisposition to arrhythmias. It might be useful to carry out an ECG examination in all patients starting methylphenidate therapy *Comments from the study authors*: the most important limitation of this study includes the lack of a long-term follow-up. More studies are needed to confirm the cardiovascular safety during long-term therapy *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Langevin 2012

Methods	A controlled before-after study of methylphenidate use for ADHD
Participants	Number of participants screened: not stated Number of participants included: 10 Number of participants included as cases: 5 and controls: 5 Number of participants followed up: 10 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV TM (subtype: combined (80%); inattentive (20%)) Age: mean 8.13 years (range 7-9) IQ: normal Sex: 8 males, 2 females Methylphenidate-naïve: not stated

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Langevin 2012 *(Continued)*

	Ethnicity: white (90%), African-Canadian (10%)
	Country: Canada
	Comorbidity: 20% ODD, 10% seasonal affective disorder
	Comedication: not stated
	Sociodemographics: not stated
Interventions	Methylphenidate type: immediate-release or moderate-release
	Methylphenidate dosage: not stated
	Administration schedule: not stated
	Duration of intervention: 6 months
	Treatment compliance: not stated
Outcomes	*Non-serious adverse events*:
	Sleep quality and numbers of hours of sleep
Notes	Sample calculation: not stated
	Ethics approval: not stated
	Funding/vested interests/authors' affiliations: this study was supported by a grant from the University of Alberta (Killam Research Fund)
	Key conclusions of the study authors: the principal results support the study's hypothesis and show a significant baseline difference (P = 0.008) between the nocturnal movements of the ADHD children and those of the control children
	Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no

Larrañaga-Fragoso 2015

Methods	A cohort study of methylphenidate use for 9 months
Participants	Number of participants screened: not stated
	Number of participants included: 14
	Number of participants followed up: 14
	Number of withdrawals: 0
	Diagnosis of ADHD: DSM-IV-TR (subtype: not stated)
	Age: mean 11 (SD 2.79) years (range: 7-17)
	IQ: not stated
	Sex: 6 males, 8 females
	Methylphenidate-naïve: 100%
	Ethnicity: 100% white
	Country: Spain

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Larrañaga-Fragoso 2015 *(Continued)*

	Comorbidity: none Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. ADHD according to DSM-V-TR 2. Starting methylphenidate treatment *Exclusion criteria* 1. Any ocular abnormality other than disturbance of refractions 2. Any other medications
Interventions	Methylphenidate type: unknown Methylphenidate dosage: unknown Administration schedule: unknown Duration of intervention: 9 months Treatment compliance: unknown
Outcomes	Ocular examination before and after cycloplegia was performed at each visit, including Pentacam imaging of the anterior chamber Visual acuity, sphere, spherical equivalent refraction, intraocular pressure, and cup:disk ratio
Notes	Sample calculation: not stated Ethics approval: clinical research ethics committee Funding/vested interests: not stated *Key conclusions of the study authors*: methylphenidate does not seem to affect refraction in most children with ADHD. After 9 months of treatment, however, there was a reduction in the anterior chamber depth, which has been described as a powerful predictor of angle closure glaucoma. Further investigation of the potential ocular side effects of methylphenidate is warranted *Comments from the study authors*: this study is limited by the small sample size and short follow-up period. Further studies are warranted, because the decrease in ACD observed in this study may be a risk factor for the development of angle closure glaucoma *Supplemental information* regarding comorbidity received through personal email correspondence with the authors in June 2016 (Larrañaga-Fragoso 2016 [pers comm]). The authors were not able to supply us with information regarding IQ, ADHD subtype, methylphenidate dosage and type

Lee 2007

Methods	A cohort of methylphenidate use for 3 weeks plus 1 week baseline
Participants	Number of participants screened: not stated Number of participants included: 119 Number of participants followed up: 110 Number of withdrawals: 9

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Lee 2007 *(Continued)*

	Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 8.5 (SD1.6) years (range 6-13) IQ: > 70 Sex: 107 males, 12 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: South Korea Comorbidity: oppositional behaviours (14.8%), conduct behaviours (2.3%), obsessive-compulsive behaviours (0.8%), generalised anxiety symptoms (7.8%), depressive symptoms (12.5%), learning problems (18.8%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. Full diagnosis based on DSM-IV criteria 2. Moderate to severe level of impairment of ADHD symptoms 3. Drug naïve or not medicated ≥ 6 months before the initiation of the study 4. No abnormalities in baseline physical examination and routine laboratory tests 5. In addition only participants who were able to comply with the study visit schedule were included *Exclusion criteria*: 1. Presence of clinically significant gastrointestinal problems, cardiovascular disease, glaucoma, seizure disorder, psychotic disorder, clinical depression or Tourette syndrome 2. Suspicion or confirmation of substance abuse 3. Receiving clonidine or other alpha-2 adrenergic receptor agonists, tricyclic antidepressants, theophylline, coumarin or anticonvulsants 4. IQ < 70 as determined by the Korean Wechsler Intelligence Scale for children
Interventions	Methylphenidate type: osmotic release oral sytem (OROS) Mean methylphenidate dosage: 0.87 mg/kg (SD 0.33) Administration schedule: daily Duration of intervention: 3 weeks Treatment compliance: 2 participants discontinued trial due to protocol non-compliance
Outcomes	*Non-serious adverse events* • 18-item list of stimulant related AE symptoms (compiled by authors), self-reported, days 7, 14 and 21 • Physical examination, general chemistry tests, blood pressure, pulse rate, ECG; observer, baseline and end of study 1 respondent withdrew from trial during first week of trial on 18 mg OROS because of decreased appetite of moderate severity while another participant withdrew in the same period because of insomnia of mild severity
Notes	Sample calculation: yes Ethics approval: not stated

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Lee 2007 *(Continued)*

Funding/vested interests: funded by Janssen Korea

Key conclusions of the study authors: these data provide support for the benefit of the once daily methylphenidate preparation Concerta, in the treatment of Korean children with ADHD. Children were initiated safely in this short-term trial, and its effectiveness was evident in the behavioural, as well as neuropsychological measurements

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: not stated

Lee 2009

Methods	A prospective 12-week, open-label, multicentre study to examine optimal dosage of osmotic release oral system methylphenidate
Participants	Number of participants screened: not stated Number of participants included: 144 Number of participants followed up: 88 Number of withdrawals: 56 Diagnosis of ADHD: not stated (subtype: not stated) Age: mean 9.43, range 6-18 years old IQ: 109.7 (SD 16.1) Sex: 77 males, 11 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: Korea Comorbidity: oppositional defiant disorder (n = 12), tic disorder (n = 9), depressive disorder (n = 3), and anxiety disorder (n = 6) Comedication: not stated Sociodemographics: not stated *Exclusion criteria* 1. Use of methylphenidate hydrochloride other than OROS-MPH within the past 24 hours 2. Use of OROS-MPH within the past 3 months 3. Use of psychotropic medication within the past 4 months (clonidine or other α-adrenaline agonist, tricyclic antidepressant, selective serotonin reuptake inhibitor, theophylline, coumarin, or anticonvulsant, antipsychotics, benzodiazepine, modafinil) 4. History of hypersensitivity reaction to methylphenidate hydrochloride or another component of OROS methylphenidate 5. Other medical problems, such as gastrointestinal disorders, glaucoma, cardiovascular disease, or hyperthyroidism neurological illnesses, such as a seizure disorder 6. Comorbid psychiatric disorders, such as pervasive development disorder, psychotic disorder, or Tourette syndrome 7. IQ < 70, as assessed by the Korean Wechsler Intelligence Scale for Children (K-WISC-III)30 8. History of substance use or abuse 9. Possible pregnancy

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Lee 2009 *(Continued)*

Interventions	Methylphenidate type: osmotic release oral system (OROS) extended release Methylphenidate dosage: 18 mg or 27 mg (depending on clinical judgment) Mean methylphenidate dosage: 0.99 mg/kg (SD 0.29) at 12 weeks (n = 88) Administration schedule: not stated Duration of intervention: 12 weeks plus 9-week initial titration Treatment compliance: not stated
Outcomes	Of the 144 participants enrolled in the study, 8 dropped out due to adverse events (28.6%) during the titration phase
Notes	Sample calculation: not stated Ethics approval: approved by the Institutional Review Boards of all 7 sites Funding/vested interests: this study was supported by Janssen Korea Ltd. The authors have no financial conflicts of interest *Key conclusions of the study authors*: high response time (RT) among Korean children with ADHD on a computerised continuous performance attention test RT variability may predict poor response to MPH treatment in children with ADHD *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* requested twice from the study authors regarding supplemental data on adverse events with no answer

Lee 2012

Methods	A cohort study of methylphenidate use in children with ADHD for 4 weeks
Participants	Number of participants screened: not stated Number of participants included: 93 Number of participants followed up: 63 Number of withdrawals: 30 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (84.1%), hyperactive-impulsive (not stated), inattentive (not stated)) Age: mean 8.58 (SD 1.61) years IQ: mean 96.39 (SD 17.01) Sex: 56 males, 7 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: Korea Comorbidity: not stated Comedication: not stated Sociodemographics: not stated

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Lee 2012 *(Continued)*

	Inclusion criteria 1. 6-12 year old elementary school children with a diagnosis of ADHD recruited from 3 university hospitals 2. Children whose ADHD accompanied by anxiety disorder, oppositional defiant disorder, or conduct disorder were included in the study *Exclusion criteria* 1. Patients with tic disorder, Tourette syndrome, schizophrenia, bipolar disorder, major depressive disorder, obsessive-compulsive disorder or a pervasive development disorder 2. An IQ below 70, epilepsy or other neurological problems 3. Those who had been taking stimulants, antidepressants, antipsychotics, atomoxetine, clonidine, and antihistamine within 4 weeks of baseline 4. Sleep problems such as heavy snoring, sleep apnoea, sleep bruxism, narcolepsy, restless legs syndrome, and periodic limb movement disorder 5. Participants were dropped from the study if they violated the study protocol by failing to take the prescribed medicine more than twice a week, or if they presented with serious adverse effects such as seizures or hallucinations
Interventions	Methylphenidate type: osmotic release oral system (OROS) or Metadate-CD Mean methylphenidate dosage: 1.0 (SD 0.25) mg/kg. Initial doses for OROS-MPH 18 mg and Metadate-CD 10 mg; dose range and maximum dose for OROS-MPH was 0.4-1.8 mg/kg and 72 mg and for Metadate-CD was 0.6-1.5 mg/kg and 60 mg) Administration schedule: daily Duration of intervention: 4 weeks Treatment compliance: the children and caregivers were visited weekly to review whether medication was taken as prescribed
Outcomes	*Non-serious adverse events* • Daily sleep diaries were completed by caregivers (parents/guardians) at baseline and for 4 weeks after taking medication • Adverse events (AEs) chart was completed weekly on the basis of direct questions, clinical observations and physical examinations by child psychiatrist
Notes	Sample calculation: irrelevant Ethics approval: the study protocols were reviewed and approved by each site's Institutional Review Board Funding/vested interests: Yeungnam University research grants in 2009. No conflicts of interest statement *Key conclusions of the study authors*: methylphenidate had negative impacts on sleep among young ADHD children, but different preparations and doses did not affect the result *Comments from the study authors*: data yielded by a sleep diary, which relies on the validity of parents' observations, may not be an accurate representation of reality. Used a flexible titration method and did not divide the participants into parallel groups from the beginning. Lack of blinding. More than 30% did not complete the procedure. *Comments from the review authors*: participants were dropped from the study if they violated the study protocol by failing to take the prescribed medicine more than twice a week, or if they presented with serious adverse effects such as seizures or hallucinations *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* requested from the study authors in August 2014. Email sent twice but no answer received

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Lee 2014

Methods	A cohort study of medication-related adverse events in children and adolescents reported to the US Food and Drugs Administration (FDA) from 2007 to 2012
Participants	Number of patients screened: not stated Number of participants included: 4055 Diagnosis of ADHD: not stated Age: mean 10.2 years (range: 1-17) IQ: not stated Sex: not stated Ethnicity: not stated Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: All patient reports submitted to the FDA Adverse Event Reporting System (FAERS) between 1 January 2007 and 27 August 2012 for children (1-11 years) and adolescents (12-17 yrs) *Exclusion criteria*: none stated
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage: not stated Administration schedule: not stated Duration of intervention: not stated Treatment compliance: not stated
Outcomes	Type of adverse event: all adverse events and adverse events with serious outcomes. The description of the adverse events is coded based on a 'preferred term' from the Medical Dictionary for Regulatory Activities (MedDRA) terminology
Notes	Sample calculation: no Ethics approval: not reported Funding/vested interests/authors' affiliations: no *Key conclusions of the study authors*: our findings highlight the high-risk medications and the corresponding adverse events commonly reported in children and adolescents. Information from this analysis can be used to prioritise drugs and adverse events that might be investigated in future studies of drug safety in children *Comments from the study authors*: our findings are consistent with other studies that have used data from spontaneous reporting systems to examine the adverse events in children

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Lee 2014 *(Continued)*

	Supplemental information regarding data and IQ requested through personal email correspondence with the authors in June 2016 (Schumock 2016 [pers comm]). The authors were not able to retrieve the information

Lewis 2012

Methods	A patient report of a paediatric patient with glaucoma receiving methylphenidate treatment for 8 years
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 10 years old IQ: within normal limits Sex: female Country: USA Comorbidity: primary open angle glaucoma. Physical examination within normal limits Comedication: latanoprost 0.005% eye drops twice daily Sociodemographics: not stated
Interventions	Methylphenidate type: extended release Methylphenidate dosage: 18 mg/day titrated to 54 mg/day over 6 months Administration schedule: once daily Duration of treatment: 8 years Treatment compliance: not stated
Outcomes	*Non-serious adverse events* No exacerbation of glaucoma: Before methylphenidate treatment: after treatment for glaucoma, the patient's intraocular pressure was brought to a stable range between 16 mmHg and 19 mmHg in both eyes During methylphenidate treatment: ophthalmic examination every 6 months showed intraocular pressure consistently in the 16-19 mmHg range bilaterally
Notes	*Key conclusions of the study authors*: this report concluded stimulant medication (methylphenidate) should not be withheld in patients with glaucoma as long as intraocular pressure (IOP) remains well controlled *Comments from the study authors*: the actual risk associated with adrenergic medications in patients with open angle glaucoma is negligible, and there are no studies proving adverse effects on IOP in normal or open angle eyes *Supplemental information* regarding IQ received through personal email correspondence with the authors in March 2014 (Lewis 2014 [pers comm])

Li 2011

Methods	An 8-week, randomised, double-blind, parallel study with 2 interventions:

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Li 2011 *(Continued)*

1. Methylphenidate
2. Ningdong granule

Participants	Number of participants screened: 136 Number of participants included: 72 Number of participants randomised to methylphenidate: 36 Number followed up: 34 Number of withdrawals: 2 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 9.2, range 3-13 years old IQ: almost all above 70 Sex: 23 males, 13 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: China Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. ADHD according to DSM-IV 2. Teacher and Parent ADHD Rating Scale (Dupau, 1991) > 20 3. Patient from the outpatient department of integrative medicine in paediatrics, Provincial Hospital Affiliated to Shandong University and the department of Neurology, Tongji Hospital of Huazhong University of Science and Technology *Exclusion criteria* 1. Taken anti-ADHD medication prior to study 2. Chronic medical condition including past history of cardiovascular disease, organic brain disorder, seizures 3. Current abuse or dependence on drugs within 6 months
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage: 1 mg/kg/day Administration schedule: not stated Duration of intervention: 8 weeks Treatment compliance: not stated
Outcomes	*Serious adverse events*: • Side effects were systematically recorded and assessed using a checklist by the psychiatrist or parents anytime during the study • No serious adverse effects were reported during the study

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Li 2011 *(Continued)*

	Non-serious adverse events: • Blood was collected at the beginning and end of the trial • No abnormal findings were observed in the blood, urine and stool routine tests
Notes	Sample calculation: no Ethics approval: all research procedures were permitted by the medical ethics committee of Provincial Hospital Affiliated to Shandong University Funding/vested interests: grants from the Chinese Medicine Administration Bureau of Shandong Province Authors' affiliations: not stated *Key conclusions of the study authors*: compared to methylphenidate, Ningdong granule is effective and safe for ADHD children in the short term, increases the homovanillic acid concentration in sera to regulate dopamine metabolism, and promises to be an alternative medication, safely and effectively *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* received through personal email correspondence with the study authors in April 2013 (Li 2013 [pers comm])

Lyon 2010

Methods	A cross-over trial with 2 interventions: 1. DEX-methylphenidate 2. No medication/no intervention 10 children with ADHD and TD were given dexmethylphenidate on 1 visit and no medication on another (day 2 and 3), using a random cross-over design
Participants	Number of participants screened: 51 Number of participants included: 13 Number of participants followed up: 10 Number of withdrawals: 3 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (50%), inattentive (50%)) Age: mean 12.7 years old, range 8-16 years old IQ: mean 104, range 85-118 Sex: 9 males, 1 female Methylphenidate-naïve: not stated Ethnicity: white 70%, African American 0%, Asian 0%, Hispanic 30%, others 0% Country: USA Comorbidity: Tourette's 100% Comedication: 70% Sociodemographics: not stated

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Lyon 2010 *(Continued)*

Inclusion criteria

1. Age 10-17 years
2. DSM-IV-TR diagnosis of ADHD combined with either: Tourette Disorder or Chronic motor/vocal Tic Disorder
3. Baseline Yale Global Tic Severity Scale Total Tic Score ≥ 14 for TD or ≥ 10 for CTD
4. Exhibited 1 or more motor or vocal tics (or both) at a rate of ≥ 1 tic per minute averaged across a 10-minute videotaped observation
5. Intellectual functioning was at least in the low-average range or above as indicated by a score of greater than 75 on the Wechsler Abbreviated Scale of Intelligence (WASI)
6. No history of behavioural treatment for tics (greater than 3 weeks in duration) or other treatment in which suppression strategies were a primary component of the intervention
7. Current tic medication at the time of the study was allowed but no change of dose
8. Previous treatment with stimulants was allowed if the participant had not received stimulants for ≥ 48 hours prior to testing proceduresADHD symptoms must have been associated with impairment in at least one domain (home, school)

Exclusion criteria

1. Participants with pervasive developmental disorder, schizophrenia, major depressive disorder, bipolar disorder, or substance abuse disorder
2. Participants currently receiving stimulant medication who could not temporarily discontinue it for study procedures
3. Participants with any medical condition that would contraindicate use of a stimulant, such as seizure disorder, previous hypersensitivity to methylphenidate, glaucoma, or a significant cardiac history, including fainting or dizziness, seizures, rheumatic fever, chest pain or shortness of breath with exercise, unexplained change in exercise tolerance, palpitations, increased heart rate, hypertension, heart murmur other than benign functional murmur, or current viral illness with chest pains or palpitations
4. Participants with a family history of sudden or unexplained death in someone less than 35 years of age, sudden death during exercise, cardiac arrhythmias, cardiomyopathy, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy or right ventricular cardiomyopathy, long QT syndrome, short QT syndrome or Brugada syndrome, Wolf-Parkinson-White syndrome or abnormal cardiac rhythms, event requiring resuscitation in family members under the age of 35, including syncope requiring resuscitation, or Marfan syndrome
5. Participants with abnormal electrocardiogram (ECG) at baseline, including prolongation of the QTc interval greater than 450 ms for males and 470 ms for females
6. Participants who meet full criteria for obsessive-compulsive disorder or another anxiety disorder requiring pharmacological or behavioural treatment

Interventions	Participants were randomly assigned to 1 of 2 possible drug condition orders of (0.15 mg/kg) methylphenidate and placebo Mean methylphenidate dosage: 7.5 mg/day Administration schedule: once a day Duration of each medication condition: 1 day Washout prior to study initiation: not stated Medication-free period between intervention: not stated Titration period: none Treatment compliance: not stated
Outcomes	*Non-serious adverse events* The Safety Monitoring Uniform Report Form (SMURF) (Greenhill et al. 2004) was administered by one of the investigators on day 1, and after TSP procedures on days 2 and 3

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Lyon 2010 *(Continued)*

	Adverse events were generally mild. 7 (70%) participants experienced ≥ 1 minor adverse event during the study. The most common adverse events possibly related to study drug were drowsiness or sedation (20%) and stomach discomfort (20%)
Notes	Sample calculation: not stated Ethics approval: all study procedures were approved by the institutional review boards (IRB) at the University of Wisconsin-Milwaukee and New York University Langone Medical Center *Key conclusions from study authors*: preliminary results suggest that dexmethylphenidate does not appear to enhance tic suppressibility in children with ADHD and TD. First, there was a clear tic-reduction effect, and not exacerbation, with a 1-time dose of dexmethylphenidate compared to no medication in these children. Second, youths with TD and ADHD appear to be able to suppress their tics with a behavioural reward comparable to youths with TD without ADHD *Comments from the study authors*: some limitations of the study design need to be taken into account. First, our sample size was small and participants were recruited from a specialised clinic. Thus, findings may not generalise to non-specialty settings. Second, 70% of participants were receiving medication for TD, anxiety, OCD, or asthma, and our results might have differed if the participants were not receiving concomitant medication. Third, investigators, parents, and participants were not blind to medication status, because medication was administered openly *Comments from the review authors*: ADHD outcome data are only available for 7 participants ('data from 3 participants were unusable as a result of computer malfunction') *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Maayan 2009

Methods	A cohort study of long-acting methylphenidate use for 4 weeks
Participants	Number of participants screened: not stated Number of participants included: 11 Number of participants followed up: 8 Number of withdrawals: 3 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (91%), hyperactive-impulsive (9%)) Age: mean 5.1, range: 4-5 years old IQ: above 70 Sex: 9 males, 2 females Methylphenidate-naïve: 100% Ethnicity: white 27%, Hispanic 73% Country: USA Comorbidity: ODD 9% Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. Symptomatic for ≥ 9 months

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Maayan 2009 *(Continued)*

	2. Parents and children had to speak English or Spanish 3. Only children who were enrolled in an educational setting with ≥ 8 same-age peers for at least 2 half days per week were eligible for the study. Participants had to have a CGI-S score of ≥ 4 (moderately mentally ill) and a C-GAS score ≥ 55. The Kaufman Brief Intelligence Test (K-BIT) was administered to confirm an intelligence quotient (IQ) ≥70 *Exclusion criteria* 1. History of intolerance or non-response to stimulants 2. Current adjustment disorders, autism, psychosis, bipolar disorder, or suicidality 3. Children with a history of significant physical, sexual, or emotional abuse and medical abnormalities that would make use of B-MPH clinically inappropriate were also excluded. 4. Concomitant treatments with antihypertensives, medication affecting blood pressure or heart rate, sedating antihistamines, antiseizure medications, diphenhydramine, and/or other psychotropic agents were not allowed during the study
Interventions	Methylphenidate type: long acting Methylphenidate dosage: 10-30 mg/day, mean 17.73 mg/day Administration schedule: morning Duration of intervention: 4 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events* Decreased appetite was experienced by 7 participants (64%) following treatment initiation. 5 out of these 7 participants continued to report decreased appetite for the duration of the study Difficulty sleeping occurred in 3 participants (27%) Emotional lability and gastrointestinal pain were reported by 2 participants (18%) These adverse events were resolved by the end of the study. 1 participant who terminated the study early experienced moderate levels of insomnia, vomiting, decreased appetite, and stomach pain, and another who also terminated early experienced moderate irritability
Notes	Sample calculation: no Ethics approval: the study was approved by the New York State Psychiatric Institute Columbia University Institutional Review Board (IRB) and was conducted in accordance with the ethical standards of the 1975 Declarations of Helsinki as revised in 2000 (World Medical Association). Funding/vested interests/authors' affiliations: Novartis Pharmaceuticals Corporation provided the study medication. No financial support was received from Novartis. Dr Maayan receives grant support from Eli Lilly and Pfizer. Dr Greenhill received support from Novartis and has an consultant arrangement with Pfizer. He has been awarded research contract to study Risperidon by Johnson and Johnson and has been awarded an investigator-initiated grant to study aripiprazole by Otsuka *Key conclusions of the study authors*: long-acting methylphenidate was safe and effective for the treatment of ADHD in the 4- and 5-year-olds participating in this study. Rates of adverse events were higher than previously reported in methylphenidate trials of school-aged children. 10-mg/day doses failed to achieve response in the 5 children who could not tolerate higher doses *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes

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MacDonald 2005

Methods	A cross-over study of 5 children, 4 boys, 1 girl all aged 10-14 years old Volunteers participated in 13 sessions
Participants	Number of participants screened: 14 Number of participants included: 5 Number of participants followed up: 5 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 12, range 10-14 IQ: not stated Sex: 4 males, 1 female Methylphenidate-naïve: none Ethnicity: not stated Comorbidity: not stated Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. ADHD diagnosis by community physician 2. Confirmed by T score ≥ 65 on CBCL Attentional Problems subscales 3. Conners' Parent Rating Scale - 48 (CPRS 48) Impulsive-Hyperactive Scale T score ≥ 65) 4. Taking methylphenidate for ≥ 1 year *Exclusion criteria* 1. Taking any other type of psychoactive medication 2. Exhibited any gross neurological, sensory, or motor impairment 3. A history of other significant learning or psychiatric problems 4. A known family history of diabetes (placebo contained sugar)
Interventions	Methylphenidate type: immediate release Methylphenidate dosage: individual maintenance dose as taken by participant prior to study enrolment, range 10 mg twice/day to 30 mg thee times/day Administration schedule: morning Duration of intervention: ≥ 1 year Treatment compliance: not stated
Outcomes	No relevant outcomes
Notes	Sample calculation: no Ethics approval: Human Subjects Institutional Review Board at Western Michigan University, Kalamazoo, MI Funding/vested interests/authors' affiliations: not stated

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MacDonald 2005 *(Continued)*

Key conclusions of the study authors: 3 of 5 participants reliably chose methylphenidate more often than placebo. Differences between the number of methylphenidate, placebo, and neither choices across participants were significant (P < 0.01)

Comments from the study authors: relevant clinical effects were not observed under methylphenidate compared to placebo conditions. Although the questionnaires used in this study have been used to measure subjective effects in children, the psychometric integrity of these instruments has not been determined in these populations. In addition, the reading level of the children may have affected the manner in which the subjective effects were evaluated, such that the participants may not have fully understood the items on the questionnaires

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: not stated

Machado 2010

Methods	A patient report of a 6-year old girl developing acute choreoathetoid movements induced by methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 6 years old IQ: above 70 Sex: female Ethnicity: not stated Country: USA Comorbidity: psychomotor developmental delay, discrete macrocephalus, congenital mild ataxia, and hyperactivity. Otherwise healthy Comedication: none Sociodemographics: her parents were first-degree relatives. No family history of neurological disease
Interventions	Methylphenidate type: extended release Methylphenidate dosage: 18 mg/day Administration schedule: once daily in the morning Duration of treatment: single dose
Outcomes	*Serious adverse events*: After single dose extended-release methylphenidate 18 mg: choreoathetoid movements of orofacial muscles, arms, and legs, with transient dystonic postures of the right arm
Notes	*Key conclusions of the study authors*: we believe that the immediate response ensuing chlorpromazine prescription argues in favor of a specific role for dopamine receptor antagonists in methylphenidate-induced chorea *Comments from the review authors*: the author is not sure that the girl fulfilled criteria E of the ADHD diagnosis (DSM-IV). The author only saw the girl once in the emergency unit *Supplemental information* regarding diagnosis and IQ received through personal email correspondence with the authors in October 2013 (Machado 2013 [pers comm])

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Maia 2008

Methods	8-week open clinical trial
Participants	Number of participants screened:159 Number of participants included: 120 Number of participants followed up: 39 Number of withdrawals: 6 Diagnosis of ADHD: DSM-IV (subtype: combined (67.7%)) Age: mean 12.17 (SD 2.67) IQ: mean 89.11 (SD 16.07) Sex: 36 males, 3 females Methylphenidate-naïve: none Ethnicity: European-Brazilian (31), other (8) Country: Brazil Comorbidity: oppositional defiant disorder (48.4%), anxiety disorder (29%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. ADHD diagnosis according to the DSM-IV criteria 2. Clinical stability with MPH-IR defined by scores below 1.5 on all Swanson, Nolan, and Pelham-IV Questionnaire (SNAP-IV) subscales (inattention, hyperactive/impulsive and opposition defiant) at last appointment *Exclusion criteria* 1. A clinically coexisting medical condition likely to impede the administration of MPH-SODAS 2. Previous diagnosis of alcohol and/or drug abuse or dependence 3. Previous diagnosis of moderate mental retardation 4. Concomitant psychotherapy
Interventions	Patients switched from equivalent dose of immediate release methylphenidate to methylphenidate SODAS. The mean methylphenidate-IR dose at baseline was 0.68 (SD 0.24) mg/kg/day and the mean methylphenidate-SODAS dose prescribed at baseline was 0.7 (SD 0.25) mg/kg/day Methylphenidate type: spheroidal oral drug absortion system (SODAS) Methylphenidate dosage: 20-40 mg Mean methylphenidate dosage: 0.7 (SD 0.25) mg/kg/day Administration schedule: once daily Duration of intervention: 8 weeks Treatment compliance: the treatment adherence was checked by direct inquiring patients on compliance at week 4 and 8
Outcomes	*Serious adverse events*: Barkley Side Effect Rating Scale (SERS)

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Maia 2008 *(Continued)*

	Non-serious adverse events: Barkley Side Effect Rating Scale (SERS) SNAP-IV Efficacy and side events were rechecked at week 4 and 8 using respectively the total, inattentive, hyperactive/impulsive scores of the SNAP-IV and the total score of the SERS
Notes	Sample calculation: no Ethics approval: yes Funding: Novartis Vested interest/authors' affiliations: none *Key conclusions of the study authors*: results suggested that switching from immediate release methylphenidate to methylphenidate SODAS did not affect stabilisation of ADHD symptoms in most patients. Methylphenidate prescription in patients with previous cardiovascular conditions must be extremely careful *Comments from the review authors*: the additional data received from the authors do not provide the numbers of adverse events in the paediatric population *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Man 2015

Methods	A cohort study of methylphenidate and the risk of trauma
Participants	Number of participants screened: 17,381 Number of participants included: 4934 Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: ICD-9-CM (subtype: not stated) Age: mean age at commencement of observation 6.9 years. Range 6-19 IQ: not stated Sex: 4309 males (87%), 625 females (13%) Methylphenidate-naïve: not stated Ethnicity: not stated Country: Hong Kong Comorbidity: acute reaction to stress (1.46%), adjustment disorder (1.42%), anxiety disorder (1.64%), autism spectrum disorder (12.7%), disturbance of conduct not elsewhere classified (2.39%), disturbance of emotions specific to childhood and adolescence (10.9%), specific delays in development (12.2%), other psychiatric comorbidities (8.84%) Comedication: no atomoxetine - not otherwise stated Sociodemographics: not stated *Inclusion criteria* 1. Participants aged 6-19 years 2. Received ≥ 1 prescription of methylphenidate 3. ≥ 1 trauma-related ED admission during the study period (January 2001-December 2013) *Exclusion criteria* 1. Patients with ≥ 1 prescription of atomoxetine

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Man 2015 *(Continued)*

Interventions	Methylphenidate type: all formulations, standard and extended release Methylphenidate dosage: median daily dosage: 20 mg, IQR of daily dosage: 20 mg (all), 20 mg(male), 15 mg (female) Administration schedule: not stated Duration of intervention: median length of prescription 70 days Treatment compliance: not stated
Outcomes	Trauma-related ED admission Non-trauma related ED admission
Notes	Sample calculation: with reference to the equation developed by Musonda 2006, an IRR of 0.9 with 80% power (2-sided 95% CI) could be detected with a minimum of 4062 trauma-related ED admissions Ethics approval: not stated Funding: funding received from the Research Grants Council (RGC, Hong Kong) under grant agreement number 781913 for the study (Effects of Attention Deficit Hyperactivity Disorder pharmacotherapy on hospital accident and emergency admission due to injury-related events (ATHAN)) Vested interests: Dr Chan reports grants from Janssen (a division of Johnson & Johnson), BMS, Pfizer, The Research Grant Council (RGC, Hong Kong), received for other work. Dr Coghill reports grants and personal fees from Shire and Vifor; personal fees from Janssen-Cilag, Lilly, Novartis, Flynn Pharma, Medice, and Oxford University Press, received for other work. Dr Douglas reports personal fees from GSK and Gilead, received for other work. Prof ICK Wong reports grants from the Research Grants Council (RGC, Hong Kong) (during the study) and grants from Shire, Janssen-Cilag, Eli Lily, the European Union FP7 programme, received for other work. The other authors have indicated they have no financial relationships relevant to this article to disclose Authors' affiliations: Dr Coghill reports grants and/or personal fees from Shire, Janssen-Cilag, Novartis, Flynn Pharma, and Medice; and Prof I.C.K. Wong was a member of the National Institute for Health and Clinical Excellence ADHD Guideline Group and the British Association for Psychopharmacology ADHD Guideline Group and acted as an advisor to Shire. The other authors have indicated they have no potential conflicts of interest to disclose *Key conclusions of the study authors*: our study findings support the hypothesis that methylphenidate is associated with a reduced risk of trauma-related ED admission in children and adolescents of both genders *Comments from the study authors*: this outcome has important clinical, resource utilisation, and public health implications. Trauma prevention should be considered in the broader clinical assessment of methylphenidate risks and benefits aside from the traditional consideration of improving academic performance

Mayes 1994

Methods	A cohort study of 69 children with attention deficit hyperactivity disorder (ADHD) who underwent blind methylphenidate trials
Participants	Number of participants screened: not stated Number of participants included: not stated Number of participants followed up: 69 Number of withdrawals: not stated Diagnosis of ADHD: DSM-IIIR (subtype: hyperactive-impulsive (100%)) Age: mean 7.1 years old, range 22 months-13 years

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Mayes 1994 *(Continued)*

	IQ: mean 86, range 23-136 Sex: not stated Methylphenidate-naïve: not stated Ethnicity: not stated Country: USA Comorbidity: 36 had ADHD alone (with or without a learning disability) and 33 had additional neurodevelopmental disorders Comedication: not stated Sociodemographics: not stated *Exclusion criteria* 1. Children with ADHD but not hyperactivity
Interventions	MPH was prescribed three times daily (8 am, noon, 4 pm) with a starting dose of 0.3 mg/kg rounded to the nearest 2.5 mg. MPH was trialled using an ABA design (A = no medication, B = MPH). Days per MPH dosage was a minimum 3 days (mean of 6 days) and no medication minimum of 6 days (mean 11 days). MPH was increased by 2.5 mg or 5 mg per dose until a response was achieved. The total mean days per MPH dosage was 8 days, mean days no medication 9 days. Doses for responders 50/69 ranged from a dosage of 2.5 mg to 10 mg. The dosage given to the 19/69 who did not respond or did not complete the trial (6/69) were not reported
Outcomes	*Non-serious adverse events* An adverse event was defined as being reported on ≥ 2 methylphenidate days (i.e. at the response dosage for responders or at the highest dosage for non-responders) and not reported on ≥ 2 methylphenidate-free days
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interests: not stated *Key conclusions of the study authors*: the results confirm and add to the research literature indicating that ADHD children who are of preschool age and/or who have co-existing neurological disorders may benefit from methylphenidate *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* has not been able to retrieve from authors due to lack of email address

McCarthy 2009

Methods	A retrospective cohort study of methylphenidate, dexamphetamine and atomoxetine use
Participants	Number of participants screened: approximately 3 million Number of participants included: 5351 Number of participants followed up: not stated Number of withdrawals: not stated

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McCarthy 2009 *(Continued)*

	Diagnosis of ADHD: not stated (subtype: not stated) Age: mean not stated, range: 2-21 years old IQ: not stated Sex: not stated Methylphenidate-naïve: not stated Ethnicity: not stated Country: UK Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. 2-21 years 2. ≥ 1 prescription for methylphenidate, dexamphetamine or atomoxetine
Interventions	Methylphenidate type: not stated Methylphenidate dosage: not stated Administration schedule: not stated Duration of intervention: not stated Treatment compliance: not stated
Outcomes	*Serious adverse events*: 5 deaths: 1. Patient aged 16-21, cause of death: overdose. No active methylphenidate prescription. Comorbid anxiety/insomnia 2. Patient aged 16-21, cause of death: unknown. No active methylphenidate prescription. Comorbid depression 3. Patient aged 16-21, cause of death: stab wounds. No active methylphenidate prescription 4. Patient aged 8-15, cause of death: suicide. Active methylphenidate prescription 5. Patient aged 8-15, cause of death: suicide. Active methylphenidate prescription. Comorbid aggressive personality
Notes	Sample calculation: not stated Ethics approval: ethics approval for the study was granted by the Independent Scientific Advisory Commitee for the Medicines and Healthcare products Regulatory Agency (MHRA) database research Funding/vested interests: the School of Pharmacy has received an education grant from Janssen Cilag for professional continued development courses. No specific funding was obtained for the conduct of this study. Ian Wong was funded by a UK Department of Health Public Health Career Scientist Award to investigate the safety of psychotropic drugs in children. Eric Taylor and CK Wong were members of the NICE guideline committee for the diagnosis and management of ADHD in children, young people and adults. The other authors have no conflict of interests relevant to the content of this study *Key conclusions of the study authors*: in this study, it was not possible to demonstrate an increase in the risk of sudden death associated with methylphenidate, dexamphetamine or atomoxetine. Although it was not an initial aim of this study, an increase in the risk of suicide was observed, particularly in the younger teenager category

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McCarthy 2009 *(Continued)*

	Comments from the study authors: clinicians should identify patients at increased risk for cardiovascular events and those patients at increased risk for suicide, particularly males with co-morbid conditions, and monitor them appropriately *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated

McCracken 2016

Methods	An 8-week double-blind randomised controlled trial
Participants	Number of participants screened: 323 Number of participants included: 69 Number of participants followed up: 61 Number of withdrawals: 8 Diagnosis of ADHD: DSM-IV (subtype: combined (46%), hyperactive-impulsive (3%), inattentive (48%)) Age: mean 10.1 (SD 2.0) years (range: 7-14) IQ: mean 101.5 (SD 13.3) Sex: 46 males (66.7%), 23 females (33.3%) Methylphenidate-naïve: not stated. The participants received placebo only the first 4 weeks of the trial before starting methylphenidate treatment Ethnicity: white 73.9%, Black 14.5%, Asian, Pacific Islander 5.8%, Hispanic 14.5%, others 5.8% Country: USA Comorbidity: oppositional defiant disorder 24 (35%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Male or female aged 7-14 years old 2. DSM-IV ADHD (any subtype) diagnosed by semi-structured diagnostic interview (Kiddie-Schedule for affective disorders and schizophrenia-PL and clinical interview) 3. Clinical Global Impression-Severity (CGI-S) scale score ≥ 4 for ADHD *Exclusion criteria* 1. Autistic disorder, any neurological disorder, chronic tic disorder, or structural heart defects 2. Current major depression, panic disorder, lifetime bipolar disorder or psychosis 3. Systolic or diastolic blood pressure > 95th or < 5th percentile for age and BMI 4. Medical condition contraindicating stimulants or alpha agonists 5. Need for chronic use of other central nervous system (CNS) medications 6. Full scale IQ < 80
Interventions	Methylphenidate type: dexmethylphenidate Mean methylphenidate dosage: 16.0 (SD 3.9) mg (range 5-20) Administration schedule: once daily

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McCracken 2016 *(Continued)*

	Duration of intervention: 4 weeks Treatment compliance: not stated
Outcomes	Side effects were measured via a structured instrument, using a modification of the Physical Symptom Checklist and open-ended clinician inquiry
Notes	Sample calculation: not stated Ethics approval: yes Funding: supported by National Institute of Mental Health (NIMH) grants Vested interests/authors' affiliations: Dr Bilder has received consulting income or honoraria from EnVivo Pharmaceuticals, Forum Pharmaceuticals, Lumos Labs, Maven Research, Neurocog Trials Inc., OMDUSA, LLC, Snapchat, Takeda-Lundbeck, and ThinkNow Inc. He has received research support from the National Institute of Mental Health, the John Templeton Foundation, and Johnson and Johnson. Dr Piacentini has received grant or research support from the National Institute of Mental Health, Pfizer Pharmaceuticals through the Duke Clinical Research Institute CAPTN Network, Psyadon Pharmaceuticals, and the Tourette Association of America. He has received financial support from the Petit Family Foundation and the Tourette Syndrome Association Center of Excellence Gift Fund. He is a co-author of the Child OCD Impact Scale-Revised (COIS-R), the Child Anxiety Impact Scale (CAIS), the Parent Tic Questionnaire (PTQ), and the Premonitory Urge for Tics Scale (PUTS) assessment tools, all of which are in the public domain therefore no royalties are received. He has received royalties from Guilford Press and Oxford University Press. He has served on the speakers' bureau of the Tourette Association of America, the International Obsessive Compulsive Disorder Foundation, and the Trichotillomania Learning Center. Dr McGough has received consultant honoraria from Neurovance; research support from Purdue; material research support for investigator initiated studies from NeuroSigma and Shire; book royalties from Oxford University Press; and DSMB honoraria from Sunovion. He has provided expert testimony for Shire. Dr McCracken has received consultant honoraria from Dart Neuroscience and Think Now, Inc. Drs. Loo, Sturm, Cowen, Walshaw, Levitt, Del'Homme, and Mr Cho report no biomedical financial interests or potential conflicts of interest *Key conclusions of the study authors*: combination medication treatment showed consistent evidence for clinical benefits over monotherapies, possibly reflecting advantages of greater combined dopaminergic and alpha2A agonists. Adverse events were generally mild to moderate, and combination treatment showed no differences in safety or tolerability *Comments from the study authors*: this design allows us to compare the medication conditions by comparing all participants and time-points for which that condition occurred, after adjusting for overall drift. *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated

McLaren 2010

Methods	A patient report of acute dystonia following withdrawal of methylphenidate treatment in the context of multiple high dose drug treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 11 years old IQ: no mental retardation Sex: male Ethnicity: not stated

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McLaren 2010 *(Continued)*

	Country: USA Comorbidity: bipolar disorder Comedication: aripiprazole, 15 mg, twice daily. Lithium carbonate, 600 mg and 300 mg at night. Clonidine, 0.2 mg, twice daily Sociodemographics: not stated
Interventions	Extended-release OROS methylphenidate dosage: 108 mg daily Administration schedule: not stated Duration of treatment: 4 years prior to withdrawal in hospital. The last 6 months the dose had not been changed. Treatment compliance: not stated
Outcomes	*Non-serious adverse events* Acute dystonia after discontinuation of OROS methylphenidate The patient experienced spasmodic muscular contractions of his jaw. The staff noticed a forceful jaw closure, contraction, and tension, and the patient had difficulties opening his mouth. Intramuscular diphenhydramine at 50 mg was administered intramuscularly, and the patient could open his mouth within 30 minutes and with no further dystonia
Notes	Funding/vested interest/authors' affiliations: none declared *Key conclusions of the study authors*: need for vigilance regarding development of acute dystonic reactions when discontinuing methylphenidate whilst using concomitant antipsychotic drugs *Comments from the review authors*: the patient was on extremely high doses, not normally given to patients of this age, of all of the medication that he was on i.e. extended-release OROS methylphenidate 108 mg (twice the recommended maximum dose), aripiprazole 15 mg twice daily (also in excess of double the normal maximum dose), lithium 900 mg daily (very high for a child of 11 years) and clonidine 0.2 mg (around double the maximum recommended dose) *Supplemental information* regarding patients diagnostic criteria and IQ received through personal email correspondence with the authors in October 2013 (McLaren 2013 [pers comm])

Miller-Horn 2008

Methods	A retrospective cohort study of patients with ADHD attending a clinic over a 2-year period taking methylphenidate
Participants	Number of participants screened: 516 Number of participants included: 150 Number of participants followed up: 137 Number of withdrawals:13 63 took MPH, of which 40 (29.2% of whole sample) took extended release methylphenidate and 23 (16.8%) took immediate release methylphenidate. Diagnosis of ADHD: DSM-IV (subtype: combined 121 (88.3%), hyperactive-impulsive 4 (2.9%), inattentive 12 (8.8%))

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Miller-Horn 2008 *(Continued)*

	Age: males: mean 9.9 (SD 3), range 4-19 years old; females: 10.9 (SD 3.4), range 4-17 years old IQ: not stated Sex: 109 males, 28 females Methylphenidate-naïve: 65% Ethnicity: not stated Country: USA Comorbidity: 87 (64%) (type: oppositional defiant disorder/conduct disorder (16%), seizures (15%), learning disabilities (14%), PDD 13%, sleep disturbances (9%), mental retardation/cerebral palsy (7%), chronic headaches (6%), Tourette's (6%), obsessive compulsive disorder/depression (6%)) Comedication: all patients were on monotherapy for medications used in the treatment of ADHD; however, some of the patients were currently being treated for comorbid conditions Sociodemographics: not stated *Inclusion criteria* 1. DSM-IV diagnosis of ADHD 2. Taking anti-ADHD medication including any form of dexamphetamine, any form of methylphenidate, atomoxetine *Exclusion criteria* 1. Treatment with any other medication including clonidine, Focalin, Metadate, guanfacine 2. Patients diagnosed and/or treated by a clinician "outside our group"
Interventions	Methylphenidate type: osmotic release oral system (OROS) and immediate release OROS-methylphenidate dosage: mean 34.2 (SD 13.6) mg/day (range 18-54) IR-methylphenidate dosage: mean 23.3 (SD 14.8) mg/day (range 5-60) Administration schedule: not stated Duration of intervention: not stated Treatment compliance: not stated
Outcomes	Retrospective database analysis. The database contained information on side effects. No other information regarding measurement available
Notes	Sample calculation: not stated Ethics approval: approved by the Institutional Review Board at St. Christopher's Hospital for Children in Philadelphia Funding/vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: atomoxetine showed a significantly lower incidence of headaches than amphetamine/dextroamphetamine XR, amphetamine/dextroamphetamine or OROS-methylphenidate *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* requested twice in June 2014 with no reply

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Mino 1999

Methods	A patient report on methylphenidate-induced psychosis in an adolescent with hyperkinetic disorder
Participants	Diagnosis of ADHD: DSM-III-R and later ICD-10 (subtype: not stated) Age: 16 years old IQ: around 70 Sex: female Ethnicity: not stated Country: Japan Comorbidity: conduct disorder and secondary neurotic symptoms Comedication: not at the time when the patient took methylphenidate Sociodemographics: lives with parents and stepsister
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 10 mg for 3 weeks, reduced to 5 mg for 1 week Administration schedule: once daily, morning Duration of intervention: 1 month Treatment compliance: not stated
Outcomes	*Serious adverse events*: 3 weeks after starting on methylphenidate (10 mg/day), the mother reported by telephone that the patient seemed depressed. Dose of methylphenidate was reduced to 5 mg/day. A week later the patient visited the clinic. The therapist diagnosed her condition as a depressive state and discontinued methylphenidate. 6 weeks after discontinuation of methylphenidate she was diagnosed with schizophrenic-like psychotic state, due to symptoms of delusions of reference and persecution, delusional mood, silly smile and thought block. There was no evident hallucination. The patient took antipsychotic medication for 2 months, and her psychotic symptoms disappeared.
Notes	*Key conclusions of the study authors*: we discuss this case as an example of methylphenidate-induced psychosis *Comments from the study authors*: we suggest that there are 2 types of methylphenidate psychosis: the first being hallucination dominant type and the second, delusion dominant type. This patient report address the second one *Comments from the review authors*: another article written in Japanese by the same authors found in our search. The abstracts of the 2 articles were identical, and the Japanese full-text has therefore not been translated Funding/vested interests/authors' affiliations: not stated

Mize 2004

Methods	A patient report of headache and mild depression during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 12 years and 3 months old

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Mize 2004 *(Continued)*

	IQ: 124 Sex: male Ethnicity: not stated Country: USA Comorbidity: none stated Comedication: not stated Sociodemographics: not stated
Interventions	Methylphenidate type: Ritalin slow release Methylphenidate dosage: 20 mg/daily Administration schedule: not stated Duration of treatment: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Headache and symptoms of mild depression
Notes	*Key conclusions of the study authors*: 10 sessions of haemoencephalograph appear to have produced significant change in attention *Comments from the review authors*: the study shortly comments that the boy has headache and symptoms of mild depression when taking methylphenidate (20 mg/daily) Funding/vested interest/authors' affiliations: not stated

Mohammadi 2004

Methods	A 6-week, parallel group, randomised trial with 2 arms: 1. Methylphenidate 2. Theophylline
Participants	Number of participants screened: not stated Number of participants included: 32 Number of participants randomised to methylphenidate: 16 Number of participants followed up: 11 Number of withdrawals: 5 Diagnosis of ADHD: DSM-IV (subtype: combined (100%)) Age: mean 8.87 years (range 6-14) IQ: > 70 Sex: 11 males, 5 females Methylphenidate-naïve: 100%

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Mohammadi 2004 *(Continued)*

	Ethnicity: 100% Persian Country: Iran Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. 6-14 years 2. ADHD according to DSM-IV diagnostic criteria 3. Newly diagnosed *Exclusion criteria* 1. Previously diagnosed with a psychiatric disorder or mental retardation (IQ < 70) 2. A clinically significant chronic medical condition, including a past history of cardiovascular disease, organic brain disorder, seizures, current abuse or dependence on drugs within 6 months and current treatment with psychotropic medications 3. Parents and children had to be willing to comply with all requirements of the study
Interventions	Methylphenidate type: not stated Methylpenidate dosage: 1 mg/kg/day Administration schedule: not stated Duration of intervention: 6 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Headaches were observed more often in the methylphenidate group
Notes	Sample calculation: yes Ethics approval: not stated Funding: the study was supported by a grant from Tehran University of Medical Sciences Vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: the results suggest that theophylline may be a useful for the treatment of ADHD. In addition, a tolerable side-effect profile is one of the advantages of theophylline in the treatment of ADHD *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no. All participants were newly diagnosed

Mohammadi 2009

Methods	42 days double-blind, parallel, randomised clinical trial with 2 arms: 1. Ritalin 2. Stimdate
Participants	Number of participants screened: not stated

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Mohammadi 2009 *(Continued)*

	Number of participants included: 60 Number of participants randomised to Ritalin: 30; Stimdate: 30 Number of participants followed up in each arm: Ritalin: 24; Stimdate: 30 Number of withdrawals in each arm: Ritalin: 6; Stimdate: 0 Diagnosis of ADHD: DSM-IV-TR (subtype: not stated) Age (Ritalin): mean 9.21 years (range 6-15) Age (Stimdate): mean 9.29 years (range 6-15) Sex (Ritalin): 23 males, 7 females Sex (Stimdate): 22 males, 8 females Methylphenidate-naïve: not stated Ethnicity: 100% Persian Comorbidity: not stated Comedication: not stated IQ: > 70 Sociodemographics: not stated *Inclusion criteria* 1. ADHD DSM-IV-TR 2. 6-15 years old 3. IQ > 70 *Exclusion criteria* 1. Current diagnosis of any other axis I psychiatric disorders 2. Substance abuse or dependency 3. A history of seizures or any other serious medical disorders and use of any psychotropic drugs in the 6 weeks prior to the study
Interventions	Participants were randomly assigned to Ritalin or Stimdate Methylphenidate type: extended release (Ritalin) or Extended release (Stimdate) Mean methylphenidate dosage: 25 mg/day. Titrated to the highest dose level; 1 mg/kg/day Ritalin or Stimdate, or a maximum of 40 mg/day Administration schedule: orally twice daily 7.30-8.00 am and 12:00 to 1:00 pm Duration: 42 days Treatment compliance: not stated
Outcomes	No usable data
Notes	Sample calculation: no Ethics approval: not stated Funding/vested interest: not stated

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Mohammadi 2009 *(Continued)*

Key conclusions of the study authors: based on the results of this study, no significant difference was observed between the 2 medications, and it seems both drugs behave in a similar way. In addition, Stimdate appears to be effective and well tolerated for ADHD in children and adolescents in Iran

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no

Supplemental data regarding side effects requested from the study authors twice in November 2013 with no reply

Mohammadi 2010

Methods	A 6-week, parallel group, double-blind, randomised clinical trial with 2 arms: 1. Methylphenidate 2. Amantadine
Participants	Number of participants screened: 65 Number of participants included: 40 Number of participants randomised to methylphenidate: 20 Number of participants followed up: 19 Number of withdrawals: 1. Diagnosis of ADHD: DSM-IV (subtype: combined (100%)) Age: mean 9.25, range 6-14 years old IQ: > 70 Sex: 13 males, 7 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Iran Comorbidity: none Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. 6-14 years old 2. DSM-IV-TR diagnosis of ADHD 3. Total or subscale scores (or both) on ADHD-RS-IV School Version of ≥ 1.5 SD above norms for patient's age and gender 4. Parents and children had to be willing to comply with all requirements of the study *Exclusion criteria* 1. A history or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders (DSM-IV axis I) 2. Any current psychiatric comorbidity that required pharmacotherapy 3. Any evidence of suicide risk and mental retardation (IQ < 70)

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Mohammadi 2010 *(Continued)*

	4. A clinically significant chronic medical condition, including organic brain disorder, seizures and, current abuse or dependence on drugs the last 6 months, hypertension or hypotension
Interventions	Methylphenidate type: Ritalin Methylphenidate dosage: 20-30 mg/day depending on weight (20 mg/day for < 30 kg and 30 mg/day for > 30 kg) Mean methylphenidate dosage. At week 6: 25.50 mg (SD 5.10) Titration period: 3 weeks after randomisation Duration of intervention: 6 weeks Treatment compliance: not stated
Outcomes	Side effects checklist that comprises 20 side effects including psychic, neurologic, autonomic and other side effects, administered by a child psychiatrist on days 7, 21 and 42 Body weight and vital signs were measured at baseline and weeks 1, 2, 4 and 6 12-lead ECG and physical examinations were evaluated at baseline and week 6 Haematology tests were collected at baseline and weeks 2, 4 and 6; serum chemistry and urinalysis were evaluated at baseline and week 6
Notes	Sample calculation: not stated Ethics approval: yes Funding: the study was supported by a grant from Tehran University of Medical Sciences. Vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: the results of this study indicate that amantadine significantly improved symptoms of ADHD and was well tolerated and it may be beneficial in the treatment of children with ADHD. Nevertheless, the present results do not constitute proof of efficacy *Supplemental information* requested from the study authors twice in July and August 2013 with no reply

Mohammadi 2012a

Methods	An 8-week double-blind parallel-group randomised controlled trial with 2 arms: 1. Methylphenidate + placebo 2. Methylphenidate + melatonin
Participants	Number of participants screened: not stated Number of participants included: 60 Number randomised to methylphenidate + placebo: 32 and methylphenidate + melatonin: 28 Number followed up in the methylphenidate + placebo group: 24 Number of withdrawals in the methylphenidate + placebo group: 8 **Methylphenidate + placebo group** Diagnosis of ADHD: ICD-10 (subtype: combined (100%))

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Mohammadi 2012a *(Continued)*

	Age: mean 8.83 years old (range 7-12) IQ: above 70 Sex: 17 males, 7 females Methylphenidate-naïve: 100% were newly diagnosed Ethnicity: not stated Country: Iran Comorbidity: no Comedication: no Sociodemographics: level of family income: low (58.8%), average (23.6%), high (17.6%) *Inclusion criteria*: 1. 7-12 years old 2. Newly diagnosed with ADHD, ICD-10 combined type 3. Clinical need to be treated with methylphenidate 4. Parental and child consent *Exclusion criteria*: 1. Use of any confounding drugs or dietary supplements 2. History of major prenatal complications such as prematurity 3. Low birthweight (reported by parents) 4. Any past or present psychosis, comorbid Tourette syndrome, celiac, phenylketonuria, autism, or other persistent developmental disorders 5. Narcotics use 6. Any confounding comorbidities
Interventions	Methylphenidate type: Ritalin Methylphenidate dosage: 1 mg/kg Administration schedule: not stated Duration of intervention: 8 weeks Treatment compliance: not stated
Outcomes	Sleep Disturbance Scale for Children (SDSC) sleep questionnaires and appetite questionnaires were completed by mothers at baseline, week 2, 4, and 8 Height, weight were measured by a dietitian at baseline and week 8. Weight was measured with minimal clothing and height without shoes in standard position 3-day food records were completed by mothers at baseline and week 8 Stimulant drug side effects questionnaires were completed by mothers at week 8 (methylphenidate + placebo, n = 18)
Notes	Sample calculation: not stated Any withdrawals due to adverse events: not stated Ethics approval: yes Funding/vested interests: the study was financially supported by Research Deputy of Tehran University of Medical Sciences

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Mohammadi 2012a *(Continued)*

Authors' affiliations: not stated

Key conclusions of study authors: melatonin with methylphenidate can partially improve symptoms of sleep disturbance by circadian cycle modification. However, it did not seem to reduce the attention deficiency and hyperactivity behaviour of ADHD children

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no

Supplemental data received through personal email correspondence with the authors in July 2013 (Mohammadi 2013 [pers comm])

Mohammadi 2012b

Methods	A a single-centre randomised, double-blind, parallel-group clinical trial of methylphenidate use for 6 weeks
Participants	Number of patients screened: 53 Number included: 46 Number randomised to methylphenidate: 23, buspirone: 23 Number followed up in each arm: methylphenidate: 20 and buspirone: 20 Number of withdrawals in each arm: methylphenidate: 3 and buspirone: 3 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (100%)) Age: mean: 9.70 (SD 3.18), range: 6-14 years old IQ: above 70 Sex: 13 males, 7 females Methlphenidate-naïve: 100% (n = 20) Ethnicity: not stated Country: Iran Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. Met the DSM-IV-TR diagnostic criteria for ADHD 2. Total or subscale scores (or both) on ADHD-RS-IV School Version of ≥ 1.5 SD above norms for patient's age and gender 3. Parents and children had to be willing to comply with all requirements of the study 4. Written informed consent was obtained from each patient's parent or guardian *Exclusion criteria*: 1. History or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders (DSM-IV axis I) 2. Any current psychiatric comorbidity that required pharmacotherapy 3. Any evidence of suicide risk

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Mohammadi 2012b *(Continued)*

	4. Mental retardation (IQ below 70) 5. A clinically significant chronic medical condition, including organic brain disorder, seizures 6. Current abuse or dependence on drugs the last 6 months 7. Hypertension or hypotension
Interventions	Methylphenidate type: immediate release (Ritalin) Mean methylphenidate dosage: 20-30 mg/day depending on weight (20 mg/day for < 30 kg and 30 mg/day for > 30 kg) Administration schedule: not stated Duration of intervention: 6 weeks Treatment compliance: not stated
Outcomes	Adverse effects were systematically recorded at each visit (baseline, 3 weeks, and 6 weeks) using a checklist (not otherwise specified) that comprised 20 side effects
Notes	Sample calculation: not stated Ethics approval: the study was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences (grant No: 8643) Funding/vested interests: this study was supported by a grant from Tehran University of Medical Sciences (grant no: 8643) Any withdrawals due to adverse events: no Authors' affiliations: not stated *Key conclusions of the study authors*: the results of this study suggest that administration of buspirone has no comparable efficacy in comparison with methylphenidate in the treatment of ADHD. Nevertheless, in our study, those in the buspirone group experienced fewer adverse events than the methylphenidate group in particular regarding decreased appetite, headache and insomnia *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* requested from the authors twice through email correspondence in June 2016. No reply

Montañés-Rada 2012

Methods	An 8-week prospective, open-label cohort study of participants receiving 8 hours extended release methylphenidate
Participants	Number of patients screened: 60 Number included: 40 Number followed up: 40 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV-TR (subtype: not stated) Age: mean: 13.6 years old (range: 10-16) IQ: above 100 Sex: 30 males, 10 females

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Montañés-Rada 2012 *(Continued)*

	Methylphenidate-naïve: not stated Ethnicity: not stated Country: Spain Comorbidity: ODD: 75%, anxiety disorder: 10%, Gilles de la Tourette syndrome: 2.5%, no comorbidity: 20% Comedication: not stated Sociodemographics: low socioeconomic status: 37.5%, medium socioeconomic status: 50%, high socioeconomic status: 12.5% *Inclusion criteria*: 1. 10-16 years old 2. Admitted to a child psychiatric consultation 3. Not candidate for atomoxetine (sufficient response to stimulant treatment) 4. Not candidate for immediate-release methylphenidate because of prior poor tolerance (but at least with a partial response to Concerta or Medikinet) 5. Not candidate for a short-acting methylphenidate (4 hours) 6. Candidate for taking methylphenidate with effect from 8 am to 9 pm defined as: patients attending school from 8 am to 3 pm or 8 am to 5 pm and needing supplemental support of stimulant treatment, and furthermore, also studying in the afternoon (at school or at home) (60%), or having challenging conduct problems and needing an extended effect until at least 9 pm (20%) or both situations 7. Either moderate or severe in symptomatology according to the 20 items Conners Scale for teachers (above 45) and Clinical global impression scale (above or equal to a severity of 5 to 7) when off medication 8. IQ above 70 *Exclusion criteria*: 1. None stated
Interventions	Methylphenidate type: Medikinet (50% extended release and 50% immediate release methylphenidate) Methylphenidate dosage: 40-50 mg/daily Administration schedule: twice daily. A fixed dose of 30 mg at breakfast (8:30 am) and either 10 mg (n = 34) or 20 mg (n = 6) in the afternoon (3:00 pm) Duration of intervention: 8 weeks (1 month of titration) Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Insomnia, spontaneous reported
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interests: HB Pharma *Key conclusions of the study authors*: at week 8, 63% of the participants reached complete remission, and 27.5% reached partial remission. Scores in all subscales of Eyberg, Conners (parents and teachers) were reduced till the level of normal population (except for the conduct subscale of the teacher rated) in a statistical significant level. Due to insomnia, 2 patients reduced the afternoon dose of 50/50-ER/IR-MPH from 20 mg to 10 mg and 3 patients changed the 20 mg 50/50-ER/IR-MPH afternoon dose to 10 mg IR-MPH

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Montañés-Rada 2012 *(Continued)*

Comments from the study authors: our sample is representative of patients with moderate and severe symptomatology

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: see inclusion criteria 4-6

Supplemental information regarding ADHD diagnostic criteria and IQ received through personal email correspondence with the authors in November 2013 (Montañes-Rada 2013 [pers comm])

The publications on this study were received from the pharmaceutical company HB Pharma in June 2013 (Fischer 2013 [pers comm])

Montiel-Nava 2002

Methods	A 6-week randomised parallel trial with 2 arms: 1. Methylphenidate 2. Parent training No placebo or no-intervention group
Participants	Number of participants screened: not stated Number of participants included: 24 Number randomised to methylphenidate: 12 and parent training: 12 Number followed up in methylphenidate-arm: not stated Number of withdrawals in methylphenidate-arm: not stated Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 7.16 years old (range: 6-10) IQ: mean: 92.25 (SD 15.64). Sex: total sample: 16 males, 8 females (not stated for the methylphenidate group) Methylphenidate-naïve: 100% Ethnicity: Marabinos (from Northwestern Venezuela) Country: Venezuela Comorbidity: academic, oppositional and various behavioural problems Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. DSM-IV diagnosis of ADHD 2. A score of 1.5 SD above the mean for the subscales of inattention, hyperactivity-impulsivity, and DSM-IV total in either Conners' Parent Rating Scale-Revised or Conners' Teacher Rating Scale-Revised 3. IQ of or above 70 4. Symptoms severe enough to interfere and impair daily functioning 5. No prior stimulant or psychological treatment *Exclusion criteria*:

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Montiel-Nava 2002 *(Continued)*

	1. Meeting diagnostic criteria for a developmental disorder, mental impairment, or any sensory disturbance at the time of screening
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 10 mg/daily at the start of the titration period Administration schedule: morning and noon Duration of intervention: 6 weeks, including 4 weeks of titration (after randomisation) Treatment compliance: not stated
Outcomes	A checklist of adverse effects were used, telephone interview with parent, once weekly during the 4-week titration period
Notes	Sample calculation: no Ethics approval: not stated Funding/vested interests: not stated Authors' affiliations: not stated *Key conclusions of the study authors*: to our knowledge this is the first article describing the effectiveness of methylphenidate and parent training in Venezuelan children diagnosed with ADHD. It should be considered as a preliminary study, that supports the thesis of positive effects of psychosocial and psychopharmacological interventions in children with ADHD. There was no difference in the effectiveness of the 2 types of treatment *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no (only inclusion of methylphenidate-naïve children) *Supplemental information* regarding ethics approval, funding, type of methylphenidate, number of males and females in the methylphenidate group, and adverse event data were not possible to receive through personal email correspondence with the authors. Emails sent twice without reply

Moungnoi 2011

Methods	A retrospective, descriptive cohort study of methylphenidate use for long-term administration and its impact on growth at 6 months, 1 years, 2 years, 3 years, 4 years, and 5 years' follow-up
Participants	Number of participants screened: not stated Number of participants included: 96 Number of participants followed up: 6 participants followed up to 5 years Number of withdrawals: more than 50% by 3rd year of follow-up Diagnosis of ADHD: DSM-IV (subtype: combined, 100%) Age: mean 8.62 years old (SD 1.70) IQ: not stated Sex: 75 males, 21 females Methylphenidate-naïve: not stated Ethnicity: not stated

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Moungnoi 2011 *(Continued)*

	Country: Thailand Comorbidity: not stated Comedication: not stated, but children who received other medication continuing more than 3 months were excluded Sociodemographics: not stated *Inclusion criteria*: 1. Age 6 years and above 2. Start short-acting methylphenidate medication at any time between 1 January 2000 to 31 31 December 2007 3. Continued medicine ≥ 1 year *Exclusion criteria*: 1. ADHD children who received other medications continuing more than 3 months 2. Concomitant genetic or neurological disorders
Interventions	Methylphenidate type: short acting methylphenidate Mean methylphenidate dosage: 6 months= 0.44 mg/kg/day, 1 year = 0.48 mg/kg/day, 2 years = 0.48 mg/kg/day, 3 years = 0.49 mg/kg/day, 4 years = 0.41 mg/kg/day and 5 years = 0.42mg/kg/day Administration schedule: not stated Duration of intervention: ≥ 1 year Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Height and weight, observer, beginning of short-acting methylphenidate medication, 6 months, 1-, 2-, 3-, 4-, 5-year follow-up
Notes	Sample calculation: yes. Margin of error 5%, estimated prevalence of ADHD 3.5-5%, CI 95% = sample size 51-73 Ethics approval: yes, Ethics Committee of the Queen Sirikit National Institute of Child Health Funding/vested interests: none Authors' affiliations: none *Key conclusions of the study authors*: prolonged medication with short-acting methylphenidate showed minimal impact on growth only at the first 6 months; however, growth could catch up in the adolescent period *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated

Munk 2015

Methods	A patient report of cardiac arrest following myocardial infarction during methylphenidate treatment
Participants	Diagnosis of ADHD: ICD-10 Age: 11 years old

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Munk 2015 *(Continued)*

	IQ: unknown Sex: male Ethnicity: not stated Country: Denmark Comorbidity: Tourette syndrome Comedication: none Sociodemographics: not stated
Interventions	Methylphenidate type and dosage: 54 mg/day Administration schedule: not stated Duration of treatment: approximately 2 years Treatment compliance: yes
Outcomes	*Serious adverse events*: Cardiac arrest following exercise without any prior complaints about chest discomfort or shortness of breath. A week before the event, he had a short episode of tachycardia. The examination showed that the myocardial infarction was of an older date (more than weeks) due to thinning of the myocardium and an adversely remodeled left ventricle. A pacemaker was inserted and methylphenidate treatment was discontinued
Notes	*Key conclusions of the study authors*: the present case demonstrates that myocardial infarction can happen due to methylphenidate exposure in a cardiac healthy child, without any other cardiovascular risk factors *Comments from the study authors*: the boy has been very thoroughly examined and the only thing that stands out is the methylphenidate treatment Funding/vested interest/authors affiliations: the authors declare that there is no conflict of interests regarding the publication of this paper *Supplemental information* regarding IQ and comedication received through personal email correspondence with the authors in April 2016 (Munk 2016 [pers comm]). Not possible to retrieve information regarding ADHD subtype

Na 2013

Methods	A 12-week, open-label, multicentre, phase 4 study of osmotic release oral system (OROS) methylphenidate use
Participants	Number of patients screened: not stated Number of participants included: 121 Number of participants followed up: 103 Number of withdrawals: 18 Diagnosis of ADHD: DSM-IV (subtype: combined (17.4%), hyperactive-impulsive (0.8%), inattentive (70.2%)) Age: mean: 13.8 years old (range: 12-18)

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Na 2013 *(Continued)*

IQ: above 70

Sex: 93 males, 28 females

Methlphenidate-naïve: not stated

Ethnicity: Korean

Country: Korea

Comorbidity: oppositional defiant disorder: 24%, conduct disorder: 5%, tic disorder: 4.1%, depressive disorder: 4.1%, social phobia: 1.7%, generalised anxiety disorder: 2.5%, enuresis: 1.7%, encopresis: 1.7%)

Comedication: no

Sociodemographics not stated

Inclusion criteria

1. DSM-IV criteria for ADHD and considered to require medication therapy
2. Participants that agreed to observe visit schedules and willingly complete the evaluation defined by participant (possibly to be completed by parents/guardians) during the treatment period
3. Participants and parents/guardians that are able to understand the participation procedures of the research and spontaneously request the discontinuation therein at any time
4. Participants that offered spontaneous consent for participation
5. Participants whose guardian/legal representative provided spontaneous written consent
6. 12-18 years of age

Exclusion criteria

1. Hypersensitivity to methylphenidate HCL
2. Participants diagnosed with major depression or anxiety disorders according to DSM-IV diagnostic criteria and who requires drug therapy
3. Significant suicidal ideation
4. Learning disabilities or mental retardation, any history of bipolar disorder, psychotic disorder, or substance use disorder
5. Diagnosed with a pervasive developmental disorder, organic brain disease, seizure disorder, and movement disorder requiring pharmacological treatment
6. Family history of Tourette syndrome
7. Previously taken OROS methylphenidate within 6 months before screening
8. Severe general medical conditions (e.g. glaucoma, severe cardiovascular, hepatic, or renal illnesses), or clinically significant gastrointestinal problems, and
9. Taking a-2 adrenergic receptor agonists, theophylline, coumarin, antidepressants, antipsychotics, benzodiazepines, modafinil, anticonvulsants, or health supplements that may influence activity of the central nervous system at the time of screening
10. Abnormalities in baseline physical examination or routine laboratory tests

Interventions	Methylphenidate type: osmotic-release oral system (OROS) Methylphenidate dosage: dose titration was allowed for up to 6 weeks (starting doses were 18 mg/day (if body weight < 30 kg) and 27 mg/day (if body weight equal to or higher than 30 kg), maximum allowed daily dose was 72 mg or 1.4 mg/kg) Mean methylphenidate dose at endpoint: 54.53 (SD 12.33, range 27-72) mg/day or 0.99 (SD 0.21) mg/kg/day Administration schedule: once a day, between 6:30 and 9:00 am Duration of intervention: 12 weeks

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Na 2013 *(Continued)*

	Washout before study initiation: ≥ 6 months Treatment compliance: not stated, but participants were required to take ≥ 70% of the study medication during the study period
Outcomes	*Non-serious adverse events*: Vital signs, body weight, and adverse events (both by general inquiry to patients and parents and by clinician rated checklist) were measured at every visit (day 0 (baseline) and at weeks 1, 3, 6, and 12) The study-specific adverse events checklist consisted of 61 methylphenidate-specific questions (Items from the Symptom Rating Scale (Barkley 1990) and the Pittsburg Side-Effects Rating Scale (Pelham 1993) were included) Chemistry tests were performed at screening and at week 12
Notes	Sample calculation: not stated Ethics approval: yes, the study was approved by the institutional review board of each study site Funding: this study was supported by grants from the Johnson & Johnson family of companies. The Johnson & Johnson family of companies was involved in the study design and approved the report Vested interests: disclosure statement "No competing financial interests exist". *Key conclusions of the study authors*: OROS methylphenidate was effective in enhancing learning skills in adolescents with ADHD. Furthermore, clinicians should supplement the subjective report on adverse events from patients or their parents with a more drug-specific checklist to obtain drug side effects more effectively. As there are some differences in the patterns of adverse events reported by patients and their parents, it is generally recommended that clinicians obtain information from both parties when possible *Comments from the review authors*: safety data comparing patients, parents and clinicians as raters from Lee 2013 concerns only 47 participants, whereas efficacy data and supplemental safety data from Na 2013 concerns 121 participants *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes, see exclusion criteria no. 1 (hypersensitivity to methylphenidate HCL) *Supplemental information* regarding safety data received through personal email correspondence with the authors in August 2014 (Lee 2014 [pers comm])

Niederhofer 2009

Methods	A patient report of dosage reduction of methylphenidate treatment by addition of atomoxetine. Adverse effects of methylphenidate are reported
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 11 years old IQ: 97 Sex: male Ethnicity: not stated Country: Italy Comorbidity: not stated Comedication: not stated

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Niederhofer 2009 *(Continued)*

	Sociodemographics: not stated
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 20 mg/day Administration schedule: not stated Duration of intervention: 2 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Methylphenidate 20 mg/day: depressed mood and appetite loss Dosage-reduction to 10 mg/day: improved the depressed mood
Notes	*Key conclusions of study authors*: the reported case mainly shows that the combination between atomoxetine and methylphenidate helped reducing the dose of methylphenidate and thus, probably the side effects while showing beneficial clinical effects Funding/vested interests/authors' affiliations: not stated *Supplemental information* regarding ADHD type received through personal email correspondence with author in July 2013 (Niederhofer 2013 [pers comm])

Niederhofer 2011

Methods	A patient series describing adverse effects (xerostomia, aggression and emotional instability) among children taking methylphenidate
Participants	**Case with xerostomia, n = 1** Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 11 years old IQ: 97 Sex: male Ethnicity: not stated Country: Italy Comorbidity: not stated Comedication: not stated Sociodemographics: not stated **Cases with aggression (n = 1) and emotional instability (n = 1)** Diagnosis of ADHD: DSM-IV (subtype: combined) Ages: 10 and 11 years old IQ: above 70 Sex: 2 males Ethnicity: not stated

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Niederhofer 2011 *(Continued)*

	Country: Italy
	Comorbidity: no
	Comedication: not stated
	Sociodemographics: not stated
Interventions	**Case with xerostomia**
	Methylphenidate type: not stated
	Mehylphenidate dosage: 40 mg/day
	Administration schedule: not stated
	Duration of intervention: 1 week
	Treatment compliance: not stated
	Cases with aggression and emotional instability
	Methylphenidate type: not stated
	Methylphenidate dosage: 20 mg
	Administration schedule: not stated
	Duration of intervention: 2 months
	Treatment compliance: not stated
Outcomes	*Non-serious adverse events*:
	Xerostomia, aggression and emotional instability
Notes	*Key conclusions of study author*: methylphenidate is first-line agent for ADHD, if monotherapy is sufficient
	Funding/vested interests/authors' affiliations: none declared
	Supplemental information regarding ADHD subtype and duration of intervention received through personal email correspondence with author in July 2013 (Niederhofer 2013b [pers comm])

Nymark 2008

Methods	A patient report of serious cardiomyopathy during methylphenidate treatment
Participants	Diagnosis of ADHD: ICD-10 (subtype: not stated)
	Age: 18 years old
	IQ: above 70
	Sex: male
	Ethnicity: not stated
	Country: Norway
	Comorbidity: obesity (BMI = 40)
	Comedication: quetiapine fumarate (900 mg/day) for 17 months

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Nymark 2008 *(Continued)*

	Sociodemographics: not stated
Interventions	Methylphenidate type: extended release (Concerta) Methylphenidate dosage: 54 mg/day Administration schedule: once daily Duration of intervention: 11 months Treatment compliance: not stated
Outcomes	*Serious adverse events*: 11 months of MPH treatment: hypoxia and dyspnoea. On investigation, signs of liver-, renal-, and heart-failure were found. Noradrenalin infusion was started. Echocardiography showed dilated left ventricle and an ejection fraction (EF) of 25%. Liver function improved, noradrenalin and dobutamine were tapered, but 3 days after admission a new echocardiography showed an EF of 10%. Intensified treatment including intra-aortic balloon pump (IABP) was instituted. Cardiac function improved, and 3 weeks later the IABP was disconnected. EF at this point was 15%. The patient was denied heart transplantation due to various cofactors. 7 months later: his clinical status was improved, function class II (New York Heart Association) with an EF estimated by echocardiography to 30%-35%
Notes	Funding/vested interests/authors' affiliations: not stated *Key conclusions of study authors*:the investigation concluded with a probable relationship between the patient's cardiomyopathy and the use of methylphenidate

Park 2013

Methods	A cohort study of methylphenidate use for 2 weeks
Participants	Number of participants screened: not stated Number of participants included: 96 Number of participants followed up: 96 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (62.5%), hyperactive-impulsive (5.2%), inattentive (27.1%), NOS (5.2%)) Age: mean: 8.70 (SD 1.41) years old (range: 6-12) IQ: not stated Sex: 79 males, 17 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Korea Comorbidity: tic disorder: 10.4%, anxiety disorder: 8.3%, oppositional defiant disorder: 9.4%, enuresis: 6.3%, depression: 1.0% Co-medication: no Sociodemographics: not stated

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Park 2013 *(Continued)*

	Inclusion criteria: 1. DSM-IV-TR diagnosis of ADHD 2. Aged 6-12 years 3. ≥ moderate symptom severity on the Clinical Global Impression-Severity (CGI-S) scale and severe enough to warrant treatment with medication 4. No previous exposure to psychostimulants *Exclusion criteria*: 1. Other mental disorders, except for transient tic disorder, oppositional defiant disorder, mild anxiety disorder, and enuresis 2. Current or previous brain damage or convulsive disorder 3. Mental retardation, autism, language difficulties, or developmental problems, including learning disabilities
Interventions	Methylphenidate type: osmotic release oral system (OROS) methylphenidate Methylphenidate dosage: children weighing less than 30 kg were treated with 18 mg per day, and children weighing more than 30 kg were treated with 27 mg/day Administration schedule: not stated Duration of intervention: 2 weeks Treatment compliance: not stated
Outcomes	Barkley Symptom Rating Scale: a 17-item list of methylphenidate-related adverse event symptoms, rated from 0 (nothing) to 9 (severe) for symptoms during the past 2 weeks. Any negative sign, symptom, syndrome, or new illness that appeared or worsened after treatment began was counted as a treatment-emergent adverse event
Notes	Sample calculation: no Ethics approval: approved by the institutional review board (IRB) for human subjects at the Seoul National University Hospital and other hospitals Funding/vested interests: the authors declare that there are no conflict of interest. The study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A111523) and by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology, Republic of Korea (20110023888) Authors' affiliations: Seoul National University College of Medicine *Key conclusions of the study authors*: ADHD participants with the A/a genotype at the NTF3 rs6332 polymorphism showed the highest 'proneness to crying' and 'nail biting' item scores, followed by those with the G/a genotype and those with the G/G genotype (P = 0.047 and P = 0.017, respectively). These data provide preliminary evidence that genetic variation in the NTF3 gene is related to susceptibility to emotional side effects in response to methylphenidate treatment in Korean children with ADHD *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Perera 2010

Methods	This study prospectively analysed an outpatient treatment programme for children with ADHD. Methylpenidate use for 6 months

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Perera 2010 *(Continued)*

Participants	Number of participants included: 102 Diagnosis of ADHD: DSM-IV (subtype: combined (100%)) Age: mean 6.92 years old (range 4-12) IQ: above 90 Sex: 90 males,12 females Ethnicity: not stated Country: Sri Lanka Comorbidity: oppositional defiant disorder, conduct disorder, specific learning disorder and tic disorder (numbers not stated) Comedication: 19 (18.3%) children were also taking other medication on a regular basis. These were anticonvulsants in 15 (14.4%) and anti-asthmatic drugs in 4 (3.9%) Sociodemographics: not stated *Inclusion criteria*: Data used for this article is confined to those children who consistently attended clinics and completed 6 months of treatment/intervention *Exclusion criteria*: 1. Children with ADHD found to be unsuitable for treatment with methylphenidate 2. Under 4 years of age 3. IQ < 90 4. Or for any other reason
Interventions	Methylphenidate type: immediate release Methylphenidate dosage: 2.5-40 mg daily Administration schedule: not stated Duration of intervention: 6 months Treatment compliance: data used for this article is confined to those children who consistently attended clinics and completed 6 months of treatment
Outcomes	*Non-serious adverse events*: A 7 item checklist of known side effects of methylphenidate. Parents responded by indicating 'present' or 'absent', which was recorded on a weekly basis, in the first 4 weeks. Loss of appetite, social withdrawal, restlessness, abdominal pain, headache, poor sleep, and sadness
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interest: no Authors' affiliations: none *Key conclusions of the study authors*: close involvement of parents in monitoring outcome of treatment of ADHD helps to focus on aspects of care relevant to them

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Perera 2010 *(Continued)*

	Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: yes, children with ADHD found to be unsuitable for treatment with methylphenidate were excluded
	Supplemental information regarding IQ, comorbidity and methylphenidate dosage received through personal email correspondence with the authors in June 2016 (Perera 2016 [pers comm])

Peyre 2012a

Methods	A non-randomised longitudinal study of methylphenidate use for up to 3 months
Participants	Number of participants screened: not stated Number of participants included: 173 Number of participants followed up: 136 Number of withdrawals: 37 Diagnosis of ADHD: DSM-IV (subtype: combined (69.12%), hyperactive-impulsive (8.09%), inattentive (22.79%)) Age: mean 10.74 (SD 2.74) IQ: > 70 Sex: 90% males, 10% females Methylphenidate-naïve: not stated Ethnicity: not stated Country: France Comorbidity: conduct disorder (7.35%); ODD (50%); anxiety (32.35%); major depressive (22.06%); bipolar (1.47%); learning (33.09%) Comedication: none Sociodemographics: not stated *Inclusion criteria* Children and adolescents younger than 18 years who were eligible for MPH treatment for DSM-IV ADHD and had parents able to speak and understand French. A subsample with complete data were re-evaluated after optimal adjustment of MPH *Exclusion criteria* Mental retardation (IQ < 70) and chronic neurological disease
Interventions	Methylphenidate type: multiple-dose immediate release or prolonged-action once-daily formulations (Ritaline LAR or ConcertaR Mean methylphenidate dosage: 0.82 mg/kg/day (SD 0.22) Administration schedule: not stated Duration of intervention: 15 days to 3 months Treatment compliance: not stated

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Peyre 2012a *(Continued)*

Outcomes	Adverse effects were elicited through systematic questions (first about adverse events in general and then with a list of frequent adverse events) and medical chart review
Notes	Sample calculation: no Ethics approval: local ethics committee (Comite de Protection des Personnes Pitie-Salpetriere) Funding: supported by grants from a Programme Hospitalier de Recherche Clinique (PHRC AOR 03006) and the Institut National de la Sante et de la Recherche Medicale (INSERM AAP-RRC-09). Vested interests: the author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of the article *Key conclusions of the study authors*: Child Behavior Checklist-Dysregulation Profile (CBCL-DP) was associated neither with poorer response to methylphenidate nor with more side effects. There were no differences in cognitive performance between participants with and without CBCL-DP

Pierce 2010

Methods	An open-label, randomised, multicentre study evaluating the pharmacokinetic properties of dl-methylphenidate after single, multiple fixed, and escalating doses of MTS (methylphenidate transdermal system) and osmotic release oral sytem (OROS) methylphenidate
Participants	Number of participants screened: not stated Number of participants included: 71 Diagnosis of ADHD: DSM-IV (subtype: not stated) **Children** Number randomised to OROS: 11 Number randomised to MTS: 24 Number of withdrawals: 0 Age: mean 9.5 years (range 6-12) IQ: not stated Sex: 19 males, 16 females Methylphenidate-naïve: not stated Ethnicity: white (25.7%), African American (74.3%) Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: not stated **Adolescents** Number randomised to OROS: 11 Number randomised to MTS: 25 Number of withdrawals: 0

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Pierce 2010 *(Continued)*

Age: mean 14.1 years (range 13-17)

IQ: not stated

Sex: 19 males, 17 females

Methylphenidate-naïve: not stated

Ethnicity: white (47.2%), African American (52.8%)

Country: USA

Comorbidity: not stated

Comedication: not stated

Sociodemographics: not stated

Inclusion criteria

1. Aged 6-17 years
2. Primary diagnosis of ADHD according to DSM-IV
3. Have blood pressure measurements within the 95th percentile for age, sex, and height
4. Normal laboratory parameters and vital signs, including ECG results

Exclusion criteria

1. Comorbid psychiatric diagnosis (except oppositional defiant disorder)
2. History of seizures or tic disorders; suicidal ideation; serious cardiac problems; substance abuse or dependence disorder (excluding nicotine dependence); skin disorder (e.g. skin cancer, skin manifestations of allergies, dermatitis, eczema, psoriasis, signs of skin irritation)
3. Known intolerance to psychostimulants in general, and to MPH in particular
4. Any illness that might jeopardise safety or compromise the study assessments
5. Female participants must not have been pregnant or lactating
6. Participants must not have consumed food or beverages containing alcohol, caffeine, or xanthine 48 hours before check-in; ingested nicotine 48 hours before check-in; taken investigational medications, hepatic or cytochrome P450 enzyme-altering agents, or medications with central nervous effects within 30 days before screening; or taken prescription medication or over-the-counter medications within 7 days before check-in
7. Participants must not have donated plasma of 500 mL or more within 56 days before screening

Interventions	Methylphenidate transdermal system dosage: 10 mg in single dose phase and 15 mg, 20 mg, or 30 mg in the multiple escalating phase Osmotic release oral system methylphenidate dosage: 18 mg in single dose phase and 27 mg, 36 mg, and 54 mg in the multiple escalating phase Administration schedule: once daily Duration of intervention: 4 weeks for the whole trial, with the 4 different phases having varying duration Treatment compliance: not stated
Outcomes	*Non-serious adverse events* • Safety was monitored throughout the study by measuring adverse events and reviewing results of physical examinations, ECGs, vital signs, and standard clinical laboratory evaluations • All clinically significant changes (determined by the investigator) were recorded as AEs and were characterised as to intensity and relationship to the study treatment • AEs were coded using the Medical Dictionary for Regulatory Activities, version 7.0 • Application Site Skin Evaluation

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Pierce 2010 *(Continued)*

- Participants receiving MTS treatment underwent skin evaluations at the application site to identify irritation and discomfort and determine the degree of patch adhesion, using the dermal response scale (DRS; 0 (no erythema) to 7 (strong reaction beyond the application site)
- The experience of discomfort and pruritus was used to evaluate the overall level of discomfort at the patch application site

Notes	Sample calculation: no Ethics approval: approved by the institutional review board Funding: Shire Vested interests/authors' affiliations: Dr Pierce is an employee of Shire Pharmaceutical Development Ltd. Dr Katic receives or has received research support, acted as a consultant, and/or served on a speakers' bureau for Forest, GlaxoSmithKline, Lundbeck, Merck, Novartis, Sanofi-Aventis, Sepracor, Shire, Somerset, and Wyeth. Ms Buckwalter is an employee of Shire Pharmaceuticals Inc. Mr Webster at the time of the study was an employee of Aptuit Ltd, a contract research organisation subcontracted to conduct work on behalf of Shire Pharmaceutical Development Ltd. *Key conclusions of the study authors*: overall, after single and multiple fixed or escalating doses of MTS or OROS methylphenidate, systemic exposure to the predominantly active d-methylphenidate was greater in children compared with adolescents. As a result of drug accumulation on repeated dosing, systemic exposure to d-methylphenidate in children after multiple escalating doses was 1.4- to 1.6-fold higher for MTS compared with OROS; however, in adolescents, systemic exposure was similar for both formulations. Plasma concentrations of l-MPH were approximately half those of d-MPH across both age groups after single and multiple doses of MTS. In contrast, plasma concentrations of l-MPH were negligible after single and multiple doses of OROS MPH. Reported AEs included those that are typical for oral methylphenidate treatment, with the exception of generally mild application site irritations associated with transdermal delivery of methylphenidate *Comments from the study authors*: no participants exhibited a DRS score higher than 2 (definite erythema, readily visible minimal oedema, or minimal popular response) immediately before the removal of the patch after 1 or 28 days. No participant had an experience of discomfort and pruritus scale score higher than 1 (mild discomfort) *Comments from the review authors*: it was the investigator who decided whether an adverse events was clinically significant or not *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes

Polanczyk 2007

Methods	A pharmacogenomic study of children and adolescents consecutively evaluated during 2 years in the ADHD outpatient clinic
Participants	Number of participants screened: 457 Number of participants included: 137 Number of participants followed up: 106 Number of withdrawals: 31 Diagnosis of ADHD: DSM-IV (subtype: combined (58.5%), hyperactive-impulsive (5.7%), inattentive (26.4%)) Age: mean 10.3 years old (range: not stated) IQ: mean: 100.4

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Polanczyk 2007 *(Continued)*

	Sex: 82 males, 24 females Methylphenidate-naïve: 100% Ethnicity: European-Brazilian (100%) Country: Brazil Comorbidity: conduct disorder (16.0%), oppositional defiant disorder (51.9%), mood disorder (9.4%), anxiety disorder (23.6%) Comedication: yes (9.4%) Sociodemographics: not stated *Inclusion criteria*: 1. ADHD diagnosis according to DSM-IV criteria (children who fulfilled all criteria except for age of onset of impairment (i.e. before 7 years) were included) 2. Age between 4 and 17 years, 3. European-Brazilian race/ethnicity 4. Drug naïve for methylphenidate 5. Prescribed daily dosage of methylphenidate hydrochloride of ≥ 0.3 mg/kg 6. Data on response to methylphenidate was available for at least the first month of treatment *Exclusion criteria*: Not stated
Interventions	Methylphenidate type: immediate release Mean methylphenidate dosage: 0.5 mg/kg (baseline) and 0.65 mg/kg at 1 month Administration schedule: 8 am and 12 pm, with extra dose at 5-6 pm for those needing evening coverage. Dosages of short-acting methylphenidate were augmented until no further clinical improvement was detected or until there were limited adverse effects Duration of intervention: 3 months (1 month for 106 participants, 3 months for 89) Treatment compliance: data were excluded from 2 children because of irregular use of methylphenidate
Outcomes	Barkley Side Effect Rating Scale measured by child psychiatrists at baseline,1 and 3 months. Data not reported
Notes	Sample calculation: no Ethics approval: yes Funding/vested interests: the ADHD program received research support from the pharmaceutical companies: Bristol Myers-Squibb, Eli Lilly and Company, Janssen-Cilag, and Novartis Pharmaceuticals. The study was supported by grant 471761/03-6 from Conselho Nacional de Desenvolvimento Cientıfico e Tecnologico, Programa de Apoio a Núcleos de Excelência, and Hospital de Clínicas de Porto Alegre *Key conclusions of the study authors*: the study documented the effect of the G allele at the ADRA2A -1291 C > G polymorphism on the improvement of inattentive symptoms with methylphenidate treatment in children and adolescents with ADHD. Our findings provide clinical evidence for the involvement of the noradrenergic system in the modulation of methylphenidate action *Comments from the study authors*: regarding adverse events, a mixed-effects model analysis demonstrated effects of treatment over time on the Barkley Side Effect Rating Scale scores, as expected (n = 106; F2,201.2=5.4; P=.005). However, neither an effect for the presence of the G allele (n = 106; F1,107.6=0.15; P=.69) nor an interaction effect between the presence of the G allele and treatment over time (n = 106; F2,201.2=0.71; P=.49) on the Barkley Side Effect Rating Scale scores was found during the 3 months of methylphenidate use *Comments from the review authors*: no data presented on side effects apart from the paragraph above

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Polanczyk 2007 *(Continued)*

	Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: not stated

Porfirio 2011

Methods	A patient report of visual hallucinations during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 7 years at diagnosis, 11 years at occurrence of hallucinations IQ: above 70 Sex: male Ethnicity: not stated Country: Italy Comorbidity: K-SADS-PL excluded any psychiatric comorbidities (at age 11) Comedication: not stated Sociodemographics: mother presented with affective seasonal disorder and binge eating disorder
Interventions	Methylphenidate type: oral immediate-release Methylphenidate dosage: 0.5 mg/kg twice daily (30 mg/day) Duration of treatment: 3 years with discontinuation of medication during summer time each year Treatment compliance: not stated
Outcomes	*Serious adverse events*: 3 years after start of MPH treatment: an episode of complex visual hallucinations (dramatic scenes appearing before going to sleep, sometimes during the day after methylphenidate-ingestion). Normal physical and neurological examinations. Standard laboratory work-up and drug screening were within normal limits. Normal visual acuity. Sleep electroencephalography (EEG) revealed no abnormalities and no evidence of epileptic activity. K-SADSPL excluded any psychiatric comorbidities Discontinuation: complete resolution of hallucinations 24 months follow-up period: no further hallucinations occurred
Notes	*Key conclusions of the study authors*: although the pathogenetic mechanism is unclear, the occurrence of hallucinations may be explained by a chronic increase in synaptic dopamine. Clinicians should be aware of this possible rare adverse manifestation occurring at therapeutic doses *Comments from the study authors*: because methylphenidate is a widely used, well studied and safe pharmacological agent, clinicians who prescribe methylphenidate should be aware of this possible rare adverse manifestation occurring at therapeutic doses Funding/vested interest/authors' affiliations: not stated *Supplemental information* regarding IQ received through personal email correspondence with the authors in October 2013 (Curatolo 2013 [pers comm])

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Poulton 2003

Methods	A retrospective cohort study of growth data
Participants	Number of participants screened: not stated Number of participants included: 19 Number of participants followed up: 6 months: 19, 18 months: 13, 30 months: 6, 42 months: 4 Number of withdrawals: 6 months: 0, 18 months: 6, 30 months: 13, 42 months: 15 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: range 3.1-11.4 years old IQ: > 70 Sex: 17 males, 2 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Australia Comorbidity: not stated Comedication: clonidine Sociodemographics: not stated *Inclusion criteria* 1. ADHD diagnosis according to DSM-IV 2. Patients from a single private practice in Penrith prescribed methylphenidate in 1999 *Exclusion criteria* 1. Methylphenidate for less than 6 months 2. Previous experience with stimulant treatment
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 10-40 mg/day Mean methylphenidate dosage: 1.0 (SD 0.24) mg/kg per day, median 27.5 mg Administration schedule: not stated Duration of intervention: 6-42 months Treatment compliance: many patients were taking less than the prescribed dose of stimulant medication, ceasing or reducing medication at weekends or during school holidays, but precise details were not available
Outcomes	*Non-serious adverse events*: • Height - measured to the nearest 1 mm by the same observer using a wall-mounted stadiometer, measured every 6th month or more frequently if clinically indicated • Weight - measured to the nearest 0.5 kg using electronic scales, measured every 6th month or more frequently if clinically indicated Both measures without shoes and outdoor clothing
Notes	Sample calculation: no

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Poulton 2003 *(Continued)*

Ethics approval: no
Funding/vested interest: none

Key conclusions of the study authors: stimulant medication is associated with a decrease in height and weight SD scores during the first 6-30 months with a characteristic pattern on the growth chart

Comments from the study authors: all children were started on dexamphetamine initially but were changed on to methylphenidate if the response was suboptimal or they experienced adverse effects. When weight loss occurred the parents were asked to reduce or omit the medication whenever possible and to encourage the child to eat more

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no

Supplemental information regarding data received through personal email correspondence with the authors in November 2013 (Poulton 2013 [pers comm])

Poulton 2012

Methods	A clinic-based, prospective, cohort study with up to 3 years of follow-up
Participants	Number of participants screened: not stated Number of participants included: 21 Number of participants followed up: 19 Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (subtype: combined (76%), inattentive (19%), hyperactive (5%)) Age: mean 7.54, range 4.99-9.04 years old IQ: > 70 Sex: 18 males, 3 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Australia Comorbidity. not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. ADHD according to DSM criteria 2. Aged < 9 years old 3. Newly diagnosed 4. Clinical indication for starting treatment with stimulant medication *Exclusion criteria* 1. Previous treated with psychotropic medication 2. Medical conditions likely to impact on growth

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Poulton 2012 *(Continued)*

Interventions	Methylphenidate type: immediate release Methylphenidate dosage: 24.3 mg/day (6.2 mg/day) at 6 months Administration schedule: not stated Duration of intervention: up to 36 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Growth: height, weight, and BMI z scores measured at baseline, 6 months, 18 months, 30 months. All measurement were made without shoes or outdoor clothing Height was measured to the nearest 1 mm using a wall mounted stadiometer Weight was measured to the nearest 0.1 kg using electronic scales BMI were corrected for age and sex by conversion to z scores based on Centers for Disease Control and Prevention (CDC) reference data
Notes	Sample calculation: yes Ethics approval: yes Funding: the research was supported by the Australian Woman and Children's research Foundation (OZWAC) and by the Nepean Medical Research Foundation Vested interests/authors' affiliations: the authors declare that they have no competing interests *Key conclusions of the study authors*: stimulant medication was associated with early fat loss and reduced bone turnover. Lean tissue including bone increased more slowly over 3 years of continuous treatment than would be expected for growth in height. There was long-term improvement in the proportion of central fat for height. This study shows that relatively minor reductions in weight on stimulant medication can be associated with long-term changes in body composition. Further study is required to determine the effects of these changes on adults *Comments from the review authors*: the study describe children both on dexamphetamine treatment and methylphenidate treatment. We have received separate data on the methylphenidate group from the study authors Exclusion of MPH non-responders/children who have previously experienced adverse events on MPH: no *Supplemental information* regarding data received through personal email correspondence with the authors in October 2013 (Poulton 2013b [pers comm])

Ramasamy 2014

Methods	A patient report of testicular failure possibly associated with chronic use of methylphenidate
Participants	Diagnosis of ADHD: DSM III-R Age: 20 years old IQ: an exact number cannot be discerned but it is likely that the participant exhibits a normal IQ without any sort of disability Sex: male Ethnicity: Latino Country: USA Comorbidity: none Comedication: none

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Ramasamy 2014 *(Continued)*

	Sociodemographics: family history was unremarkable
Interventions	Methylpenidate type: not stated Methylphenidate dosage: varied with age Administration schedule: not stated Duration of treatment: approximately 17 years with voluntary cessation a few years ago Treatment compliance: not stated
Outcomes	*Serious adverse events*: The patient's complaint was initially delayed puberty. He complained of high-pitched voice, lack of libido, low energy level, chronic fatigue and poor erectile function. The results of laboratory tests were consistent with the patient's idiopathic testicular failure and warranted further exploration of the link between chronic methylphenidate use and effects on reproductive parameters
Notes	*Key conclusions of the study authors*: the patient described in our case study seemed to exhibit characteristics related to the effects of chronic use of methylphenidate on development of human reproductive function. The unknown effects of methylphenidate are currently being studied, but as can be seen, one should exercise caution and patients should be followed closely when prescribing methylphenidate *Comments from the study authors*: because the developmental changes that occurred in the participant occurred over a number of years of treatment with methylphenidate, there is very little information about the patient's condition and how it developed during that period of time *Comments from the review authors*: this case has been included although the patient is 20 years old since he had been taking methylphenidate for approximately 17 years Funding/vested interest/authors' affiliations: no competing interests were disclosed Grant information: Ranjith Ramasamy is an NIH K12 Scholar supported by a Male Reproductive Health Research Career (MHRH) Development Physician-Scientist Award (HD073917-01) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Program *Supplemental information* regarding ADHD diagnosis and type, comorbidity and comedication received through personal email correspondence with the authors in April 2016 (Pranav 2016 [pers comm])

Rappaport 2004

Methods	A patient report of side effects during methylphenidate treatment in a 14-year-old boy with ADHD and a number of other co-morbid conditions
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 14 years old IQ: 80-85 Sex: male Ethnicity: Latino Country: USA Comorbidity: PTSD, bipolar disorder, attachment disorder, language-based learning disorder Comedication: olanzapine

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Rappaport 2004 *(Continued)*

	Sociodemographics: working single mother, sporadic contact with father. Patient and his siblings were intermittently exposed to domestic violence
Interventions	Both IR and ER MPH tried dosage: not stated Administration schedule: not stated time points: not stated Duration of treatment: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: While taking immediate release methylphenidate (Ritalin): loss of appetite While taking extended release methylphenidate (Concerta): nausea and vomiting
Notes	*Key conclusions of the study authors*: the patient's course and symptoms are illustrative of the maladaptive sequelae of untreated ADHD, complicated by a language-based learning disorder. Funding/vested interest/authors' affiliations: not stated *Supplemental information* regarding ADHD diagnosis and IQ received through personal email correspondence with the authors in November 2013 (Rappaport 2013 [pers comm])

Rapport 1996

Methods	Patient report of 2 6-year-old dizygotic twins with ADHD and ODD treated with methylphenidate
Participants	ADHD diagnosis: DSM-III-R at time of examination. Authors state that both would have achieved the then new DSM-IV diagnoses of ADHD combined type at the time of publication. Age: 6 years old IQ: 100 and 93 Sex: 2 girls, dizygotic twins Ethnicity: mixed white/Japanese Country: USA Comorbidity: ODD (100%) Comedication: not stated Sociodemographics: low socioeconomic status
Interventions	Methylphenidate type: immediate release methylphenidate Methylphenidate dosage: 4 doses: 5 mg (0.29 mg/kg), 10 mg (0.58 m/kg), 15 mg (0.87 mg/kg), 20 mg (1.16 mg/kg), placebo. Both children received each of the 4 methylphenidate doses Administration schedule: administration "was intentionally counterbalanced to allow for direct contrasts between no-dose and moderate dose conditions (placebo vs 10 mg), low and high dose conditions (5 mg vs 15 mg) and identical high dose conditions (20 mg) between the 2 children Duration of intervention: not stated Treatment compliance: not stated

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Rapport 1996 *(Continued)*

Outcomes	None of the active treatment conditions (methylphenidate and attentional training) resulted in higher frequency or greater severity of complaints compared to baseline *Non-serious adverse events*: Measures: Side Effects Rating Scale (SERS) 1. 1 girl experienced moderate to severe stomach discomfort approximately 60 minutes post-ingestion of her scheduled 15 mg dose. This was attributed to her failure to eat lunch earlier (reported by parent). Decrease of distress followed ingestion of a sandwich after 30 minutes
Notes	Funding/vested interest: not stated *Key conclusions of the study authors*: brief mention should be made of the relative absence of emergent symptoms found in the present study. Although side effects are frequently reported in children undergoing psychostimulant trials (often as a function of increasing dosage), severity is typically mild, and it is advisable to gauge both frequency and severity against a placebo control owing to the high base rate of physical complaints reported by children with ADHD

Rashid 2007

Methods	A patient report of intensified somatic hallucinations during dose increase of methylphenidate treatment at the hospital
Participants	Diagnosis of ADHD: DSM-IV (subtype: unknown) Age: 10 years old IQ: > 70 Sex: male Ethnicity: unknown Country: USA Comorbidity: chronic pattern of somatisation Comedication: unknown Methylphenidate-naïve: no. OROS methylphenidate, 36 mg/day, ≥ 2 years Sociodemographics: history of several foster placements, now adopted
Interventions	Methylphenidate dose: regular-release methylphenidate, 10 mg, twice daily, then titrated to regular-release methylphenidate, 15 mg, twice daily, 2 days Treatment compliance: not stated
Outcomes	*Serious adverse events*: Hallucinations Regular-release methylphenidate, 10 mg, twice daily Regular-release methylphenidate, 15 mg, twice daily, 2 days: somatic hallucinations Discontinuation of methylphenidate: complete resolution of the psychotic phenomena within 2 days Follow-up 1 year later: no unexplained somatic complaints

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Rashid 2007 *(Continued)*

Notes	Funding/vested interest: no financial relationships to disclose Authors' affiliations: no affiliations to pharmaceutical companies stated *Key conclusions of the study authors:* here we describe a case of a 10-year-old boy with ADHD with a chronic pattern of somatisation, which evolved into overt somatic hallucinations with an increase in the methylphenidate dose. This pattern of somatisation was retrospectively recognised as partial somatic hallucinations *Supplemental information* regarding ADHD diagnostic criteria and IQ received through personal email correspondence with the authors in October 2013 (Rashid 2013 [pers comm])

Remschmidt 2005

Methods	A 21-day multicentre, open-label study of osmotic release oral system (OROS) methylphenidate in children and adolescents with ADHD switched from immediate release (IR) methylphenidate followed by a 12-month follow-up
Participants	Number of participants screened: not stated Number of participants included in the main study: 105 Number of participants followed up: 101 Number of withdrawals: 4 Number of participants included in the follow-up: 89 Number of participants followed up: 56 Number of withdrawals: 33 Diagnosis of ADHD: DSM-IV (subtype: combined (69.5%), hyperactive-impulsive (7.6%), inattentive (22.8%)) Age: range 6-16 years old IQ: not stated Sex: 90 males, 15 females Methylphenidate-naïve: none Ethnicity: not stated Country: UK and Germany Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Children and adolescents aged 6-16 years 2. DSM-IV diagnosis of ADHD 3. Receiving MPH-IR for ≥ 4 weeks (10-60 mg/day) and the most recent dose for ≥ 3 weeks 4. Able to comply with study visit schedules 5. Agree to take only the supplied study medication during the study 6. Parents/caregivers and teachers had to be willing to complete assessments

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Remschmidt 2005 *(Continued)*

	7. Participants who 'benefited' from OROS-methylphenidate could continue in a 12-month extension period *Exclusion criteria*: 1. Known hypersensitivity to methylphenidate 2. Clinically significant gastrointestinal problems, glaucoma, a seizure or psychotic disorder, Tourette syndrome, cardiovascular disease including moderate to severe hypertension, hyper-excitability or agitated state, hyperthyroidism, depression, known or suspected substance abuse (current or past) 3. Females who had reached menarche 4. Participants receiving ≥ 1 of the following: clonidine, other alpha-2 adrenergic receptor agonists, tricyclic antidepressants, theophylline, coumarin or anticonvulsants, monoamine-oxidase inhibitors
Interventions	Methylpenidate type: osmotic release oral system Methylphenidate dosage: 18 mg, 36 mg, or 54 mg. 11.9% received 18 mg; 54.4% received 36 mg, and 33.7% received 54 mg at the end of the 21-day main study Administration schedule: once daily, morning Duration of intervention: main study: 21 days, follow-up: 12 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Reports of any adverse events, sleep and appetite patterns, and tics were reported by parents/caregivers up to day 21, and at months 2, 4, 6, 8, 10 and 12
Notes	Sample calculation: not stated Ethics approval: independent Ethics Committees in each country reviewed the study protocol Funding/vested interest: this company-initiated study was supported by a grant from Janssen-Cilag GmbH *Key conclusions of the study authors*: children and adolescents can effectively and safely be switched from IR-methylphenidate to OROS-methylphenidate with improved symptom control and compliance *Comments from the study authors*: current international guidelines recommend the use of long-acting stimulant preparations over short-acting stimulants for the management of ADHD. The results of this study provide further support for this recommendation. These data cannot necessarily be generalised to unselected children and adolescents in clinical practice who may not be responsive to methylphenidate *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes *Supplemental information* requested from the review authors in June 2014 with no reply

Ririe 1997

Methods	A patient report on unexpected interaction of methylphenidate (Ritalin) with anaesthetic agents
Participants	Diagnosis of ADD/ADHD: DSM-IV (subtype: not stated) Age: 6 years old IQ: > 70 Sex: male

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Ririe 1997 *(Continued)*

	Ethnicity: not stated Country: USA Comorbidity: history of William's syndrome and supravalvar aortic stenosis Comedication: only during anaesthesia: midazolam 20 mg + 10 mg, ketamine 60 mg, Glycopyrrolat IV 0,1 mg, midazolam IV 5 mg Sociodemographics: living at home with parents
Interventions	Immediate release methylphenidate (Ritalin) dosage: 10 mg/day Administration schedule: twice daily Duration of treatment: 2 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Difficulty with conscious sedation. No previous problems with sedation. Despite additional oral doses of sedatives the child remained alert and unable to lie still, until intravenous sedative drugs were given. After discharge, the child developed nausea, vomiting, lethargy and dehydration, which led to hospitalisation
Notes	Funding/vested interest/authors' affiliations: Novartis *Key conclusions of the study authors*: there could be a potential risk of unwanted interactions between methylphenidate and anaesthetic agents. Based on the observations from the patient report, a more detailed and systematic investigation of methylphenidate in patients undergoing anaesthesia or sedation is warranted *Comments from the study authors:* no previous problems with anaesthesia. The child had no apparent limitations of activity and no cardiac symptoms. We believe that the stimulant effect of methylphenidate may have played a major role in antagonising the sedative effect of the oral midazolam in the clinically recommended doses. The stimulant effect of methylphenidate makes it potentially very difficult to attain a desirable level of sedation without requiring large and potentially unsafe doses of sedative drugs or administration of general anaesthesia. The gastrointestinal side effects of methylphenidate, particularly decreased appetite and nausea and vomiting, may be aggravated by many of the drugs used for sedation or general anaesthesia *Supplemental information* regarding intellectual function and diagnostic criteria received through personal email correspondence with the authors in October 2013 (Ririe 2013 [pers comm])

Sabuncuoglu 2007

Methods	3 patient reports of hyperactivity and irritability during switch from risperidone to methylphenidate
Participants	**Case 1** Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 5 years old IQ: no developmental delay Sex: male Ethnicity: not stated Country: Turkey

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Sabuncuoglu 2007 *(Continued)*	Comorbidity: ODD Comedication: none Sociodemographics: not stated **Case 2** Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 6 years old IQ: 70-90 Sex: female Ethnicity: not stated Country: Turkey Comorbidity: borderline intellectual functioning Comedication: none Sociodemographics: not stated **Case 3** Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 15 years old IQ: > 90 Sex: female Ethnicity: not stated Country: Turkey Comorbidity: ODD and learning disorder Comedication: none Sociodemographics: not stated
Interventions	**Case 1**: immediate release methylphenidate dosage: 15 mg/day. Administration schedule: not stated. Duration of treatment: not stated. Treatment compliance: not stated **Case 2**: immediate release methylphenidate dosage: 15 mg/day. Administration schedule: not stated. Duration of treatment: not stated. Treatment compliance: not stated **Case 3**: immediate release methylphenidate dosage: 18 mg/day. Administration schedule: once, morning. Duration of treatment: not stated. Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: **Case 1**: methylphenidate introduced 2 days after abrupt discontinuation of risperidone 1 mg/day (8 months) and produced agitation, irritability, vigilance, and violent behaviour. No dyskinetic movements. Methylphenidate was discontinued and the adverse events disappeared. After a 6-week long drug-free period, methylphenidate was reintroduced at 15 mg/day. No adverse events were observed **Case 1**: methylphenidate introduced after discontinuation of risperidone 1 mg/day (2 years) and produced a near manic state, irritability, agitation, racing thoughts, and distractibility. No dyskinetic movements. Methylphenidate was discontinued and the adverse events disappeared. After a couple of months methylphenidate was reintroduced at 15 mg/day and was well-tolerated

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Sabuncuoglu 2007 *(Continued)*

	Case 1: methylphenidate introduced after a 1-week medication free interval after treatment with risperidone 1 mg, and produced irritability, agitation and discomfort. Methylphenidate was discontinued and the adverse events disappeared. The patient did not retry the medication
Notes	Funding/vested interest/authors' affiliations: not stated *Key conclusions of the study authors*: this report of 3 patients draws attention to a unique condition that arises in switching from atypical antipsychotic to stimulant medication. A drug-free interval is recommended in switching from risperidone to methylphenidate *Comments from the study authors:* the severity of adverse events correlated well with methylphenidate administration, ceased upon discontinuation of treatment and, interestingly, readministration of methylphenidate after an interval was associated with no adverse events in the first and second patient *Supplemental information* regarding IQ received through personal email correspondence with the authors in October 2013 (Sabuncuoglu 2013 [pers comm])

Sahin 2014

Methods	A study of methylphenidate use for 2 months
Participants	Number of patients screened: not stated Number of participants included: 30 Number of participants followed up: 30 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype: combined (46.7%), hyperactive-impulsive (10%), inattentive (43.3%)) Age: mean 9.54 (SD 2.83), range 6-18 years old IQ: > 70 Sex: 24 males, 6 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Turkey Comorbidity: disruptive behaviour disorder (DBD): 17, anxiety disorder: 5, learning disability: 3, enuresis/encopresis: 3, tic disorder: 2 Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. Children and adolescents aged 6-18 years who were to receive sustained release methylphenidate for DSM-IV diagnosed ADHD *Exclusion criteria* 1. Previously received methylphenidate 2. Used any other psychotropic drug for more than 7 days 3. Used any drug within the last 1 month

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Sahin 2014 *(Continued)*

	4. Any systemic or metabolic disease, mood disorder, extensive developmental disorder, psychotic disorder, substance abuse, progressive neurological disease, visual and/or auditory disability, or mental retardation (IQ < 70)
Interventions	Methylphenidate type: osmotic release oral system (OROS) Mean methylphenidate dosage: 0.70 (SD 0.20) mg/kg/day (0.64 (SD 0.16) mg/kg/day in the 1st month and 0.76 (SD 0.25) mg/kg/day in the 2nd month) Administration schedule: not stated Duration of intervention: 2 months Treatment compliance: 100%
Outcomes	*Non-serious adverse events*: 1. Barkley Side Effects Rating Scale after 2 months of treatment 2. Height and weight measured pre- and post-treatment
Notes	Sample calculation: no Ethics approval: yes Funding: sponsored by Ondokuz Mayis University project number PYO.TIP.1904.12.013. Vested interests/authors' affiliations: none of the authors report conflicts of interest *Key conclusions of the study authors*: leptin and brain-derived neurotrophic factor (BDNF) were not associated with poor appetite and/or weight loss due to methylphenidate treatment. However, ghrelin and adiponectin might be biomolecules that play a role in underlying neurobiological mechanisms of methylphenidate-related appetite or weight loss. *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Saieh 2004

Methods	A patient report of hospitalisation due to hypertension during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 8 years old IQ: normal Sex: male Ethnicity: not stated Country: Chile Comorbidity: not stated Comedication: not stated Sociodemographics: maternal family history of hypertension
Interventions	Methylphenidate type: Ritalin Methylphenidate dosage: 0.32 mg/kg

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Saieh 2004 *(Continued)*

	Administration schedule: not stated Duration of treatment: 6 months Treatment compliance: not stated
Outcomes	*Serious adverse events*: 72-hour hospitalisation, emergency unit: Abdominal pain for 4 days prior to hospitalisation, intermittent accentuation (hours), no other symptoms Secondary hypertension: persistent hypertension (158/88 - 170/105, pulse: 78-98 bpm). Normal physical examination. Normal eye fundus and normal cardiological examination. Discontinuation of methylphenidate: hypertensive treatment only necessary for 24 hours. Normal blood pressure after 1 week
Notes	*Key conclusions of the study authors*: we want to draw attention to our experience of a patient who had hypertension, which was clearly related to the administration of MPH, and which disappeared when MPH was discontinued *Comments from the study authors*: unfortunately, only a few relevant publications and no national studies on the subject exist, so we do not know exactly the extent of this problem, although from anecdotal experience of verbal communication the incidence of tachycardia and hypertension appear to be low. Prospective studies should be performed to find the true incidence of complications with the use of methylphenidate and thus further establish careful and appropriate control of MPH-treated patients to avoid these complications Funding/vested interest/authors affiliations: no affiliations to pharmaceutical companies stated *Supplemental information* regarding ADHD diagnostic criteria, IQ, type and dose of MPH, and duration of hospitalisation received through personal email correspondence with the authors in October and December 2013 (Saieh 2013 [pers comm])

Sangal 2006

Methods	A 7-week randomised, double-blind, cross-over trial of: 1. Methylphenidate 2. Atomoxetine
Participants	Number of participants screened: 107 Number of participants included: 85 Number of participants followed up: 75 Number of withdrawals: 10 Diagnosis of ADHD: DSM-IV (subtype: combined (67.9%), hyperactive-impulsive (2.4%), inattentive (29.8%)) Age: mean 10.1 (SD 2.0), range 6 to 14 years old IQ: not stated Sex: 64 (males, 21 females) Methylphenidate-naïve: 43.5%

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Sangal 2006 *(Continued)*

	Ethnicity: white: 72.9%, others: 27.1% Country: USA Comorbidity: ODD (48.2%); conduct disorder (3.5%); anxiety/agoraphobia (1.2%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Diagnose of ADHD DSM-IV criteria and severity criteria 2. ADHD Rating Scale-IV Parent Version: Investigator-Administered and Scored (ADHD RS)16 score ≥ 1.0 SD above normative values for age and sex 3. WISC-III > 80 *Exclusion criteria* 1. Serious medical illness 2. Symptoms suggestive of a primary sleep disorder (obstructive sleep apnea, periodic limb movement disorder, insufficient sleep syndrome, and abnormal laboratory values or electrocardiogram
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage: 42.29 mg/day (range 15 to 60), or 1.12 mg/kg per day Administration schedule: 3 time points Duration of treatment: 7 weeks Medication-free period between intervention: 10-20 days Treatment compliance: measured by pill counts at visits in 7-12 day intervals, ranging from 87.5% to 100%
Outcomes	*Non-serious adverse events* 1. Actigraph monitoring of sleep onset latency, number of arousals, sleep offset. DIfficulty falling asleep, difficulty waking up (rated by child) difficulty falling asleep, difficulty waking up, behaviour in morning, behaviour in evening (rated by parent) 2. Blood pressure, ECG, blood tests 3. Polysomnography (n = 39, stratified): total time in bed, time to onset of first sleep, time to onset of persistent sleep, total sleep time, time in stage 1, 2 and 3/4 sleep, number of awakenings, number of arousals, time in REM sleep, REM latency, sleep efficiency 4. Treatment emergent adverse effects
Notes	Sample calculation: yes Ethics approval: yes Funding: this research was funded by Eli Lilly and Company, which markets atomoxetine. Some patients received doses that were off-label Vested interests/authors' affiliations: this was an industry supported study sponsored by Eli Lilly. The data were analysed by statisticians at Eli Lilly, including Dr Sutton, one of the authors. The manuscript was written as a combined effort of all authors. Dr Sangal has received research support from Eli Lilly, Merck, Organon, Cephalon, and Novartis. Dr Owens has received research support from Cephalon, Sanofi- Aventis, Johnson & Johnson, Sepracor, and Eli Lilly; is a member of the speakers' bureau for Eli Lilly; is a consultant for Cephalon; and is an advisory board member for Cephalon, Pfizer, and Eli Lilly. Drs. Sutton, Allen, Schuh, and Kelsey are employees of Eli Lilly

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Sangal 2006 *(Continued)*

Key conclusions from study authors: patients receiving atomoxetine twice daily had shorter sleep-onset latencies, relative to methylphenidate 3 times daily, based on objective actigraphy and polysomnography data

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no

Supplemental information requested from the study authors twice in January/February 2014. No reply received

Santosh 2006

Methods	2 separate retrospective cohort studies (only study 2 is used here due to polypharmacy)
Participants	Number of participants screened: not stated Number of participants included: 52 (ADHD: 25, ADHD + ASD: 27) Number of participants followed up: 52 Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 11.08 years old IQ: mean 89.56 Sex: ADHD group 80% males, 20% females. ADHD + ASD group 88.89% males, 11.11% females Methylphenidate-naïve: not stated Ethnicity: not stated Country: UK Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. DSM-IV ADHD with or without ASD
Interventions	Methylphenidate type: not stated Methylphenidate dosage: not stated Administration schedule: not stated Duration of intervention: range of follow-up was between 1 and 6 months, mean: 87 days Treatment compliance: not stated
Outcomes	*Non-serious adverse events* Pre- and post-treatment: routine ratings using the side effects module of the Treatment Outcome Rating Scale
Notes	Sample calculation: no Ethics approval: not stated

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Santosh 2006 *(Continued)*

Funding/vested interests: both the pilot study and current development and deployment of the DEN-EM™ system have been supported by an award from Guys' and St Thomas' Charity
Authors' affiliations: no affiliations to pharmaceutical companies stated
Key conclusions of the study authors: both studies presented here support previous findings from smaller studies that show children with autism and ADHD can respond as well to stimulants as children with ADHD alone. Although randomised controlled trials remain the gold standard for efficacy studies, systems like this that allow clinicians to continue rigorous and consistent monitoring for many years have a valuable role to play. Furthermore, such monitoring systems which now exist electronically can easily accumulate large data sets and reveal details about long-term effectiveness and long-term side effects of medication that are unlikely to be discovered in short-term trials
Comments from the review authors: the article describes 2 studies. Some of the participants in the first study are not receiving MPH but dexamphetamine instead, and for this reason the first study is excluded from our review. The second described study is included
Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: not stated
Supplemental information and data have not been possible to retrieve through personal email correspondence with the authors in February-June 2014

Schertz 1996

Methods	A retrospective study examining predictors of weight loss in children with ADHD treated with methylphenidate or dextroamphetamine sulfate
Participants	Number of participants screened: not stated Number of participants included: 60 (total) Number of participants included in methylphenidate group: 32 Number followed up: 60 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III-R (subtype: not stated) Age: mean 7.5 years old (range: 3.6-15.5) IQ: no mental retardation Sex: 29 males, 3 females Methylphenidate-naïve: 0 Ethnicity: white 77%, African American 10%, Asian: 3%, Hispanic: 10% Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. DSM-III-R diagnosis of ADHD 2. ≥ 5 months treatment with methylphenidate in the Developmental and Behavioral Pediatrics of the Schneider Children's Hospital *Exclusion criteria*: 1. Prior trial of methylphenidate stimulant medication

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Schertz 1996 *(Continued)*

	2. Concurrently taking a medication that can affect weight (e.g. clonidine) 3. Having a major developmental disability (e.g. mental retardation, cerebral palsy or autism) 4. If complete information was not available in the chart
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage: 25.5 mg or 1 mg/kg/day Administration schedule: not stated Duration of intervention: mean duration 11.2 months (range 6-20 months) Treatment compliance: not assessed
Outcomes	Weight and body mass index (BMI) were the 2 measures of adiposity used. Weight was expressed in terms of z scores derived from US normative data
Notes	Sample calculation: no Ethics approval: not stated Funding: not stated Vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: pretreatment weight, adjusted for age, gender and height is a significant predictor of weight loss in children with ADHD treated with either methylphenidate or dextroamphetamine sulphate. In contrast, pretreatment age, duration of treatment, and weight-adjusted dose were not found to be significant predictors *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* regarding height and weight for the methylphenidate group requested from the authors by email correspondence in January 2014. No reply

Schmidt 2002

Methods	A retrospective cohort study analysing the EEGs of 124 children and adolescents treated with methylphenidate
Participants	Number of participants screened: not stated Number of participants included: 124 Number of participants followed up: 124 Number of withdrawals: 0 Diagnosis of ADHD: ICD-10 (subtype: F90.0, predominantly inattentive type (64,5%), F90.1, predominantly hyperactive type (35,5%)) Age: mean 10.3: years old (range 6.1-17.1) IQ: 4% were intellectually disabled Sex: 113 males, 11 females Methylphenidate-naïve: both methylphenidate naïve and not methylphenidate naïve participants included in the study

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Schmidt 2002 *(Continued)*

	Ethnicity: not stated Country: Germany Comorbidity: nocturnal enuresis (4%), mild intellectual disability (4%), mixed disorders of conduct and emotions (3.2%), absence epilepsy (0.8%), focal epilepsy (1.6%), developmental anomaly or developmental delay (0%), no comorbidity (64.5%) Comedication: 94.4% of the sample did not use another type of medicine apart from methylphenidate. 2.4% used anticonvulsant, and 0.8% were treated with different medicines Sociodemographics: not stated *Inclusion criteria*: 1. Patient at the clinic for children and adolescents psychiatry and psychotherapy, University of Cologne 2. Diagnosis of ADHD according to ICD-10 criteria 3. EEG-assessment before and during treatment *Exclusion criteria*: None stated
Interventions	Methylphenidate type: Ritalin Mean methylphenidate dosage: 0.5-1.0 mg/kg Administration schedule: not stated Mean duration of intervention: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: EEG (according to the German guidelines) measures by medical staff and under supervision from one of the authors (a doctor). A total of 4 categories were formed to evaluate the EEG: 1. Normal (age appropriate basic activity, no hypersynchronous activity (HSA)), no side difference, no focal localised affection, no general changes) 2. Subnormal (dysrhythmic age appropriate basic activity, no HSA, no focal localised affection, no side difference, individual occurrence of steeper sequences) 3. Abnorm (age appropriate basic activity, no HSA, no site difference, no focal localised affection, occurrence of inconstant amplitude differences, individual occurrence of steeper sequences) 4. Pathological (slowed or increased activity, occurrence of HSA, side difference, focal localised affection, general changes)
Notes	Sample calculation: no Ethics approval: yes Funding/vested interest: no funding Authors' affiliations: no affiliations to pharmaceutical companies stated *Key conclusions of the study authors*: whether or not methylphenidate medication influences the occurrence of epileptic seizures remains unsettled. Given the data from this study, we would conclude that an EEG during therapy with methylphenidate is not necessary. Before commencing a planned methylphenidate therapy, however, an EEG should be performed. *Comments from the review authors*: there were several parameters from the EEG assessment in the article. However since we in the review have chosen to analyse it according to EEG changes yes/no we have only used the 4 categories that the authors formed

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Schmidt 2002 *(Continued)*

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no

Supplemental information regarding funding, ethics approval received through personal email correspondence with the authors in December 2013 (Sinzig 2013 [pers comm]). Not able to get separate data on the participants without intellectual disability

Schulz 2010

Methods	A multicentre, randomised, cross-over trial with 2 interventions: 1. Minimal breakfast 2. Standard breakfast Phases: 2 phases of 1 week each. All participants were treated with Ritalin LA
Participants	Number of participants screened: 159 Number of participants included: 150 Number of participants followed up: 145 Number of withdrawals: 5 Diagnosis of ADHD: DSM-IV (subtype: combined (67.3%), hyperactive-impulsive (6%), inattentive (26.7%)) Age: mean 9.7 (SD 1.6) years old (range 6-12) IQ: not stated, but patients not meeting minimum intelligence requirements were excluded Sex: 112 males, 38 females Methylphenidate-naïve: 0% Ethnicity: white: 95.3%, African American: 1.3%, Asian: 2%, others: 1.3% Country: Germany Comorbidity: not clear, see exclusion criteria 1 Comedication: not clear, see exclusion criteria 8 Sociodemographics: not stated *Inclusion criteria*: 1. Children aged 6-12 years with a known diagnosis of ADHD according to DSM-IV criteria 2. On stable treatment with any methylphenidate medication for ≥ 1 month prior to screening 3. Male and female patients aged 6-12 4. Patients having a confirmed diagnosis of ADHD of any type according to DSM-IV criteria, as established by history and adequate exploration 5. Patients whose symptoms are adequately controlled by a stable and well-tolerated dose of an immediate release- or extended release-methylphenidate equivalent of 20 or 40 mg immediate release methylphenidate for 1 month before screening 6. Patients with parents or a legal guardian, who will give written informed consent for the child to participate in the study. Additionally, consent to participate must be obtained from all children entering the study if the child is able to judge the nature, the meaning and the significance of the clinical trial (according to §40 para. 4 No. 4 AMG). Consent will be documented by the child's signature on the consent form

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Schulz 2010 *(Continued)*

	Exclusion criteria: 1. Major clinical psychiatric or somatic comorbidities 2. Contraindications against methylphenidate treatment 3. Patients with comorbid psychiatric conditions with symptoms requiring current pharmacological treatment (e.g. major depression, psychosis) 4. Patients with comorbid psychiatric or somatic conditions that may contraindicate treatment or confound efficacy and safety assessments 5. Patients with comorbid moderate to severe eating disorder (e.g. bulimia, anorexia nervosa, binge eating) 6. Clinically significant diseases or significant abnormal findings during the initial exam in the opinion of the investigator 7. Patients with a BMI outside the 10th and 90th age percentile 8. Patients who are taking any concomitant medications likely to interfere with the study drug or to confound efficacy or safety assessments, e.g. a. Tricyclic antidepressants, buproprion, clonidine, buspirone 2 weeks before randomisation b. Atomoxetine 2 weeks before randomisation c. Fluoxetine or antipsychotics 1 month before randomisation d. Pemoline and amphetamines 1 week before randomisation
Interventions	Methylphenidate type: Ritalin LA (extended release) Mean methylphenidate dosage: 20 mg or 40 mg Administration schedule: not stated Duration of intervention: 14 days Treatment compliance: not stated
Outcomes	*Serious adverse events*: No deaths or serious adverse events occurred in the study *Non-serious adverse events*: A total number of 36 patients (24%) experienced a total of 64 adverse events, 33 of which were considered to be related to study medication No mentioning of how the adverse events were measured
Notes	Sample calculation: no Ethics approval: yes, Central Ethics Committee University Freiburg Funding/vested interest: sponsored by Novartis Pharma GmbH, Germany Authors' affiliations: several authors have received funding from medical companies *Key conclusions of the study authors*: all of the clinical rating scales showed consistently no difference between the 2 breakfast conditions. The clinical efficacy of Ritalin LA is not influenced by breakfast and works independently of food intake *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes

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Schwartz 2004

Methods	A patient report of stuttering priapism associated with withdrawal from sustained-release methylphenidate
Participants	Diagnosis of ADHD: DSM- IV-TR (subtype: inattentive) Age: 15 years old IQ: not stated Sex: male Methylphenidate naïve: yes Ethnicity: white Country: USA Comorbidity: not stated Comedication: no Sociodemographics: not stated
Interventions	Methylphenidate type: osmotic release oral system, OROS (Concerta) Methylphenidate dosage: begun at 27 mg/day Monday through Saturday with drug holiday on Sunday, then increased to 36 mg/day, followed by 7 days where medication was not taken, then a dose increase to 54 mg/day Administration schedule: once daily, in the morning Duration of treatment: 2 months Treatment compliance: not stated
Outcomes	*Serious adverse events*: Intermittent painful priapism beginning on the second drug holiday (the Sunday after the dosage was increased to 36 mg/day). 5-10 episodes lasting up to an hour were experienced for at least half of the week with a pain score of 5/10. With the increase dose of 54 mg/kg the duration and pain associated with episodes increased When the patient was weaned off methylphenidate, the symptoms resolved and had not re-occurred at either 2 weeks or 6 months follow-up
Notes	Funding/vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: it is likely that withdrawal from OROS methylphenidate was the cause of this adolescent boy's priapism *Comments from the study authors*: it is possible that this adverse event is underreported due to embarrassment about discussing the problem *Supplemental information* regarding IQ and ADHD diagnosis received through personal correspondence with the authors in September 2013(Schwartz 2013 [pers comm])

Shang 2015

Methods	A cohort study of methylphenidate use for 24 weeks
Participants	Number of participants screened: 174

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Shang 2015 *(Continued)*

	Number of participants included: 160 Number included in the methylphenidate group: 80 Number of participants followed up: 66 Number of withdrawals: 14 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean: 9.64 (SD 2.42) years old (range: 7-16) IQ: mean: 106 Sex: 70 males, 10 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Taiwan Comorbidity: not stated Comedication: no Sociodemographics: not stated *Inclusion criteria*: 1. 7-16 years old 2. ADHD diagnosis according to DSM-IV *Exclusion criteria*: 1. Serious medical illness 2. IQ above 80 3. History of bipolar I or II, psychosis, any substance abuse, pervasive developmental disorder, depression or anxiety disorder based on DSM-IV criteria at study entry, history of seizure disorder, prior EEG abnormalities related to epilepsy 4. Had ever used any psychotropic medications before the study
Interventions	Methylphenidate type: osmotic release oral system (OROS) Mean methylphenidate dosage: 27.83 mg/day (SD 12.44) Administration schedule: once daily Duration of intervention: 24 weeks Treatment compliance: assessed by pill count and interview, results not reported
Outcomes	*Non-serious adverse events*: Safety measures, including decreased appetite, vomiting, insomnia, somnolence, dizziness, stomachaches, headaches, palpitations, and dry mouth, were assessed at each visit by open-ended questions during a clinical interview first Structured interview listing all the potential adverse effects at each visit Vital signs and body weight monitored at each visit
Notes	Ethics approval: yes. The Research Ethics Commitee of National Taiwan University Hospital approved this study prior to implementation

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Shang 2015 *(Continued)*

	Funding/vested interest: no Authors' affiliations: SSG, CYS and HYL were on the speakers' bureau for Janssen-Cilag and Eli-Lilly & Co., Taiwan *Key conclusions of the study authors*: both drugs are associated with significant improvement in symptoms while also being safe *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no Supplemental information regarding comorbidity and treatment compliance requested through personal email correspondence with the authors in June 2016. No reply

Shibib 2009

Methods	A report of 4 cases of psychosis during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined 100%) Age: 14, 8, 10, and 14 years old IQ: above 70 Sex: 1 female, 3 males Ethnicity: not stated Country: UK Comorbidity: conduct disorder (Case 4) Comedication: no, and no use of illicit substances Sociodemographics: not stated
Interventions	**Case 1** Methylphenidate type: extended release (Equasym XL) Methylphenidate dosage: gradually increased to 30 mg over 4 weeks Administration schedule: once daily Duration of treatment: 1 month titration, hereafter 4 months treatment Treatment compliance: not stated **Case 2** Methylphenidate type: immediate release (Ritalin) Methylphenidate dosage: gradually increased from 5 mg once daily to 10 mg twice daily Administration schedule: once/twice daily Duration of treatment: 7 days Treatment compliance: not stated **Case 3** Methylphenidate type: immediate release and extended release (Concerta XL)

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Shibib 2009 *(Continued)*

Methylphenidate dosage: immediate release: gradually increased to 15 mg daily. Extended release: 36 mg, later increased to 54 mg daily

Administration schedule: immediate release: not stated. Extended release: once daily

Duration of treatment: immediate release: not stated. Extended release: 3 weeks

Treatment compliance: because compliance became an issue treatment with immediate release methylphenidate was stopped, and extended release methylphenidate was initiated. No information about compliance during treatment with extended release methylphenidate

Case 4

Methylphenidate type: extended release (Concerta XL)

Methylphenidate dosage: 18 mg

Administration schedule: not stated

Duration of treatment: 24 hours

Treatment compliance: because compliance became an issue treatment with immediate release methylphenidate was stopped, and extended release methylphenidate was initiated. No information about compliance during treatment with extended release methylphenidate

Outcomes

Serious adverse events:

Case 1

Psychosis. Visual hallucinations. Paranoid

Discontinuation: symptoms resolved spontaneously

Case 2

Psychosis. Auditory and visual hallucinations. Suspicious

Discontinuation: symptoms resolved spontaneously

Case 3

Psychosis. Suspicious. Auditory hallucinations

Discontinuation: symptoms resolved spontaneously

Readministration of extended release methylphenidate (low dose) as an adjunct to atomoxetine, 5 weeks: "completely uncharacteristic behaviour", throwing furniture, making "silly" noises, and irritability. "Being unable to feel himself"

Discontinuation: this behaviour resolved spontaneously within 72 hours

Readministration of immediate release methylphenidate (15 mg, twice daily): no psychotic symptoms reported

Case 4

Psychosis. Suspicious. Paranoid ideation. Denied any hallucinatory experiences although he was observed to be responding to possible auditory hallucinations

Discontinuation: symptoms resolved spontaneously

Re-challenged with immediate release methylphenidate (10 mg 3 times daily): well tolerated

Non-serious adverse events

Case 1

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Shibib 2009 *(Continued)*

	Extended release methylphenidate gradually increased to 30 mg over 4 weeks: loss of appetite **Case 3** Immediate release methylphenidate gradually increased to 15 mg daily: poor appetite
Notes	*Key conclusions of the study authors*: psychosis is an important, unpredictable side effect of stimulant medication. Symptoms resolve with discontinuation of treatment. Reemergence of ADHD symptoms are rapid and re-challenge is often indicated *Comments from the study authors*: it would be advisable for all professionals involved in the care and treatment of patients with ADHD to receive mental health training to aid the early recognition and appropriate management of such side effects Funding/vested interest/authors' affiliations: not stated *Supplemental information* regarding ADHD diagnostic criteria, ADHD subtype, and IQ received through personal email correspondence with the authors in August-October 2013 (Shibib 2013 [pers comm])

Shin 2016

Methods	Self-controlled patient series analysis of cardiovascular events associated with methylphenidate treatment in children and young people with ADHD
Participants	Number of participants screened: not stated Number of participants included: 1224 Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: ICD-10 (subtype: not stated) Age: under 17 or 17 IQ: not stated Sex: 75-80% males Methylphenidate-naïve: 100% Ethnicity: not stated Country: Korea Comorbidity: the prevalence of comorbidities varied across adverse events. Depressive episode was the most common comorbidity (n = 15, 29% in participants with myocardial infarction), though only 9 (13.4%) participants with ischaemic stroke had this condition. In contrast, mental retardation occurred in 12 (18%) participants with an ischaemic stroke, while only 2 (5%) with heart failure had this condition comedication: antidepressants and antipsychotics were often co-prescribed (15-27%) Sociodemographics: not stated *Inclusion criteria*: 1. Children and young people aged ≤ 17 years 2. Diagnosis of ADHD (ICD-10 (ICD, 10th revision) code F90) that had been submitted by healthcare providers from 1 January 2007 to 31 December 2011 3. Taking methylphenidate (ATC (Anatomical Therapeutic Chemical) code N06BA04) 4. Had an incident cardiovascular adverse event with a recorded diagnosis during the study period

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Shin 2016 *(Continued)*

	5. New user (of MPH) with first incident cardiovascular event or symptom *Exclusion criteria*: None stated
Interventions	Methylphenidate type: not described Mean methylphenidate dosage: not stated Mean duration of methylphenidate exposure: 0.5 years for all events except heart failure, which was 0.3 years
Outcomes	All data used were obtained from secondary electronic records for the study participants. This study had both comparative cohort data and non-comparative cohort data *Non-serious adverse events*: These were all patients aged ≤ 17 years who had at least one recorded diagnosis of ADHD (ICD-10 code F90), had started taking methylphenidate (ATC (Anatomical Therapeutic Chemical) code N06BA04), and had an incident cardiovascular adverse event with a recorded diagnosis during the study period (1 January 2008 and 31 December 2011)
Notes	Ethics approval: this study was approved by the institutional review board of the Korea Institute of Drug Safety and Risk Management, Seoul. Obtaining informed consent from the study population was waived by the board Funding: this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. EER was supported by an NHMRC fellowship (GNT1110139). NP was supported by an NHMRC early career fellowship (GNT1035889) Vested interests: all authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work *Key conclusions of the study authors*: our self-controlled patient series study suggests an increased risk of cardiac events associated with methylphenidate use *Comments from the study authors*: methylphenidate exposure in children/young people with a diagnosis of ADHD is associated with arrhythmia and potentially with myocardial infarction in specific time periods of use. With the increased use of drugs for ADHD globally, the benefits of methylphenidate should be carefully weighed against the potential cardiovascular risks of these drugs in children and adolescents Inclusion of methylphenidate responders only or exclusion of children who have previously experienced adverse events on methylphenidate: no

Shyu 2015

Methods	A case-control study
Participants	Number of patients screened: for ADHD group: 146,063. Control group: 1,000,000 Number included: 146, 098 Number included as cases (MPH): 73,049 and controls (no intervention): 73,049 Number followed up in each arm: MPH: 73,049 and C: 73,049

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Shyu 2015 *(Continued)*

	Number of withdrawals in each arm: 73,014 were excluded from the ADHD group. No data on control group Diagnosis of ADD: DSM-?/ICD-? diagnosis of ADHD (combined (%), hyperactive-impulsive (%), inattentive (%)). Age: cases (mean 9.4 years, SD 3.3), controls (mean 9.6 years, SD 3.8) IQ: no data Sex: cases: 14,742 females, 58,302 males. Controls: 20,057 females, 52,992 males MPH-naïve: no data Ethnicity: no data Country: Taiwan Comorbidity (type: %): cases: ODD/conduct disorder (11.1%), PDD (8.7%), tic disorders (6.6%), intellectual disability (14.2%), psychotic disorder (1.7%), and schizophrenia (0.9%) Controls: ODD/conduct disorder (0.3%), PDD (0.3%), tic disorders (0.9%), intellectual disability (0.9%), psychotic disorder (0.2%), and schizophrenia (0.1%) Comedication (no/yes) no data Sociodemographics (e.g. double or single parent family, low, middle or upper class). No data *Inclusion criteria* 1. Diagnosed with ADHD between January 1999 and December 2011 2. Was a part of the National Health Insurance Research Database of Taiwan (NHIRD-TW) *Exclusion criteria* 1. Were diagnosed with ADHD before 31 December 1999 2. Had a diagnosis of psychotic disorders that preceded the diagnosis of ADHD 3. Born after 31 December 1999
Interventions	Methylphenidate type: no data MPH dosage: no data Administration schedule: no data Duration of intervention: medical records followed from January 2000 to December 2011 Treatment compliance: no data
Outcomes	Outcomes were defined as having diagnoses of schizophrenia spectrum disorders, including schizophrenia, schizophreniform disorder, schizoaffective disorder (ICD-9-CM code 295.X), delusional disorder (ICD-9-CM code 297.X), brief psychotic disorder and psychotic disorder NOS (ICD-9-CM code 298.X). Diagnoses of schizophrenia spectrum disorders and date of diagnosis were identified based on the insurance status, and outpatient and hospitalisation claims databases. Having a diagnosis of any psychotic disorder (ICD-9-CM code 295.X, 297.X or 298.X) and schizophrenia (ICD-9-CM code 295.X) were set as 2 different outcomes and were analysed separately *Serious adverse events*: "Compared to ADHD patients who were never exposed to MPH, MPH use among ADHD patients significantly increased the risk of developing any psychotic disorder (aHR 1.20, 95% CI 1.04 to 1.40). Howev-

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Shyu 2015 *(Continued)*

	er, MPH use did not significantly increase the specific risk of developing schizophrenia (aHR 1.16, 95% CI 0.94 to 1.42) among patients with ADHD"
Notes	Sample calculation: no data Ethics approval: no data Funding: supported by the Chang Gung Memorial Hospital Research Project Vested interests/authors' affiliations: the authors declare no conflicts of interest *Key conclusions of the study authors*: compared to ADHD patients who were never exposed to MPH, MPH use among ADHD patients significantly increased the risk of developing any psychotic disorder; however, it did not significantly increase the specific risk of developing schizophrenia

Silva 2004

Methods	Open-label cohort study to determine efficacy of a single daily dose of dexmethylphenidate (d-MPH) in 22 children with ADHD
Participants	Number of participants screened: not stated Number of participants included: 22 Number of participants followed up: 20 Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 8.7 years old (range 6-12) IQ: not stated Sex: 17 males, 5 females Methylphenidate-naïve: n = 18 Ethnicity: white 54%, African American 23%, Hispanic 23% Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. Children and adolescents aged 6-18 years with a DSM-IV diagnosis of ADHD and a CGI severity score which was at least moderate and in otherwise good health 2. Sexually active females were negative for pregnancy screens and using accepted method of contraception *Exclusion criteria* 1. Contraindication to methylphenidate 2. Allergy 3. Anxiety or agitation 4. Hypertension

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Silva 2004 *(Continued)*

	5. Glaucoma 6. A seizure or psychiatric disorder 7. Diagnosis or family history of Tourette syndrome 8. Tics 9. Current or past substance abuse 10. Pregnant or lactating females 11. Using MAOIs within previous 30 days 12. Use of other stimulants 13. Any cardiovascular 14. Renal, enterohepatic 15. Respiratory, or immunological disorder 16. Could not communicate with investigator or were unlikely to cooperate with study
Interventions	Methylphenidate type: dexmethylphenidate (d-MPH) Mean methylphenidate dosage: the starting dose was 2.5 mg/day and titrated to up to a maximum 30 mg/day based on clinical effect and tolerability over 8 weeks. The mean daily dose was 16.0 mg/day Administration schedule: once daily in the morning Duration of treatment: not stated Treatment compliance: was confirmed by tablet and bottle counts
Outcomes	*Non-serious adverse events* Participants were seen at least weekly and monitored for adverse events. Apart from nightmares, data were only recorded for adverse events when reported by ≥ 2 participants
Notes	Sample calculation: not stated Ethics approval: approved by Institutional Review Board Funding/vested interest: supported by Celgene Corporation and the NIH Authors' affiliations: New York University, 4 Rivers Clinical Research and Celgene Corporation (4/8 authors) *Key conclusions of the study authors*: a single daily dose of d-MPH is safe and effective in controlling ADHD symptoms alleviating the need for midday dosing. Patients who failed prior therapy including dl-MPH may respond to d-MPH. A controlled study to confirm these data are warranted *Comments from the study authors*: in controlled clinical trials, d-MPH was at least as efficacious and safe as dl-MPH, at half the dose. In contrast to dl-MPH it was effective on objective measures 6 hours post-dose *Comments from the review authors*: although the only outcome which was measured into the extension period after the 8-week trial was adverse events, only data up to the end of the 8-week trial are reported. This study examines the efficacy of d-MPH, which is not identical to standard methylphenidate (i.e. d- and l- isomers) *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes, see exclusion criteria 1 *Supplemental information* regarding data requested from the authors in April 2014. No reply received

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Sobanski 2013

Methods	A cohort study of methylphenidate use for 6-12 weeks
Participants	Number of participants screened: not stated Number of participants included: 381 Number of participants followed up: 347 Number of withdrawals: 34 Diagnosis of ADHD: ICD-10 (subtype: combined (64.8%), hyperactive-impulsive (32.3%), inattentive (2.6%)) Age: mean 14.0 years old (range: 12-17) IQ: not stated Sex: 307 males, 74 females Methylphenidate-naïve: 7.3% Ethnicity: not stated Country: Germany Comorbidity: speech and language disorders and learning disabilities (8.9%), depressive disorders (3.1%) and anxiety disorders (2.4%). Asperger's syndrome (1%) tic disorders (1.3%) Comedication: yes, 42 patients (11%) (type: not stated) Sociodemographics: not stated *Inclusion criteria*: 1. Male and female patients between 12 and 17 years 2. Confirmed ADHD diagnosis according to ICD-10 3. Treatment-naïve patients with indication for treatment with Medikinet retard or previously treated patients with indication for switch of medication to Medikinet retard *Exclusion criteria*: 1. Contraindications against Medikinet retard according to the summary of product characteristics (SPCs) 2. Comorbid psychiatric or somatic disorder
Interventions	Methylphenidate type: Medikinet retard (50% extended-release component) Mean methylphenidate dosage: 35.7 (SD 15.1, range 5-120) mg/d, and at end point 0.7 (SD 0.3, range 0.2-2.8) mg/kg of the body weight Administration schedule: all patients received Medikinet retard in the morning, 16% received a second dose at lunchtime and 4% on a pro re nata basis Duration of intervention: the median observational period for the treatment with Medikinet retard was 70 days Treatment compliance: not stated
Outcomes	Adverse events were assessed by spontaneous report during the clinical interview at each visit (at T1 and T2)
Notes	Sample calculation: no Ethics approval: yes

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Sobanski 2013 *(Continued)*

Funding/vested interest/authors affiliations: the study was funded by Medice. Esther Sobanski has received consulting income and research support from Eli Lilly, Medice, Novartis and Shire and research support from the German Research Foundation, German Ministry of Education and Research. She receives royalties from books by Medizinisch Wissenschaftliche Verlagsgesellschaft and Dansk Psykologisk Forlag. Manfred Dopfner received consulting income and research support from Lilly, Medice, Shire and Vifor and research support from the German Research Foundation, German Ministry of Education and Research. He receives royalties from books and psychological tests published by Hogrefe, Beltz and Huber. Claudia Ose has received an unrestricted educational grant for statistical and administrative support from Medice. Roland Fischer is the medical director of Medice

Key conclusions of the study authors: the findings suggest that pharmacologically treated adolescents with ADHD and insufficient symptom reduction and/or treatment adherence benefit from switching to Medikinet retard and that it is well tolerated when given in clinical routine care

Comments from the study authors: adverse events were assessed by spontaneous reports but not by the use of structured measures possibly resulting in underreporting. Most patients that were included in the study had an indication for a medication switch. Thus, the study does not allow for conclusions about general effectiveness or superiority of Medikinet retard compared to alternative medications
Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: not stated
Supplemental information on adverse events requested through personal email correspondence with the authors in July 2014 (Sobanski 2014 [pers comm]). Authors not able to provide further information

Song 2012

Methods	A 12-week, multicentre, open-label trial of osmotic release oral system (OROS) methylphenidate in Korean children with ADHD
Participants	Number of participants screened: not stated Number of participants included: 143 Number of participants followed up: 116 Number of withdrawals: 27 Diagnosis of ADHD: DSM-IV (subtype: combined 35.4%, hyperactive-impulsive 6.3%, inattentive 34.3%, not specified 24.5%) Age: mean 9.36 years old (range 6-18) IQ: mean 108 Sex: 121 males, 22 females Methylphenidate-naïve: 89.5% Ethnicity: 100% Asian Country: Korea Comorbidity: tic disorder 7%, anxiety disorder 3.9%, depression 4.1%, oppositional defiant disorder/conduct disorder 27.3% Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. ADHD diagnosis according to DSM-IV

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Song 2012 *(Continued)*

	2. Not exposed to OROS-methylphenidate within 3 months prior to enrollment 3. Age 6-18 *Exclusion criteria*: 1. Mental retardation (IQ under 70) 2. Tourette syndrome 3. Chronic tic disorders 4. Psychotic disorders 5. Seizure disorders 6. Brain injury 7. Pervasive developmental disorders 8. Severe medical or surgical disorders 9. Planning to start or change behavioural therapy 10. Taking selective serotonin reuptake inhibitor within 4 weeks 11. Taking antipsychotics within 4 weeks
Interventions	Methylphenidate type: osmotic release oral system (OROS) Mean methylphenidate dosage: 30.05 mg/day Administration schedule: once daily, in the morning Duration of intervention: 12 weeks Treatment compliance: not stated
Outcomes	Barkley Side Effects Rating Scale
Notes	Sample calculation: not stated Ethics approval: yes. Approved by the institutional review boards for all participating centres Funding/vested interest: supported by Janssen Korea *Key conclusions of the study authors*: optimal mean dose of OROS-methylphenidate was significantly different by age groups. Higher doses was needed in older aged groups than younger groups. Effectiveness and tolerability of OROS-methylphenidate in symptoms of ADHD sustained for up to 12 weeks *Comments from the study authors*: positive bias may have resulted from enrolment of only participants who could tolerate OROS-methylphenidate and experienced efficacy during the dose titration period. Our findings may not be generalised to long-term effects of methylphenidate *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* requested through email correspondence with the authors in May 2014. No reply

Spencer 1992

Methods	A cohort study of methylphenidate use for 14.2 (SD 10.7) months
Participants	Number of participants screened: not stated Number of participants included: 29 Number followed up: 29

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Spencer 1992 *(Continued)*

	Number of withdrawals: not stated Diagnosis of ADHD: DSM-III-R (subtype: not stated) Age: mean 7.8 SD 2.4 IQ: not stated Sex: not stated Methylphenidate-naïve: not stated Ethnicity: not stated Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. DSM-III-R diagnosis of ADHD
Interventions	Methylphenidate type: immediate release Mean methylphenidate dosage: 31.4 (SD 17.6) mg (1 mg/kg SD 0.5) Administration schedule: not stated Duration of intervention: 14.2 (SD 10.7) months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Assessment of growth deficits: simple growth deficit, percent deficit, change in cumulative frequency percentiles, percent change, standardised height deficit, deficits in growth velocity Malnutrition index
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interest: not stated Authors' affiliations: not stated *Key conclusions of the study authors*: although there were statistically significant weight deficits in children treated with both desipramine and methylphenidate compared with normal controls, only those treated with methylphenidate sustained height deficits that attained statistical significance *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* requested through personal email correspondence with the authors in September and October 2013. No reply

Steele 2006

Methods	An open-label, 8-week, multicentre, randomised, parallel trial with 2 arms: 1. Osmotic release oral system (OROS) methylphenidate

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Steele 2006 *(Continued)*

	2. Usual care with immediate release (IR) methylphenidate
Participants	Number of participants screened: 187 Number of participants included: 147 Number randomised to OROS-methylphenidate: 73 and IR-methylphenidate: 74 Number of participants followed up: OROS-methylphenidate: 61; IR-methylphenidate: 62 Number of withdrawals: OROS-methylphenidate: 12; IR-methylphenidate: 12 Diagnosis of ADHD: DSM-IV (subtype: combined (79.3%), hyperactive-impulsive (2.1%), inattentive (18.6%) Age: mean: not stated (range: 6-12) IQ: above 70 Sex: 121 males, 24 females Methylphenidate-naïve: not stated Ethnicity: white: 86.9%, African American: 3.4%, Asian: 0.7%, others: 9.0% Country: Canada Comorbidity: oppositional defiant disorder (40.7%), conduct disorder (0.7%), anxiety (4.1%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. Physically healthy 2. Aged 6-12 years inclusive 3. ADHD diagnosis according to DSM-IV 4. Medication naïve or currently on ADHD medication therapy 5. A baseline Clinical Global Impression-Severity (CGI-S) score of 4 or greater (at least 'moderate' severity) 6. Had to demonstrate significant after-school/evening behavioural difficulties as assessed by the clinician via parent/child interviews 7. To approximate clinical practice settings, psychotropic medications to treat non-ADHD disorders and psychological interventions were permitted as long as the treatment/intervention had been stable for a minimum of 4 weeks prior to entry and did not change nor newly commence during the trial *Exclusion criteria*: 1. Known methylphenidate non-responders, hypersensitivity, or adversely affected by methylphenidate 2. Concomitant use of contraindicated medication likely to interfere with the safe administration of study medication 3. Marked anxiety, tension, aggression/agitation 4. Glaucoma 5. Ongoing seizure disorder 6. Psychotic disorder 7. Diagnosis or family history of Tourette disorder 8. Bipolar disorder 9. Suspected mental retardation or significant learning disorder 10. Medication/alcohol abuse/dependence by either the child or parent 11. History of, or current eating disorder

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Steele 2006 *(Continued)*

	12.Severe gastrointestinal narrowing 13.Inability to swallow study medications 14.And any serious/unstable medical illness
Interventions	Methylphenidate type: osmotic release oral system and immediate release methylphenidate (patients were randomly assigned) Mean daily dose of OROS-methylphenidate: 37.8 (SD 11.9) mg (1.17 (SD 0.52) mg/kg; range 18-54 mg) Mean daily dose of IR-methylphenidate: 33.3 (SD 13.2) mg (1.03 (SD 0.46) mg/kg; range 10-70 mg) Administration schedule: OROS-methylphenidate once daily in the morning and IR-methylphenidate 2-3 times daily Duration of intervention: 8 weeks Titration period: 4 weeks initiated after randomisation Washout: at study entry, patients on stimulant or non-stimulant medication to treat ADHD underwent a minimum 3-day washout Treatment compliance: the percentage of participants who missed any dose during the trial: IR-methylphenidate (84%) and OROS-methylphenidate (56%)
Outcomes	*Non-serious adverse events*: Adverse events, physical examination, vital signs, and body weight, height
Notes	Sample calculation: yes (130 participants) Ethics approval: yes Funding/vested interest: this research was supported by Janssen-Ortho Inc., Canada Authors' affiliations: no affiliations to pharmaceutical companies stated *Key conclusions of the study authors*: once-daily OROS-methylphenidate is significantly more effective than usual care with IR-methylphenidate based on multiple outcome measures including remission rate Exclusion of methylphenidate non-responders: yes, known non-responders excluded (see exclusion criteria 1) *Supplemental information* requested through email correspondence with the authors in September 2013. No reply

Stein 2002

Methods	A comparative cohort study of 32 non-medicated ADHD male adolescents, 35 ADHD male adolescents receiving methylphenidate, and 77 controls (no ADHD)
Participants	Number of participants screened: 150 Number of participants included: 95 (non-medicated: 32; medicated: 35; controls: 77) Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-III (subtype: not stated)

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Stein 2002 *(Continued)*

	Age: mean: non-medicated: 13.06 years; medicated: 13.26 years old (range not stated) IQ: not stated Sex: 144 males Methylphenidate-naïve: non-medicated group had not been receiving any medication for the treatment of ADHD for ≥ 6 months prior to the study Ethnicity: Jewish-Ashkenazi (European descent) 46%, Jewish-Sepharadi (Middle Eastern descent) 54% Country: Israel Comorbidity: not stated Comedication: no Sociodemographics: not stated *Inclusion criteria*: 1. ADHD *Exclusion criteria*: 1. If positive in 1 of 10 items of ICID-I (no other Axis I disorder) 2. Current/lifetime neurological disorder 3. Current/lifetime use of any psychotropic medication 4. Mental retardation *Controls*: 1. Any current or lifetime medical, neurological, or mental disorder
Interventions	Methylphenidate type: immediate release Mean methylphenidate dosage: 18 mg/day Administration schedule: once or twice/day (morning/noon) Duration of intervention: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Questionnaires on sleep
Notes	Sample calculation: no Ethics approval: the Israel Ministry of Education and the principals of the 2 participating schools approved the study. Written informed consent was obtained Funding/vested interests: not stated *Key conclusions of the study authors*: the study did not find a greater severity of sleep disturbances among non-medicated male adolescents diagnosed with ADHD in childhood compared to control participants. Sleep disturbance among male students receiving methylphenidate treatment was significantly greater compared with the non-medicated group *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated

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Stein 2002 *(Continued)*

	Supplemental information requested through personal email correspondence with the authors in April 2014. No reply

Stevens 2010

Methods	A cross-sectional study of youths treated with high-dose osmotic release oral system (OROS) methylphenidate
Participants	Number of participants screened: not stated Number of participants included: 17 Diagnosis of ADHD: DSM-IV (subtype: combined 11, inattentive 6) Age: mean 16.2 years old (range 11-20) IQ: not stated Sex: 13 males, 4 females Methylphenidate-naïve: no Ethnicity: white 88%, Native American 12% Country: USA Comorbidity: depressive spectrum disorders 47%, pervasive developmental disorders 41%, oppositional defiant disorder 41%, bipolar spectrum disorders 29%, fetal alcohol syndrome 12% Comedication: bupropion (n = 10), SSRIs (n = 8), lithium (n = 5), alpha-2 agonists (n = 4), atypical antipsychotics (n = 3), lamotrigine (n = 3), trazodone (n = 2), SNRIs (n = 1), oxcarbazepine (n = 1), tricyclic antidepressants (n = 1) Sociodemographics: not stated *Inclusion criteria*: 1. Children and adolescents 2. Higher than FDA-approved dose of OROS methylphenidate 3. Diagnosed with ADHD with DSM-IV criteria *Exclusion criteria*: 1. 1 patient was excluded because of concerns about medication adherence
Interventions	Methylphenidate type: osmotic release oral system (OROS) Mean methylphenidate dosage: 169 mg/day SD 31 (range: 126-270) Administration schedule: not stated Duration of intervention: not stated, but ≥ 2 weeks stabilised on same dose Treatment compliance: not stated
Outcomes	Heart rate, systolic blood pressure, and diastolic blood pressure measured No adverse events or adverse cardiovascular outcomes were reported
Notes	Sample calculation: not stated Ethics approval: yes

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Stevens 2010 *(Continued)*

	Funding/vested interest: the data analysis of this research was funded by institutional funds from the Pediatric Psychopharmacology Unit at Massachusetts General Hospital Authors' affiliations: George is a speaker for McNeil, Shire, Novartis and Lilly, consultant for McNeil and Shire. Wilens receives grant support from Abbott, McNeil, Lilly, Merck and Shire, is a speaker for Lilly, McNeil, Novartis and Shire, is a consultant for Abbott, McNeil, Lilly, NIH, Novartis, Merck and Shire *Key conclusions of the study authors*: high-dose OROS methylphenidate used in combination with other medications, was not associated with either unusually elevated plasma methylphenidate concentrations or with clinically meaningful changes in vital signs *Comments from the review authors*: requirement to be stabilised on OROS methylphenidate de facto excludes patients with poor or adverse response *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: see above *Supplemental information* regarding data requested through email correspondence with the authors in June 2014. No reply

Strandell 2007

Methods	A series of spontaneously reported cases of suicidal and self-damaging behaviour from VigiBase
Participants	Number of cases reported: 116 Diagnostic criteria not stated, nor subtype Age(range): 5-17 years old IQ: not stated Sex: not stated Ethnicity: not stated Country: not stated Comorbidity: 78 were depressed, otherwise not stated Comedication: in 33 cases methylphenidate and atomoxetine were co-reported. 17 depressed patients were on antidepressants, and 42 were on antidepressants (without depression) - (not clear if they were on atomoxetine or methylphenidate) Sociodemographics: not stated
Interventions	Methylphenidate type: not stated Methylphenidate dosage: not stated Administration schedule: not stated Duration of intervention: not stated Treatment compliance: not stated
Outcomes	*Serious adverse events*: Depression suicidal Intentional overdose

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Strandell 2007 *(Continued)*

	Intentional self-injury
	Non-accidental injury
	Suicidal tendency
	Suicide
	Suicide attempt
	Thoughts of self-harm
Notes	Ethics approval: not stated
	Funding/vested interest/authors' affiliations: not stated
	Key conclusions of the study authors: the number of reports with suicidal behaviour in children and adolescents raises concern. The reports do not only imply possible suicidal behaviour: young patients actually commit suicide
	Comments from the review authors: this case-series is based on a database of spontaneously reported adverse events. Therefore, some of these cases might have been reported in other case-reports
	Supplemental information, specifically asking for full-text article and additional information, requested through email correspondence with the authors in November 2013. No reply

Su 2015

Methods	A multicentre, prospective, single-arm, open-label study on methylphenidate use for 8 weeks with extended observation for up to 24 weeks
Participants	Number of participants screened: 248
	Number of participants included: 239
	Number of participants followed up: 205
	Number of withdrawals: 34
	Diagnosis of ADHD: DSM-IV (subtype: combined 61.1%, predominantly inattentive type: 34.3%, predominantly hyperactive-impulsive type: 3.8%, not specified: 0.8%)
	Age: mean: 9.2 (SD 2.02) years old (range 6-16)
	IQ: not stated
	Sex: 203 male, 36 females
	Methylphenidate-naïve: all the children were psychotropic drug naïve or had received anti-ADHD drugs (including OROS-methylphenidate, atomoxetine, monoamine oxidase inhibitors, clonidine, other α2-adrenergic receptor agonists, tricyclic antidepressants, theophylline, and bishydroxycoumarin) for 6 months or longer before the trial with the treatment course not more than 1 month or were currently having effective immediate release methylphenidate treatment
	Ethnicity: Asian 94.6%, other 5.4%
	Country: China
	Comorbidity: not stated
	Comedication: recorded, but not stated
	Sociodemographics: not stated

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Su 2015 *(Continued)*

	Inclusion criteria: 1. DSM-IV ADHD diagnosis 314.00 and 314.01 by evaluation with Kiddie Schedule for Affective Disorders and Schizophrenia 2. 6-16 years of age 3. Body weight 20-60 kg *Exclusion criteria*: 1. History of bipolar I or II affective disorder, anxiety disorder, schizophrenia, mental retardation, pervasive development disorder, cardiovascular disease 2. Diseases that may be aggravated because of accelerated pulse or high blood pressure including hypertension, glaucoma, tic disorder including Tourette syndrome 3. Family history of tic disorder
Interventions	Methylphenidate type: osmotic release oral system (OROS) Methylphenidate dosage: 18 mg/day, 36 mg/day and 54 mg/day Administration schedule: for methylphenidate-naïve dose participants: adjustment phase for 3 weeks, optimal dosage treatment for 5 weeks. For non-naïve participants: 18 mg/day for previous 5 mg 2-3 times a day, 36 mg/day for previous 10 mg 2-3 times a day and 54 mg/day for previous 15 mg 2-3 times a day or higher Duration of intervention: 8-24 weeks Treatment compliance: most patients (> 90%) in the full analysis set had compliance between 80% and 120%, during the 8- and 24-week treatment periods
Outcomes	Safety and tolerability were monitored throughout the study by the evaluation of the incidence and type of treatment emergent adverse events and changes in clinical laboratory test results, vital signs, sleep status, tics, appetite, height, and weight
Notes	Sample calculation: none Ethics approval: approved the institutional review board of Peking University sixth Hospital and other independent ethics committees at all sites Funding/vested interests: sponsored by Xi'an Janssen Pharmaceutical Ltd, and supported by the Major State Basic Research Development Program of China. YW has served on advisory boards of Xi'an Janssen Pharmaceutical Ltd and Eli Lilly & Company. JZ and JQ are full-time employees of Xi'an Janssen Pharmaceutical Ltd. *Key conclusions of the study authors*: most of the children experienced symptom relief with no severe adverse events. The OROS-methylphenidate at the dosage levels of 18 mg, 36 mg, and 54 mg once daily was generally well tolerated in Chinese children with ADHD between the ages of 6-16 years *Comments from the study authors*: an open-label, non-comparator, non-randomised study design is a major limitation for this study. No blinded trained clinician raters collected the study data. Also, the outcome measures were mainly based on the parent reports. As the role of measurement in ADHD makes school settings critical, hence, the data of ADHD symptom expression in school settings are not presented. To further improve this situation, we recommend the incorporation of direct evaluations from teachers/instructors in the follow-up studies in China *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* requested through personal email correspondence with the authors in May 2016. No reply

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Sudarmadji 2009

Methods	A double-blind, randomised parallel trial of methylphenidate use for 2 weeks
Participants	Number of participants screened: not stated Number of participants included: 84 1 group randomised to 5 mg methylphenidate daily, other group to 10 mg methylphenidate daily (number of participants in each group not stated) Number followed up in each arm: not stated Number of withdrawals in each arm: not stated Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean not stated (range: 6-14) IQ: above 70 (attending elementary school) Sex: not stated Methylphenidate-naïve: not stated Ethnicity: not stated Country: Indonesia Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. Attending 1 of 7 specific elementary schools 2. 6-14 years old 3. Both sexes 4. DSM-IV diagnosis of ADHD *Exclusion criteria*: None stated
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 5 mg or 10 mg Administration schedule: once daily Duration of intervention: 2 weeks Treatment compliance: not stated
Outcomes	No description of measures
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interests: not stated Authors' affiliations: not stated *Key conclusions of the study authors*: treatment with 5 mg methylphenidate was more effective compared with 10 mg methylphenidate to improve the attention, decrease hyperactivity and increase the cognitive function. The side effects of 5 mg/daily methylphenidate were milder compared with 10 mg/daily

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Sudarmadji 2009 *(Continued)*

	Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: not stated *Supplemental information* was attempted to be retrieved through contact with the authors in July 2014. We were not able to find contact information on any of the authors

Tang 2010

Methods	A patient report of stool and urinary incontinence during treatment with osmotic release oral system (OROS) methylphenidate
Participants	Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 8 years old IQ: above 70 Sex: male Ethnicity: not stated Country: Taiwan Comorbidity: no Comedication: no Sociodemographics: not stated
Interventions	Methylphenidate type: immediate and extended release Methylphenidate dosage: immediate release, 10 mg. OROS 18 mg/day then 36 mg/day Administration schedule: immediate release, each morning. OROS methylphenidate, once daily Duration of intervention: immediate release methylphenidate, 2 weeks. OROS methylphenidate, 2 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events* Side effects reported by the mother: Immediate release methylphenidate 10 mg: no side effects OROS methylphenidate 18 mg/day: no side effects OROS methylphenidate, 36 mg/day: double incontinence. Stool incontinence (every day, frequent during daytime) and urinary incontinence (almost every day). The double incontinence completely resolved after the discontinuation of OROS methylphenidate 36 mg
Notes	*Key conclusions of study authors*: the causality in this case might be dose-related, and careful monitoring is highly suggested *Comments from the authors*: the Adverse Drug Reaction Probability score in this patient was 7, denoting a probable adverse reaction caused by OROS methylphenidate 36 mg. Because of ethical considerations, this patient did not undergo re-challenge with OROS methylphenidate Funding/vested interests/authors' affiliations: not stated

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Tasdelen 2015

Methods	A prospective cohort study of methylphenidate use
Participants	Number of participants screened: not stated Number of participants included: 22 Number of participants followed up: 17 Number of withdrawals: 5 Diagnosis of ADHD: DSM-IV (subtype: combined (100%)) Age: mean 9.59 years old (range: 7-12) IQ: mean: 102 (SD 10) Sex: 17 males, 5 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Turkey Comorbidity: not stated Comedication: no Sociodemographics: not stated *Inclusion criteria*: 1. ADHD DSM-IV diagnosis 2. CGI-S score of ≥ 4 *Exclusion criteria*: 1. Psychological, neurological or psychiatric diseases other than ADHD 2. ADHD type other than combined 3. Medication that influences cognitive processes or history of such medication 4. Wechsler intelligence (WISC-R) lower than 80 or higher than 120
Interventions	Methylphenidate type: osmotic release oral system (OROS) 36-54 mg Mean methylphenidate dosage: 0.9 mg/kg/day Administration schedule: not stated Duration of intervention: mean 7 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Several adverse events (loss of appetite, abdominal pain, irritability, tingle, headache, nausea, insomnia and tics) were observed in 12 out of 22 patients receiving OROS methylphenidate. Not stated how these adverse events were reported or measured
Notes	Sample calculation: not stated Ethics approval: yes

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Tasdelen 2015 *(Continued)*

	Funding/vested interests: none Authors' affiliations: none *Key conclusions of the study authors*: behaviour and cognitive functionality are recovered simultaneously using OROS-methylphenidate *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no, all patients were newly diagnosed and methylphenidate naïve *Supplemental information* regarding IQ and specific adverse events received through personal email correspondence with the authors in June 2016 (Tasdelen 2016 [pers comm])

Tekin 2015

Methods	A patient report of focal dystonic reaction during MPH treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 15 years old IQ: not known Sex: female Ethnicity: not stated Country: Turkey Comorbidity: none Comedication: none Sociodemographics: uneventful pregnancy and delivery. Family members had no history of psychiatric or movement disorders
Interventions	Methylphenidate type: modified-release Methylphenidate dosage: 27 mg/day Administration schedule: not stated Duration of treatment: 9 days Treatment compliance: not stated
Outcomes	*Serious adverse events*: After 9 days of methylphenidate treatment: involuntary extensor muscular contraction of right hand and wrist, tension and severe pain. The dystonic reaction subsided after biperiden and diazepam administration. No opportunity for re-challenge, because the patient refused to take methylphenidate again
Notes	*Key conclusions of the study authors*: clinicians should consider acute dystonia as a rare adverse event that might emerge during modified release methylphenidate treatment *Comments from the study authors*: to our knowledge, this is the first reported case of focal dystonia after initiation of methylphenidate in a drug-naïve otherwise healthy attention-deficit/hyperactivity disorder (ADHD) patient. The patient had a history of similar adverse effects due to immediate-release methylphenidate. Therefore, acute dystonic reaction was considered to be due to methylphenidate treatment. Naranjo Adverse Drug Reaction Probability Scale score was 5

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Tekin 2015 *(Continued)*

	Funding/vested interests/authors' affiliations: the authors have no financial relationships or conflicts of interest to disclose. There was no financial support relevant to the article
	Ethics approval: the patient and the patient's mother gave written informed consent for the publication of this patient report
	Supplemental information regarding ADHD diagnosis and any comedication received through personal email correspondence with the authors April 2016 (Soyata 2016 [pers comm]). No information regarding the patient's IQ was available

Thorell 2009

Methods	A cross-sectional study of children on stimulant treatment studying positive and negative effects
Participants	Number of participants screened/questionnaires sent out to: 132 Number of participants included/returned questionnaires: 79 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 13.14 years old (range 9-17) IQ: above 70, except for 2 children with mild mental retardation Sex: 62 males, 17 females Methylphenidate-naïve: none Ethnicity: not stated Country: Sweden Comorbidity: Aspergers (7.6%), Tourette syndrome (13.9%), obsessive-compulsive disorder (2.5%), mild mental retardation (2.5%), oppositional defiant disorder/conduct disorder (2.5%) Comedication: no Sociodemographics: not stated *Inclusion criteria*: 1. ADHD according to criteria DSM-IV 2. Currently on stimulant medication 3. Between the ages of 9 and 17 years
Interventions	Methylphenidate type: 96% were taking methylphenidate and 4% amphetamine Dosage: not stated Administration schedule: not stated Duration of intervention: mean 3.12 years (range: 6 months to 12 years) Treatment compliance: most children knew how it felt to be off medication. Only 8% of the parents in the present study indicated that the child never forgot to take his or her medication
Outcomes	*Non-serious adverse events* Children's and parents questionnaire of negative events (4-point Likert-type scale), parent and self-reported
Notes	Sample calculation: none reported

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Thorell 2009 *(Continued)*

Ethics approval: yes, the study was approved by the local ethics committee

Funding: the study was supported by a grant from Majblommans Riksförbund

Vested interests/authors' affiliations: no affiliations to pharmaceutical companies stated

Key conclusions of the study authors: Swedish children treated with stimulants generally experienced positive treatment effects in many areas, especially in the school setting, and a majority wished to continue taking their medication. There was, however a small group of children who reported a relatively large number of negative effects. Few differences between parents and children were found for positive effects, although parents reported higher levels of negative effects

Comments from the study authors: excluding the children with comorbid diagnoses did not make any significant changes in the results. The 4 participants not taking methylphenidate and who were mentally retarded are excluded from the data

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no

Supplemental information regarding adverse event data for patients taking methylphenidate without intellectual disability (n = 75) received through personal email correspondence with the authors in October 2013 (Thorell 2013 [pers comm])

Tomás Vila 2010a

Methods	A patient report of visual hallucinations during methylphenidate treatment
Participants	Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 10 years old IQ: above 70 Sex: male MPH-naïve: no Ethnicity: not stated Country: Spain Comorbidity: none stated Comedication: not stated Sociodemographics: lives with his grandmother
Interventions	Methylphenidate type: 50% immediate release and 50% extended release Methylphenidate dose: 30 mg/day (1 mg/kg/day) Administration schedule: not stated Duration of treatment: 2 weeks Treatment compliance: not stated
Outcomes	*Serious adverse events*: After 2 weeks of 50% immediate release and 50% extended release methylphenidate: visual hallucinations (insects on hands, feet, abdomen and thorax) with associated itching, initiated 2 hours after ingestion and ceased 5 hours after

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Tomás Vila 2010a *(Continued)*

	Discontinuation of methylphenidate and initiation of risperidone: no visual hallucinations No readministration of methylphenidate due to ethical reasons
Notes	*Key conclusions of the study authors*: this is the first patient report of visual hallucinations caused by 50% immediate release, 50% extended release methylphenidate, which is no wonder when you consider that the preparation has been marketed recently Funding/vested interests/authors' affiliations: not stated *Supplemental information* regarding diagnostic criteria and IQ received through personal email correspondence with the authors in September 2013 (Tomás 2013 [pers comm])

Tomás Vila 2010b

Methods	A multicentre 3-month cohort study that investigates the impact of methylphenidate treatment on sleep
Participants	Number of participants screened: not stated Number of participants included: 114 Number of participants followed up: 114 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype: combined (54.5%), hyperactive-impulsive (6.3%), inattentive (39.3%)) Age: mean 8.8 years old (range 4-15) IQ: normal intelligence Sex: 79% males, 27% females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Spain Comorbidity: not stated Comedication: no Sociodemographics: not stated *Inclusion criteria*: 1. Diagnosis of ADHD and initiation of methylphenidate treatment between 1 January and 30 June 2009 2. Maintenance of methylphenidate treatment for ≥ 3 months *Exclusion criteria*: 1. Younger than 2 years old 2. Comedication
Interventions	Methylphenidate type and mean dosage: immediate release methylphenidate, mean dose: 18.5 mg (n = 42). Intermediate release-methylphenidate, mean dose: 23.3 mg (n = 34). Extended release-methylphenidate, mean dose: 32.9 mg (n = 38) Administration schedule: not stated

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Tomás Vila 2010b *(Continued)*

	Duration of intervention: minimum 3 months
	Treatment compliance: not stated
Outcomes	*Non-serious adverse events*
	Spanish abbreviated (18 questions chosen) version of the Paediatric Sleep Questionnaire (PSQ) rated by neuro-paediatricians
Notes	Sample calculation: not stated
	Ethics approval: not stated
	Funding/authors' affiliations: the authors declare no conflicts of interest
	Key conclusions of the study authors: the results of the study suggest that methylphenidate does not have a negative impact on sleep in patients with ADHD and comorbid sleep disorders. Methylphenidate improves the quality of sleep in those patients
	Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no
	Supplemental information regarding ADHD diagnostic criteria and IQ received through personal email correspondence with the authors in October 2013 (Tomás 2013b [pers comm])

Trugman 1988

Methods	A patient report of cerebral arteritis during methylphenidate treatment
Participants	Diagnosis of ADHD: ICD-9 (unspecified hyperkinetic syndrome)
	Age: 12 years old
	IQ: not stated
	Sex: male
	Ethnicity: not stated
	Country: USA
	Comorbidity: not stated
	Comedication: not stated
	Sociodemographics: not stated
Interventions	Methylphenidate type: not stated
	Methylphenidate dosage: 10 mg
	Administration schedule: twice daily
	Duration of treatment: 5-12 years of age (7 years)
	Treatment compliance: not stated
Outcomes	*Serious adverse events*:
	Right hemiparesis, 7 years following daily consumption of methylphenidate
	Aphasia

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Trugman 1988 *(Continued)*

	Non-serious adverse events: Headaches, intermittently before onset of stroke
Notes	*Key conclusions of the study authors*: cerebral arteritis and infarction were caused by chronic oral methylphenidate use. The CSF profile and angiogram support the diagnosis of inflammatory arteritis, yet laboratory evaluation revealed no identifiable cause. In the 6 years since the stroke, while not on methylphenidate there has been no evidence of active central nervous system or systemic vasculitis *Comments from the study authors*: given its pharmaceutical similarity to amphetamine, the association of methylphenidate with cerebral vasculitis is not unexpected, yet has not been previously reported. Physicians who prescribe methylphenidate for long-term use should be aware of this potential complication and specifically question patients regarding symptoms of cerebral ischaemia, including headache *Supplemental information* regarding diagnostic criteria received through personal email correspondence with the authors in September 2013 (Trugman 2013 [pers comm])

Tzang 2012

Methods	A prospective observational study for 48 weeks. Patients categorised into 4 groups based on occurring treatment: 1. No treatment 2. Immediate release (IR) methylphenidate 3. Osmotic release oral system (OROS) methylphenidate 4. Immediate release and osmotic release oral system methylphenidate
Participants	Number of participants screened: not stated Number of participants included: 757 Number of participants included in each group: IR methylphenidate: 265, OROS methylphenidate: 293, IR and OROS methylphenidate: 129, controls (no intervention): 70 Number of participants followed up in each arm: IR methylphenidate: 265, OROS methylphenidate: 293, IR and OROS methylphenidate: 129, controls: 70 Number of withdrawals in each arm: IR methylphenidate: 0, OROS methylphenidate: 0, IR and OROS methylphenidate: 0, controls: 0 Diagnosis of ADHD: DSM-IV (combined (58.52%), hyperactive-impulsive (4.76%), inattentive (36.72%)) Age: mean 10.05 (SD 2.65) years old (range: 6-18 years) IQ: not stated Sex: 607 males, 150 females Methylphenidate-naïve: not stated Ethnicity: white (0%), African American (0%), Asian (100%), Hispanic (0%), others (0%) Country: Taiwan Comorbidity: oppositional defiant disorder (21.80%), conduct disorder (1.85%), anxiety disorder (3.04%), depressive disorder (0.40%), tic disorder (2.64%), Tourette disorder (1.59%), somatisation (5.15%), others (7.40%) Comedication: 6.61%

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Tzang 2012 *(Continued)*

	Sociodemographics: not stated *Inclusion criteria*: 1. Age 6-18 years 2. ADHD according to DSM-IV 3. No ADHD medication for ≥ 4 weeks 4. Living with parents/caregivers who could complete questionnaires during the study 5. Ability of parents or guardians to provide signed and dated informed consent for the participations of their children/wards in the study 6. Being still at school *Exclusion criteria*: 1. Parents/caregivers with known or suspected psychotic disease, mental retardation or any mental condition that may affect their ability to complete the questionnaires 2. Glaucoma or seizures 3. Parents/caregivers with drug or alcohol abuse/dependence within the prior 6 months 4. Serious or uncontrolled medical illness 5. Use of one or both of the study drugs within the past month
Interventions	Methylphenidate type: immediate release (IR) and osmotic release oral system (OROS) Methylphenidate dosage: not stated Administration schedule: OROS-methylphenidate once a day, other groups not stated Duration of intervention: 48 weeks Treatment compliance: not stated
Outcomes	The frequency of adverse effects was determined using a symptom checklist that included the following items: decreased appetite, nausea, somnolence, insomnia, headache, dizziness, abdominal pain, and stomachache at 12, 24, 36, and 48 weeks
Notes	Sample calculation: no information Ethics approval: not stated Funding/vested interests/authors' affiliations: supported by Janssen-Cilag, Taiwan *Key conclusions of the study authors*: OROS methylphenidate treatment at the adequate dosage can achieve higher remission and recovery rates, produce greater functional improvement, and result in better treatment adherence that IR methylphenidate treatment *Supplemental information* requested through email correspondence with the authors in December 2013 and January 2014. No reply

Tølløfsrud 2006

Methods	A patient report of death caused by heart failure (acute dilated cardiomyopathy) during methylphenidate treatment
Participants	Diagnosis of ADHD: ICD-10 (subtype: not stated) Age: 17 years old IQ: no intellectual disability

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Tølløfsrud 2006 *(Continued)*

	Sex: male Ethnicity: not stated Country: Norway Comorbidity: Tourette's syndrome Comedication: none Sociodemographics: not stated
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 15 mg Administration schedule: 3 times daily Duration of treatment: 10 years Treatment compliance: not stated
Outcomes	*Serious adverse events*: Heart failure resulting in death
Notes	*Key conclusions of the study authors*: heart failure leading to death, possibly caused by methylphenidate treatment *Comments from the study authors*: dilated cardiomyopathy can be a rare side effect of methylphenidate use Funding/vested interest/authors' affiliations: none *Supplemental information* regarding ADHD diagnosis and IQ received through personal email correspondence with the authors in November 2013 (Tølløfsrud 2013 [pers comm])

Valdizán Usón 2004

Methods	A 12-month cohort study
Participants	Number of participants screened: not stated Number of participants included: 170 Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV-TR (subtype: not stated for the total sample. Subtype for the sample with polysomnography data: combined (40%), hyperactive-impulsive (9%), inattentive (57%)) Age: mean 8 years old (range not stated) IQ: above 70 Sex: 121 males, 27 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Spain

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Valdizán Usón 2004 *(Continued)*

	Comorbidity: immunological diseases (33.3%) Comedication: no medication for sleep initiation Sociodemographics: not stated *Inclusion criteria*: 1. First consultation between 1998 and 2002 2. ADHD according to DSM-IV-TR 3. Free of other diseases 4. Normal neurological examination without seizure, hearing loss or amblyopia 5. Meet criteria for initiating methylphenidate treatment: ≥ 6 items of inattention, theta/alfa ratio > 1 in quantified EEG or predominance of theta in cerebral cartography, school or environmental repercussion *Exclusion criteria*: 1. Gilles de la Tourette syndrome, autism spectrum disorders, dyslexia and dysphasia 2. Epilepsy, especially absence seizures 3. Mental retardation and obsessive-compulsive disorder
Interventions	Methylphenidate type: immediate release Methylphenidate dosage: 10-40 mg/day, adjusted as needed Administration schedule: morning and noon Duration of intervention: 12 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events* Reports of side effects Complete blood test Thyroid hormones and cortisol levels Nocturnal polysomnography (n = 46), initiated at 10 pm and disrupted at 7 am. Evaluated parameters: sleep efficiency, total registered time, latency time of sleep initiation, number of awakenings, total time of sleep and efficiency, duration of each phase and latency time of REM sleep
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interest: not stated Authors' affiliations: not stated *Key conclusions of the study authors*: it is more likely that the ADD subgroup continues in the adult age and, although as a minority, immunological disorders and/or epileptiform paroxysms are associated. The effect of methylphenidate may be observed by seriated recording of digitalised cortical bioelectrical activity, with synchronic course to the clinical response *Comments from the review authors*: EEG was conducted every 6th month, but the methylphenidate treatment was paused 24 hours before, so we cannot use these data *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

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Valdizán Usón 2004 *(Continued)*

	Supplemental information regarding ethics approval, funding, protocol, patient demographics, and data not possible to receive through personal email correspondence with the authors. Emails sent several times in December 2013. No reply

Valdizán Usón 2013

Methods	A cohort (observational, retrospective, non-interventional, multicentre) study of methylphenidate use for 1 month, 3 months, 6 months, and 1 year
Participants	Number of participants screened: not stated Number of participants included: 680 Number of participants followed up: 680 (safety population), 561 (4-16 years old) Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV TR (subtype: combined (64.9%), hyperactive-impulsive (5%), inattentive (30.05%)) Age: mean 9.497 SD 2.538 (under 6 years old: mean: 5.27, range: not stated; 6-16 years old: mean 9.77, range: 6-16) IQ: above 80 Sex: 454 males, 105 females (under 6 years old: 31 males, 3 females; 6-16 years old: 423 males, 102 females) Methylphenidate-naïve: 0% Ethnicity: not stated Country: Spain Comorbidity: anxiety disorder (13.01%), oppositional defiant disorder (23.35%), learning disorder (50.09%), conduct disorder (30.30%), depressive disorder (5.35%), tics (6.95%). Other associated symptoms were substance abuse (0.36%), apathy (9.68%) and anhedonia (4.36%), developmental coordination disorder (12.66%), pervasive developmental disorder (10.52%), and generalised epilepsy (1.78%) Comedication: yes (under 6 years old: 10 (29.41%); 6-16 years old: 114 (21.63%)) Sociodemographics: not stated *Inclusion criteria*: 1. Patients of both genders 2. Aged 4-65 years 3. Diagnosed with ADHD according to DSM-IV TR criteria 4. Having an intelligence quotient higher than 80 5. Treated with immediate release methylphenidate at the start of follow-up *Exclusion criteria*: 1. Patients whose response to immediate release methylphenidate could not be evaluated 2. Participating in other clinical trials
Interventions	Methylphenidate type: immediate release Mean methylphenidate dosage: mean starting dose: 16.72 mg/day, mean dose at 1-month follow-up: 18.76 mg/day; mean dose at 6-month follow-up: 20.58 mg/day; mean dose at 1-year follow-up: 22 mg/day. Administration schedule: not stated

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Valdizán Usón 2013 *(Continued)*

	Duration of intervention: medical records for the years 2002-2006 (mean = 10.01 months) Follow-up after 1 month, 6 months and 1 year Treatment compliance: not stated
Outcomes	A year after treatment information on adverse events was obtained Safety outcomes included adverse events and serious adverse events reported, and their recurrence, duration, and relationship with the study drug Obtained by a single questionnaire - presence or absence and number of adverse events per patient
Notes	Sample calculation: not stated Ethics approval: yes Funding/vested interest: the authors report no conflicts of interest in this work *Key conclusions of the study authors*: good efficacy and safety results were found for immediate-release methylphenidate in patients with ADHD *Comments from the study authors*: a limitation of the study is that even when favorable results were found overall in reduction of the number of symptoms and a significant global improvement, these results are only preliminary due to the limited numbers of patients included *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* received through personal email correspondence with the authors in July 2014 (Valdizán 2014 [pers comm])

Van der Oord 2007

Methods	A 4-week pseudorandomised, placebo-controlled, cross-over study investigating the additional value of short-term intensive multimodal behaviour therapy to optimally titrated methylphenidate Follow-up 4.5 to 7.5 years after treatment
Participants	Number of participants screened: not stated Number of participants included in methylphenidate group: 23; included in methylphenidate + multimodal behaviour therapy: 27 Number of participants followed up in methylphenidate group: 21 Number of withdrawals in methylphenidate group: 2 Diagnosis of ADHD: DSM-IV/I (subtype: combined (n = 31), hyperactive-impulsive (n = 3), inattentive (n = 16)) Age: mean 9.6 years old IQ: 96.81 Sex: not stated Methylphenidate-naïve: 100% Ethnicity: white: 89%, others: 11% Country: Netherlands

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Van der Oord 2007 *(Continued)*

	Setting: Comorbidity: oppositional defiant disorder/conduct disorder 61.9%, oppositional defiant disorder 46%, conduct disorder 4% Comedication: no Sociodemographics: most parents medium to high education level *Inclusion criteria*: 1. ADHD according to DSM-IV 2. Full scale IQ above 75 (WISC-R) *Exclusion criteria*: 1. Inadequate mastering of Dutch language by the child or both parents 2. A history of methylphenidate use
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 5 mg, 10 mg, and 20 mg in titration period Administration schedule: 7:30 am, 12:30 pm Duration of intervention: 4 week pseudo randomised cross-over design, 1 week medication-free, 5 weeks optimal dose Treatment compliance: high, weekly phone calls to parents and teachers
Outcomes	The MTA Side Effect Rating Scale was used to assess side effects
Notes	Sample calculation: yes (power calculation) Ethics approval: not stated Funding: not stated Vested interest/authors' affiliations: not stated *Key conclusions of the study authors*: no evidence was found for the additive effect of multimodal behaviour therapy next to optimally titrated methylphenidate *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* regarding data on adverse events received through personal email correspondence with the authors in January 2014 (Van der Oord 2014 [pers comm])

Varley 2001

Methods	A retrospective chart review
Participants	Number of participants screened: 555 Number of participants included: 517 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 11 years old (range not stated) IQ: not stated

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Varley 2001 *(Continued)*

	Sex: not stated Methylphenidate-naïve: not stated Ethnicity: not stated Country: not stated Comorbidity: tics Comedication: no Sociodemographics: not stated *Inclusion criteria*: 1. ADHD *Exclusion criteria*: 1. Comedication
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage: not stated Administration schedule: not stated Duration of intervention: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events* Retrospective review of medical records. It was recorded whether the participants did or did not have a reported history of tic emergence in the course of pharmacologic treatment in that clinic. 8.3% (31 of 374) of participants treated with methylphenidate developed tics
Notes	Sample calculation: no Ethics approval: not stated Funding/vested interest: supported by a National Institutes of Health Biomedical Research Support Grant, 1991 Authors' affiliations: not stated *Key conclusions of the study authors*: tics was not related to dose nor treatment length, and may not be related to stimulants *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* requested through personal email correspondence with the authors in April 2014. No reply

Vashi 2011

Methods	A patient report on allergic contact dermatitis caused by methylphenidate transdermal system
Participants	Diagnosis of ADHD: DSM-IV (subtype: not known)

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Vashi 2011 *(Continued)*

	Age: 9 years old IQ: above 70 Sex: female Ethnicity: not stated Country: USA Comorbidity: none Comedication: not stated Sociodemographics: not stated
Interventions	Methylphenidate type: transdermal system Methylphenidate dosage: not known Administration schedule: not stated Duration of intervention: 8 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Allergic contact dermatitis: after 8 months of using a methylphenidate patch the patient presented with pruritic dermatitis. She had itchy, burning, red lesions. Symptoms began on her hip at the area of patch placement, then progressively spread to her arms, legs, abdomen, and back Methylphenidate discontinued: symptoms lasted for 2 months. First and second patch test. Re-tested with methylphenidate patch: 9 days after the first test the patient presented with recall reaction, characterised by a return of the original pruritic dermatitis to her entire back, similar to the eruption that had occurred months previously after therapeutical use of methylphenidate patch Avoidance of methylphenidate patches: symptom-free
Notes	*Key conclusions of study authors*: this is the first reported case of allergic contact dermatitis caused by methylphenidate present within the transdermal system *Supplemental information* regarding diagnosis and IQ received through personal email correspondence with first author in August 2013 (Vashi 2013 [pers comm])

Verret 2010

Methods	A comparative cohort study assessing the impact of methylphenidate on physical functioning and gross motor performance
Participants	Number of participants screened: not stated Number of participants included: 70 Number included in each group: ADHD + methylphenidate: 24, ADHD no methylphenidate: 19 Number followed up in each group: ADHD + methylphenidate: 24 and ADHD no methylphenidate: 19 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (94.3%), hyperactive-impulsive (5.7%)

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Verret 2010 *(Continued)*

	Age: mean not stated (range: 7-12) IQ: not stated Sex: 70 males, 0 females Methylphenidate-naïve: the ADHD no methylphenidate group: 19 Ethnicity: not stated Country: Canada Comorbidity: ADHD + methylphenidate group: opposition or anxiety (29%), anxiety, opposition or obsessive-compulsive disorder (13%); ADHD no methylphenidate group: opposition or anxiety (37%) Comedication: no Sociodemographics: not stated *Inclusion criteria*: 1. ADHD diagnosis according to DSM-IV-TR 2. For the 'ADHD no MPH'-group never having used medication was a requirement *Exclusion criteria*: 1. ADHD inattentive subtype, learning disorder, autism, Tourette syndrome, intellectual disabilities, epileptic disorders 2. Taking any medication other than methylphenidate
Interventions	Methylphenidate type: not stated Methylpheniate dosage: not stated Administration schedule: not stated Duration of intervention: average 24 months (range 5-72 months) Treatment compliance: not stated
Outcomes	*Non-serious adverse events* Anthropometric and vital measures (height, weight, BMI, resting heart rate and blood pressure)
Notes	Sample calculation: no Ethics approval: yes, Research Ethics Committee of the Riviere-des-Prairies Hospital Funding/vested interest: none stated Authors' affiliations: none stated *Key conclusions of the study authors*: fitness level of children with ADHD using medication or not, including body composition, flexibility and muscular endurance was similar to that of the control group. The only difference was observed for BMI which was lower in children with ADHD using medication. Both groups of children with ADHD presented significantly lower scored for locomotion skills *Comments from the study authors*: in this study, it was not possible to obtain precise data for dosage of medication. Because of this methodological issue, the impact of dosage and time of prescription on growth parameters could not be established *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

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Vincent 1990

Methods	A retrospective cohort study of medical records
Participants	Number of participants screened: not stated Number of participants included: 31 Number of participants followed up: 31 Number of withdrawals: 0 Diagnosis of ADHD: DSM-III (subtype: not stated) Age: mean 12.9 (SD 0.8) years old (range not stated) IQ: not stated Sex: 25 males, 6 females Methylphenidate-naïve: 0% Ethnicity: not stated Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. DSM-III diagnosis of ADHD 2. Received methylphenidate continuously for ≥ 6 months sometime after their 12th birthday 3. Available medical record at the clinic *Exclusion criteria*: 1. Other major illnesses
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage: 34 (SD 14) mg/day or 0.75 (SD 0.29) mg/kg/day Administration schedule: not stated. Duration of intervention: 15 participants received methylphenidate for 6-12 months, 9 participants for 1-4 years, 7 participants for 5-7 years (range: 6 months to 6 years and 11 months) Treatment compliance: not stated
Outcomes	*Non-serious adverse events* Weight and height: participants were measured in indoor clothing and stocking feet on a platform scale twice, 6-12 months apart (mean: 221 SD 57 days) by treating physician. Weight to nearest 0.1 kg, height to nearest cm. Initial measurements were randomly distributed throughout the year so as to eliminate any seasonal effects. Expected height and weight obtained from National Center for Health Statistics
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interest: not stated

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Vincent 1990 *(Continued)*

	Authors' affiliations: not stated *Key conclusions of the study authors*: the results of this retrospective study suggest that methylphenidate use at customary doses does not noticeably impair adolescent growth velocities over 6-12 months treatment *Comments from the study authors*: analysis of age, gender, dose, and other characteristics on the basis of length of treatment was not feasible because of sample size *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated *Supplemental information* requested through email correspondence with the authors in September and October 2013. No reply

Walitza 2007

Methods	A prospective study analysing genomic damage in children with ADHD (initial sample size 38 children) before and 1 (30 children), 3 (21 children), and 6 (8 children) months after initiation of methylphenidate therapy. In addition a group of 9 children receiving chronic methylphenidate treatment were investigated
Participants	**Prospective group** Number of participants screened: not stated Number of participants included: 38 Number of participants followed up: 1 month: 30, 3 months: 21, 6 months: 8 number of withdrawals: 1 month: 8, 3 months: 17, 6 months: 30 Diagnosis of ADHD: DSM-IV-TR (subtype: not stated) Age: mean: 10 years old (range: 4.9-17.0) IQ: above 70 Sex: 29 males, 9 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Germany Comorbidity: not stated Comedication: no Sociodemographics: not stated **Chronic group** Number of participants screened: not stated Number of participants included: 9 Diagnosis of ADHD: DSM-IV-TR (subtype: not stated) Age: mean 11.2 years old (range 7.1-16.0) IQ: above 70

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Walitza 2007 *(Continued)*

	Sex: 9 males, 0 females Methylphenidate-naïve: 0%. All treated previously 6 months to 2 years Ethnicity: not stated Country: Germany Comorbidity: yes, 4 patients received additional medicine, but diseases not specified Comedication: yes, 4 patients; 1 received valproic acid and 3 received risperidone Sociodemographics: not stated **Both groups** *Inclusion criteria*: 1. ADHD according to DSM-IV-TR criteria 2. For the prospective group: drug-naïvety 3. For the chronic methylphenidate group: methylphenidate use prior to study initiation *Exclusion criteria*: 1. Current smoking 2. Current infection or an infection 14 days before blood sampling 3. Extreme food patterns (e.g. vegans) 4. Other psychiatric diagnoses such as anorexia nervosa, schizophrenia, any pervasive developmental disorder 5. Neurologic disorders such as epilepsy 6. History of acquired brain damage 7. Evidence of fetal alcohol syndrome, and/or reports of severe prenatal, perinatal, or postnatal complications other severe diseases
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage: **prospective group**: 0.54 mg/kg/day (5-40 mg/day) increasing to 0.74 mg/kg/day (15-45 mg/day) by the end of the trial. **Chronic methylphenidate users**: 0.83 mg/kg/day Administration schedule: not stated Duration of intervention: 1-6 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events* Vital signs ECG Micronucleus analysis (in peripheral lymphocytes): blood samples (7.5 mL each) were collected 1 day before, and 1, 3, and 6 months after methylphenidate treatment. The micronucleus scoring was carried out by a single scorer 6 times for each sample in blinded manner Clinical laboratory values: white and red blood cell count, electrolytes, transaminases measured The measure for genomic damage was the frequency of micronuclei, a subset of chromosomal aberrations, in peripheral lymphocytes, obtained from blood samples No abnormal parameters were observed except slightly reduced values of total iron, without signs of hypochromic microcytic anaemia, which occurred in some patients before and during the treatment, independent of micronucleus deviation

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Walitza 2007 *(Continued)*

Notes	Sample calculation: not stated Ethics approval: approved by the ethics committee of the University of Würzburg (study no. 140/03) Funding/vested interests: partially funded by grants from the German Research Foundation (Deutsche Forschungsgemeinschaft; KFO 125/1-1) and from the Interdisciplinary Center for Clinical Research (IZKF N-5 (1)) and was performed independent of financial or other support by companies producing or selling methylphenidate Authors' affiliations: the authors declare they have no competing financial interest *Key conclusions of the study authors*: the concern regarding a potential increase in the risk of developing cancer later in life after long-term methylphenidate treatment is not supported. The study did not find any alteration in the number of micronucleated cells after methylphenidate treatment at 3 follow-up intervals (up to 6 months) *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: 2 withdrew after 1 month of treatment due to lack of effect *Supplemental information* regarding information on whether any of the children had intellectual disability received through personal email correspondence with the authors in October 2013 (Stopper 2013 [pers comm]). Also asked for vital signs and ECG in August 2014 (Stopper 2014 [pers comm]). The author no longer has access to this

Walitza 2009

Methods	A prospective study (both cohort study: the drug naïve group, and cross-sectional study: the chronically treated group) analysing genomic damage in 3 different group of children: 1. Healthy control group 2. ADHD and chronically methylphenidate-treated (more than 12 months) group 3. Drug naïve group of ADHD affected children who initiated methylphenidate treatment
Participants	**Drug-naïve group** Number of participants screened: not stated Number of participants included: 26 Number of participants followed up: 3 months: 17, 6 months: 11 Number of withdrawals: 3 months: 9, 6 months: 15 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 8.6 years old (range 5-16) IQ: above 70 Sex: 20 males, 6 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Germany Comorbidity: not stated Comedication: not stated Sociodemographics: not stated

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Walitza 2009 *(Continued)*

	Chronically methylphenidate-treated group Number of participants screened: not stated Number of participants included: 21 Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean: 11.4 years old (range 9-16) IQ: above 70 Sex: 16 males, 5 females Methylphenidate-naïve: none. All but 1 treated more than 12 months with methylphenidate Ethnicity: not stated Country: Germany Comorbidity: yes, but not specified Comedication: 4. 1 also took atomoxetine, 1 sulthiame, and 2 risperidone Sociodemographics: not stated **Both groups** *Inclusion criteria*: 1. DSM-IV-TR diagnosis of ADHD 2. Drug naïve group: drug naïve 3. Chronically treated group: methylphenidate treatment more than 12 months (1 patient only treated the past 10 months) *Exclusion criteria*: 1. Current smoking 2. Current infection or an infection in the last 14 days before blood sampling 3. Extreme food patterns (e.g. vegans) 4. Psychiatric diagnosis, such as: anorexia nervosa, schizophrenia, any pervasive developmental disorders, neurological disorders such as epilepsy, a history of any acquired brain damage or evidence of fetal alcohol syndrome
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage: after 3 months: 0.46 (SD 0.22) mg/kg/day. After 6 months: 0.46 (SD 0.24) mg/kg/day. **Chronically treated group:** 0.80 (SD 0.31) mg/kg/day Administration schedule: not stated Duration of intervention: 6 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events* Vital signs, blood pressure, pulse, ECG Blood test to detect haematological abnormality.

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Walitza 2009 *(Continued)*

	Micronucleus analysis (measure of genomic damage): blood sampling and sampling of buccal mucosa cells: baseline, 3, and 12 months after initiation of treatment. Only 1 blood sample/buccal mucosa sample at a certain point of time for the chronic group
Notes	Sample calculation: not stated Ethics approval: approved by the ethics committee of the University of Würzburg (study no. 124/06) Funding/vested interest: this study (124/06) was funded by grants from the IZKF Wuerzburg (Interdisciplinary Clinical Center of the University of Wuerzburg), project N5-1, and supported by a grant from the Deutsche Forschungsgemeinschaft (KFO 125) Authors' affiliations: during the course of this study, HS was asked to serve as an independent consultant for Novartis Pharmaceutical Company. Consulting occurred after this study was finished (all data evaluated) and did not influence any aspect of this study. The other authors declare no potential conflicts of interest *Key conclusions of the study authors*: in this study, we did not find any alteration in the number of micronucleated cells in the group of chronically treated (> 12 months) children compared to the ADHD group before treatment initiation. We also did not find any elevation after initiation of methylphenidate treatment at 2 follow-up intervals at 3 and 6 months after treatment initiation. This is the result from both investigated tissues, peripheral blood lymphocytes and buccal mucosa cells. Therefore, no induction of genomic damage in ADHD patients due to methylphenidate therapy was detectable, supporting our previous study (124/06) *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: 2 withdraw after 1 month of treatment due to lack of effect *Supplemental information* regarding the children's intellectual function received through personal email correspondence with the authors in October 2013 (Stopper 2013 [pers comm]), and mean and SD on measure of genomic damage received in March 2014 (Stopper 2014b [pers comm])

Wang 2007

Methods	A multicountry, multicentre, randomised, double-blind, 8-week study in children and adolescents with ADHD to test the hypothesis that atomoxetine is non-inferior to methylphenidate on conventional ADHD symptom measures
Participants	Number of participants screened: 361 Number of participants included: 166 included Number of participants followed up: 152 Number of withdrawals: 14 Diagnosis of ADHD: DSM-IV (subtype: combined (57.2%), hyperactive-impulsive (3.6%), inattentive (39.2%)) Age: 9.9 (SD 2.3) years IQ: not stated Sex: 134 males (80.7%), 32 females (19.3%) Methylphenidate-naïve: 74.7% Ethnicity: Asian (91.6%), Hispanic (8.4%) Country: China (n = 242), Korea (n = 60), Mexico (n = 28) Comorbidity: ODD (17.5%)

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Wang 2007 *(Continued)*

	Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Out clinic patient 2. 6-16 years 3. Weight between 20 and 60 kg 4. ADHD according to DSM-IV, confirmed by structured diagnostic interview using Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version with a score of ≥ 25 for boys or ≥ 22 for girls, or > 12 for a specific subtype on the ADHD Rating Scale- IV Parent Version: Investigator administrated and scored, as well as Clinical Global Impressions-ADHD-Severity ≥ 4 *Exclusion criteria* 1. Any history of bipolar, psychotic or pervasive developmental disorders 2. Suicidal risk 3. Ongoing use of psychoactive medications other than the study drug 4. Patients with motor tics 5. A diagnosis or family history of Tourette syndrome 6. Patients meeting DSM-IV criteria for anxiety disorder
Interventions	Methylphenidate type: immediate release Methylphenidate dosage: 0.2-0.6 mg/kg/day Administration schedule: morning and lunch Duration of intervention: 8 weeks Treatment compliance: the study completion rate was high 91.6% Titration: treatment titrated from 0.2mg/kg/day to 0.4 mg/kg/day on Day 5 and either maintained or titrated upward or downward within the range 0.2-0.6 mg/kg/day
Outcomes	*Non-serious adverse events* Tolerability measures - assessment of treatment emergent adverse events via open-ended questions Monitoring of vital signs - ECG and clinical laboratory tests (chemistries, haematology and urinalysis) 6 patients (3.6%) discontinued due to: 1. Anorexia: 1 2. Decreased appetite: 2 3. Nausea: 1 4. Dizziness: 1 5. Palpitations: 1
Notes	Sample calculation: yes, approximately 330 patients between the 2 arms Ethics approval: not stated Funding: not stated Vested interest/authors' affiliations: not stated *Key conclusions of the study authors*: atomoxetine was non-inferior to methylphenidate in improving ADHD symptoms based on response rates. Treatment-emergent adverse effects experienced significantly more frequently in the atomoxetine group compared with the methylphenidate group

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Wang 2007 *(Continued)*

	Supplemental information requested through personal email correspondence with the authors in January 2014 with no reply

Wang 2011

Methods	1. An observational, 24-week, prospective, non-randomised study of methylphenidate treatment 2. A 24-week cross-sectional study
Participants	Number of participants screened: not stated Number of participants included: 50 Number of participants followed up: 30 Number of withdrawals: 20 Diagnosis of ADHD: DSM-IV diagnosis (subtype: combined (48%), hyperactive-impulsive (22%), inattentive (30%)) Age: mean 7.56, range 6-12 years old IQ: above 70 Sex: 40 males, 10 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: Taiwan Comorbidity: none Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. Age between 6 and 12 years 2. ADHD according to DSM-IV 3. Newly diagnosed or had not taken medication for ADHD during the previous 6 months or more *Exclusion criteria* 1. History of major physical or psychiatric diseases (such as pervasive developmental disorder, oppositional defiant disorder, conduct disorder, bipolar disorder, depressive disorder, anxiety disorder, psychotic disorder, or substance use disorder)
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 5-15 mg/day Mean methylphenidate dosage: 10.62 mg/daily at 1 month, 14.15 mg/daily at 3 months and 12.84 mg/daily at 6 months. Administration schedule: not stated Duration of intervention: 24 weeks

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Wang 2011 *(Continued)*

	Treatment compliance: the drug compliance at each visit was confirmed to the reports of patients' parents and the remnant drug
Outcomes	*Non-serious adverse events* No reporting of adverse events 3 patients discontinued prematurely due to decreased appetite and weight loss
Notes	Sample calculation: no Ethics approval: approved by the Institutional Review Board of Chang Gung Memorial Hospital Funding: the study was funded by the Chang-Gung Memorial Hospital Research Project Vested interests/authors' affiliations: the authors have no conflicts of interest to declare *Key conclusions of the study authors*: DHEA (dehydroepiandrosterone), but not the cortisol basal level, may be a biological laboratory marker for ADHD, particularly for performance on the CPT. Both the causal relationship between DHEA and ADHD and the role of DHEA in treating ADHD require further investigation *Supplemental information* received through personal email correspondence with the authors in December 2013 (Wang 2013 [pers comm])

Warshaw 2010

Methods	Methylphenidate transdermal system use for 7 weeks. 4 weeks dose optimisation followed by 3 weeks on optimised dose. Follow-up visit 30 days after last dose
Participants	Number of participants screened: 309 Number of participants included: 305 Number of participants followed up: 260 Number of withdrawals: 45 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 9.1, range: 6-12 years old IQ: not stated Sex: 215 males, 90 females Methylphenidate-naïve: not stated Ethnicity: white (77.7%), African American (11.5%), Asian (0.7%), Hispanic (23.9%), others (10.2%) Country: USA Comorbidity: not stated Comedication: only medication non concomitant with central nervous system effects Sociodemographics: not stated *Inclusion criteria* 1. Boys and girls aged 6-12 years, inclusive, who met DSM-IV-TR criteria for a primary diagnosis of ADHD

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Warshaw 2010 *(Continued)*

2. At baseline, eligible participants had a total score ≥ 26 on the ADHD Rating Scale-Version-IV (ADHD-RS-IV) and no comorbid illnesses that could affect safety or tolerability or interfere with the person's participation in the study. At screening and baseline, eligible female participants of childbearing potential had a negative result on a urine pregnancy test, and all included participants' blood pressure measurements were within the 95th percentile for age, gender, and height

Exclusion criteria

1. Comorbid psychiatric diagnosis (except oppositional defiant disorder)
2. Risk for suicidal or violent behaviour
3. History of suicide attempt
4. Structural cardiac abnormality, cardiomyopathy, cardiac rhythm abnormality, or other serious cardiac problem
5. History of non-response to psychostimulants
6. History of seizures during the previous 2 years (except infantile febrile seizures)
7. Tic disorder or conduct disorder
8. Current diagnosis or family history of Gilles de la Tourette syndrome
9. History of substance abuse or dependence
10. Abnormal thyroid function
11. Concurrent illness
12. Treatment with hepatic and/or cytochrome P450 enzyme-altering agents
13. Concomitant medications with central nervous system effects
14. Skin disease, history of chronic skin disease, or sensitive skin syndrome (defined as participants who often develop nonspecific skin irritancy reactions to bland materials); or clinical signs or symptoms of skin irritation

Interventions	Methylphenidate type: transdermal system Methylphenidate dosage: 10, 15, 20, 30 mg Mean methylphenidate dosage: 20.1 mg Administration schedule: MTS 9 hours per day Duration of intervention: 7 weeks Treatment compliance: 260 (84.1%) completed the study
Outcomes	*Non-serious adverse events*: Safety was assessed at each clinic visit (baseline, at weeks 1 through 5, week 7, and week 11) by evaluating adverse events reported spontaneously; analysing changes in vital signs, and conducting physical examinations. Dermal reactions were classified as an adverse event when pharmacologic treatment for the reaction was required Experience of Discomfort scale, Transdermal System Adherence scale, and Dermal Response Scale
Notes	Sample calculation: not stated Ethics approval: yes Funding: the study was funded by Shire Development, Inc., Wayne, Pennsylvania Vested interests/authors' affiliations: Dr Warshaw has served as a consultant to Shire. Dr Squires is a full-time employee of Shire and a stock shareholder in Johnson & Johnson, Pfizer, and Shire. Dr Li was a full-time employee of Shire at the time of the study and is now an employee of Cerexa, Inc, Oakland, California. Dr Civil is a full-time employee of Shire. Dr Paller has served as a consultant to Shire *Key conclusions of the study authors*: the results of this study indicate that dermal reactions with methylphenidate use were predominantly mild to moderate. Dermal reactions appeared to be of an

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Warshaw 2010 *(Continued)*

	irritant contact dermatitis form; they dissipated rapidly with time and most resolved with continued treatment. Overall, less than 1% of participants manifested sensitisation to methylphenidate *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes *Supplemental data* requested through personal email correspondence with the authors in May 2016 but none were available

Weber 2003

Methods	A retrospective cohort study investigating the side effects of methylphenidate in children
Participants	Number of participants screened: 73 Number of participants included: 57 Number of participants followed up: 45 Number of withdrawals: 12 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 11.1, range 7.2-18.0 years old IQ: range 85-115 Sex: 42 males, 3 females Methylphenidate-naïve: 100% Ethnicity: not stated Country: Germany Comorbidity: anxiety, depression, disturbance in attention, antisocial behaviour and aggressive behaviour Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. A detailed neuromotor and neuropsychological assessment 2. Had to be on methylphenidate treatment for the whole study period 3. Evaluable data returned from parents
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage: 16.8 mg Administration schedule: not stated Duration of intervention: mean 2.7 years, range 0.2-12.3 years Treatment compliance: questions regarding compliance were included in the mailed questionnaire; however, no results are reported
Outcomes	*Non-serious adverse events* German version of Barkley Side Effects Rating Scale (17 items), parent rated every sixth week

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Weber 2003 *(Continued)*

Notes	Sample calculation: not stated Ethics approval: not necessary at the time the study were carried out Funding/vested interests: no funding Authors' affiliations: no affiliations to pharmaceutical companies stated *Key conclusions of the study authors*: the application of methylphenidate in therapy of attention deficit disorder and the interpretation of side effects of methylphenidate is a multimodal task. Adverse effects are not correlated with daily doses, age, the severity of body complaints and the presence of neuroticism and extraversion. The children with more side effects showed more emotional comorbidity *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* regarding diagnostic criteria, ethics approval, funding, ratings and drug naïvety received through personal email correspondence with the authors in December 2013 (Weber 2013 [pers comm])

Weiss 2007

Methods	A 5-11 week randomised, double-blind, cross-over comparison of 1. Long duration multi-layer release (MLR) methylphenidate 2. Immediate release (IR) methylphenidate 6-month open-label extension period on MLR-methylphenidate
Participants	**Cross-over phase** Number of participants screened: 110 Number of participants included: 90 Number of participants followed up: 79 Number of withdrawals: 11 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 11.0, range 6.4-17.5 years old IQ: above 80 Sex: 74 males, 16 females Methylphenidate-naïve: 59% Ethnicity: white: 83%, African American: 6%, Asian: 4%, others: 7%) Country: Canada Comorbidity: oppositional defiant disorder (37.5%) Comedication: none Sociodemographics: not stated **Open-label phase** Number of participants included: 76 Number of participants followed up: 61 Number of withdrawals: 15

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Weiss 2007 *(Continued)*

Diagnosis of ADHD: DSM-IV (subtype: not stated)

Age: mean 11.0, range 6.4-16.8 years old

IQ: above 80

Sex: 62 males, 14 females

Methylphenidate-naïve: not stated

Ethnicity: not stated

Country: Canada

Comedication: none

Sociodemographics: not stated

Inclusion criteria

1. Children 6-17 years of age with a DSM-IV diagnosis of ADHD, all subtypes
2. Patients who are currently taking MPH for ADHD and who have responded positively to the treatment, or methylphenidate naïve patients
3. Intelligence quotient of 80 or greater on the Wechsler Intelligence Scales for Children (WISC-III) within the previous 12 months
4. Participants parents must have been mentally and physically competent to provide written informed consent for their child with an ability to read, speak, and understand English and otherwise able to comply with the study protocol
5. Patients who are otherwise able to comply with the study protocol
6. The patient must have had a score of 1.5 or greater SD from the norm on the Conners' ADHD Index as assessed during a no-treatment baseline week using the Conners' Teacher Rating Scale-Revised (CTRS-R)

Criteria for entering the open-label phase: the patients must choose to continue receiving MLR-MPH after completion of the first part of the study

Exclusion criteria

1. Patients with a true allergy to methylphenidate or amphetamines, history of serious adverse reactions to methylphenidate or are known to be methylphenidate non-responders. Non-response defined as methylphenidate use at various doses for a period of ≥ 4 weeks at each dose with little or no clinical benefit
2. Patients with a history of tension, agitation, glaucoma, thyrotoxicosis, tachyarrhythmias or severe angina pectoris or patients with serious or unstable medical illness
3. Patients with anxiety of sufficient severity to warrant treatment
4. Patients with Tourette's syndrome of sufficient severity to warrant treatment
5. Patients currently receiving guanethidine, pressor agents, MAOIs, coumarin anticoagulants, anticonvulsants, phenylbutazone, tricyclic antidepressants, selective serotonin reuptake inhibitors and herbal remedies
6. Patients known or suspected to have a history of drug or alcohol abuse
7. Patients with a history of disorders of the sensory organs, particularly deafness, severe or profound mental retardation, pervasive developmental disorders, such as autism or childhood schizophrenia, or seizure disorders
8. Patients with any other unstable psychiatric conditions

Interventions	**Cross-over** Methylphenidate type: long duration multi-layer release methylphenidate or immediate release methylphenidate Mean methylphenidate dosage: MLR-MPH: 32.0 (SD 8.4) mg; IR-MPH: 32.5 (SD 8.6) mg

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Weiss 2007 *(Continued)*

	Administration schedule: MLR-MPH: once daily in the morning. IR-MPH: twice daily, morning and noon Duration of each medication condition: 2 weeks on a stable dose Washout: 1 week baseline medication washout period Titration period: initial daily dose was based on body weight. Daily dose was titrated in 10-mg increments over a period of 2-3 weeks at weekly clinical visits. Titration was halted if the dose was not tolerated, or if the investigator-rated CGI-I scale was rated 1-2. There were 2 weeks of observation on this stable dose Treatment compliance: not stated
Outcomes	*Non-serious adverse events* **Cross-over** Clinical assessment of Side Effects (CASE). The scale consist of 26 possible adverse events. Teacher and parent rated by telephone interview before next clinical visit. Side effects, including sleep quality, were assessed on daily basis **Open-label** 3 follow-up visits at 2, 4 and 6 months. CASE; teacher and parent rated by telephone interview just before next clinical visit The 4 cases that dropped out due to side effects dropped out because of the following events: Long-duration multi-layer release methylphenidate 1. Apathy, nervousness, somnolence 2. Insomnia, nervousness, somnolence, vocal tics Immediate release methylphenidate 1. Anorexia, dizziness, headache, nausea, pain 2. Apathy, asthenia, depression
Notes	Sample calculation: yes Ethics approval: the study protocol and consent form were approved by the Research Ethics Committees at each site Funding: Purdue Pharma Vested interests/authors' affiliations: the study was sponsored by Purdue Pharma (Canada). Dr Weiss is a consultant for Eli Lilly, Janssen-Ortho, Novartis, Purdue Pharma and Shire. Dr Hechtman is a consultant for Eli Lilly, Janssen-Ortho, Novartis, Purdue Pharma and Shire. Drs. Hechtman, Jain, Quinn, and Weiss are on the advisory board for Purdue Pharma. Dr Turgay is a consultant for the same company. Mr. Donnelly, Mr. Reiz, Mr. Harsanyi, and Dr Darke are employees of Purdue Pharma. The other authors have no financial relationships to disclose *Key conclusions of the study authors*: clinical implications of the study results include that once daily, MLR-MPH is an effective treatment for ADHD that produces equivalent improvements to twice-daily dosing of IR-MPH in home and school situational behaviour, while maintaining a favourable side-effect profile and a prolonged duration of effect *Comments from the study authors*: a large portion of participants were previous methylphenidate responders, which may have reduced any chance of finding differences. As participants received active medication in both phases if the study, higher effect sizes could be expected because of investigators' and participants' expectation, although this would more closely approximate the clinical situation than a comparison placebo *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes

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Weiss 2007 *(Continued)*

	Supplemental information regarding protocol, data for CASE, adverse events on the 4 dropouts, and data on all periods received through personal email correspondence with study funder, Purdue Pharma in August 2013 (Harsanyi 2013 [pers comm])

Wigal 2011

Methods	A double blind, double-dummy randomised cross-over study with osmotic release oral system (OROS) methylphenidate and immediate release methylphenidate given with 5 different breakfast conditions
Participants	Number of participants screened: not stated Number of participants included: 32 Participants were randomly assigned to 1 of 6 possible drug condition orders Number of participants followed up: 30 Number of withdrawals: 1 Diagnosis of ADHD: DSM (subtype: not stated) Age: mean 10.1 (SD 1.5), range 7-12 years old IQ: not stated Sex: 26 males, 5 females Methylphenidate-naïve: none Ethnicity: white: 67.7%, African American: 1%, Hispanic: 3%, others: 6% Comorbidity: not stated Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. Methylphenidate treatment for at least 3 months previously at dose = 5-20 mg IR methylphenidate twice daily or SR methylphenidate 20 mg-60 mg daily 2. On a stable methylphenidate dose for ≥ 4 weeks before enrolment 3. Known to be positive responders 4. No treatment for methylphenidate related insomnia, anticonvulsants or any 'investigational' treatments for 4 weeks prior to study 5. No medication affecting CNS of blood pressure in any way, for 7 days before study 6. No changes in methylphenidate medication for 7 days before start of study *Exclusion criteria* 1. Any clinical condition that would interfere with the conduct of the study 2. Any gastrointestinal conditions, marked anxiety, tension, agitation, depression, psychosis, seizures, Tourette Hypertension (mean of 2 BP measurements > 95th percentile for age, sex or height) 3. Patients in whom the primary focus of treatment ODD, CD, tics or mood disorders
Interventions	Participants were randomly assigned to 1 of 5 possible drug condition orders of equivalent to OROS MPH 18 mg, 36 mg and 54 mg and IR MPH 5 mg, 10 mg and 15 mg based on pre-study established doses. Group 1

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Wigal 2011 *(Continued)*

	1. OROS methylphenidate once a day after high-fat breakfast 2. OROS methylphenidate once a day in fasting state 3. IR methylphenidate 3 times daily in fasting state Group 2 1. OROS methylphenidate once a day after high-fat breakfast 2. OROS methylphenidate once a day after normal breakfast 3. OROS methylphenidate 3 times daily, 1st dose after normal breakfast Mean MPH dosage: not stated. Administration schedule: not stated. Duration of each medication condition: not stated. Washout prior to study initiation: not stated. Medication-free period between intervention: not stated. Titration period: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events* Vital signs measured pre-dose, then every 1.5-2.5 h until 11.5 h postdose
Notes	Sample calculation: not stated Ethics approval: not stated, but UC Irvine Institutional Review Board approved consent procedures Funding/vested interest/authors' affiliations: Sharon Wigal on a number of drug company advisory boards. Suneel Gupta is a full-time employee of Impax Pharmaceuticals and previously worked for a number of drug companies. Lynne Starr and Erica Everin are employees of a drug company. The study was sponsored by ALZA corporation. Ortho-McNeil Janssen Scientific Affairs funded an editorial on the study *Key conclusions of the study authors*: the results of this study demonstrate that in children with ADHD administering OROS methylphenidate with or without food produces similar PK and PD profiles *Comments from the review authors*: despite lack of information about ADHD diagnostic criteria, the article is included - because it reports data on serious adverse events (n = 0), deaths (n = 0). This means, that only data regarding serious adverse events should be extracted. Wrong NCT-number reported *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes *Supplemental information* received through personal email correspondence with the authors in August 2014. No answer received

Wigal 2013

Methods	4-6 weeks open-label treatment (dose optimisation), cross-over, and 2-week double-blind with 2 interventions: 1. Methylphenidate (NWP06 - liquid formulation of extended release methylphenidate) 2. Placebo
Participants	Number of participants screened: 45 Number of participants included: 44 Number of participants followed up: 39 Number of withdrawals: 6 Diagnosis of ADHD: DSM-IV diagnosis of ADHD (subtype: combined (70.5%), hyperactive-impulsive (2.3%), inattentive (27.3%))

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Wigal 2013 *(Continued)*

	Age: mean 8.8, range 6-12 years old IQ: not stated Sex: 32 males, 12 females Methylphenidate-naïve: none Ethnicity: white (79.5%), Black/African American (9.1%); Asian (6.8%); other (4.5%) Country: USA Comorbidity: elimination disorder (9.1%); oppositional defiant disorder (18.2%); specific phobias (4.5%) Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. ADHD diagnosis by psychiatrist, psychologist, developmental paediatrician, or paediatrician 2. Pharmacological treatment for ADHD and either experienced suboptimal efficacy, a safety or tolerability issue with their current regimen, or been in need of a long-acting liquid formulation 3. CGI-S score ≥ 3 4. ≥ 90th percentile for age and gender on the ADHD-RS (either total score, or hyperactive-impulsive subscale or inattentive subscale) *Exclusion criteria* 1. Comorbidity (DSM-IV axis I), with the exceptions of: specific phobia, motor skills disorders, oppositional defiant disorder, sleep disorders, elimination disorders, adjustment disorders, learning disorders, or communication disorders 2. IQ lower than 80 3. Chronic disease: seizure disorder, thyroid disease, Tourette disorder or family history of Tourette disorder or tics, serious cardiac conditions, cardiomyopathy, serious arrhythmias, structural cardiac disorders, glaucoma, or severe hypertension. 4. Any investigational medication 15 days prior screening 5. Atomoxetine or monoamine oxidase inhibitor 30 days prior screening
Interventions	Participants were randomly assigned to different sequences of methylphenidate and placebo Methylphenidate type: liquid formulation of extended release methylphenidate Mean methylphenidate dosage: 32.8 mg/day Administration schedule: 4 times daily Duration of each medication condition: 1 week Washout prior to study initiation: yes (1 day for stimulants) Medication-free period between intervention: no Titration period: 3 weeks initiated before randomisation Treatment compliance: 2 withdrawals of assent/consent, 2 adverse events, 1 lack of efficacy, 1 lost to follow-up
Outcomes	*ADHD symptoms* - SKAMP, ADHD-RS (open-label phase) *Non-serious adverse events*

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Wigal 2013 *(Continued)*

	42 participants (93.3%) experienced a treatment-emergent adverse event 3 (6.7%) participants with severe (affect lability, aggression, and initial insomnia) and 2 (4.4%) participants had to discontinue medication (affect lability and aggression) **Open-label phase**: decreased appetite (55.6%), abdominal pain upper (42.2%), affect lability (26.7%), initial insomnia (22.2%), insomnia (17.8%), and headache (17.8%) Other AEs reported in ≥ 5% of the participants during the open phase: vomiting, diarrhoea, logorrhea, aggression, dizziness, irritability, fatigue, upper respiratory tract infection, cough, and flushing **Double-blind phase**: 11 (24.4%) participants had a AE while receiving NWP06 and 5 (11.1%) participants had a AE while receiving placebo
Notes	Sample calculation: no Ethics approval: yes *Key conclusions from study authors*: NWP06 resulted in significant improvements in the SKAMP-combined score at 4 hours post-dose as compared with placebo in the completers. This study shows that NWP06 significantly improved ADHD symptoms in school-aged children and was well tolerated *Comments from the study authors*: "This study of NWP06 allowed inclusion of patients who were either treatment naïve or had previously been treated with stimulants" "Subjects were required to have been in need of pharmacological treatment for ADHD" "Our population more closely reflects a real-world population and provides a more rigorous test of the study drug." Comments from the review authors: laboratory school environment, and lack of the ADHD-RS. Race/ethnicity doesn't reflect a real-world population *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not clear *Supplemental information* requested from study authors in August 2014. No reply

Wigal 2015

Methods	A multicentre study of 4 phases: screening, double-blind (1 week placebo controlled), open-label (11 week dose optimisation), and a 30 day safety follow-up
Participants	Number of participants screened: 280 Number of participants included: 230 Number of participants followed up: 200 Number of withdrawals: not stated Diagnosis of ADHD: DSM- IV-TR (subtype: combined (61%), inattentive (33%)) Age: mean 10.8 years (range 6-18) IQ: > 80 Sex: 154 males, 76 females Methylphenidate-naïve: 148 Ethnicity: white: 68.7%, African American: 23%, Asian:1.3%, others: 7% Country: USA

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Wigal 2015 *(Continued)*

	Comorbidity: ODD 22, enuresis 14 Comedication: not stated Sociodemographics: unknown *Inclusion criteria* 1. Pharmacological treatment for ADHD *Exclusion criteria* 1. Estimated Full Scale intellectual level < 80 using the 4-subtest form of the Wechsler Abbreviated Scale of Intelligence (WASI) 2. Current primary psychiatric diagnosis of severe anxiety disorder, conduct disorder, psychotic disorder, pervasive developmental disorder, eating disorder, obsessive-compulsive disorder, major depressive disorder, bipolar disorder, substance use disorder, chronic tic disorder personal or family history of Tourette syndrome 3. Chronic medical illness (seizure, cardiac disorders, untreated thyroid disease, glaucoma) 4. Using monoamine oxidase inhibitors or psychotropic medication within 14 days of screening or another experimental drug or device within 30 days of screening 5. A clinically significant electrocardiogram (ECG) or clinical laboratory abnormality at screening and/or baseline 6. Pregnant or lactating
Interventions	Methylphenidate type: extended release Methylphenidate dosage: 10-60 mg/day Methylphenidate dosage during 11 weeks open-label titration phase: 30 mg (27.7%), 40 mg (25.2%), 50 mg (17.8%), 20 mg (16.8%), 60 mg (8.9%), 15 mg (2.0%), 10 mg (1.5%) Administration schedule: once daily, in the morning, no later than 10 am Duration of intervention: 11-12 weeks Treatment compliance: not stated
Outcomes	Vital signs, physical examination, ECG, clinical laboratory evaluations, C-SSRS, and AEs were collected at each visit
Notes	Sample calculation: not stated Ethics approval: the study protocol, amendments, and informed consent were reviewed and approved by an Institutional Review Board for each study site Funding: this research was funded by Rhodes Pharmaceuticals LP Vested interests/authors' affiliations: Dr Wigal has been an advisory board and speakers bureau member/consultant for Eli Lilly, Ironshore, Neos, NextWave, Noven, NuTec, Pfizer, Purdue, Rhodes Pharmaceuticals LP, Shionogi, Shire, and Tris and has received grant and research support from Eli Lilly, Forest, Ironshore, the National Institutes of Health, NextWave, Noven, NuTec, Purdue, Rhodes Pharmaceuticals LP, Shire, Sunovion, and Tris. Dr Nordbrock is a consultant for Rhodes Pharmaceuticals LP Dr Adjei and Dr Kupper are employees of Rhodes Pharmaceuticals LP Dr Childress has received research support from Shire, Novartis, NextWave, Lilly, Forest Research Institute, Johnson & Johnson, Sepracor, Otsuka, Sunovion, Pfizer, Shionogi, Noven, Ironshore, Rhodes, Theravance, Neurovance, Neos, Arbor, Tris, and Purdue. She has received consulting fees or honoraria from Ironshore, Pfizer, Shionogi, Rhodes, Shire, Novartis, and Neos; support for travel from Ironshore, Pfizer, Shire, Novartis, and NextWave; writing assistance on projects from Shire, Novartis, NextWave, Pfizer, Ironshore, and Arbor; and payment for lectures from Shire, Novartis, and Pfizer. Dr Greenhill has received research support from the National Institute on Drug Abuse/National Institutes of Health and Shire and is on the advisory board for BioBehavioral Diagnostics

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Wigal 2015 *(Continued)*

	Key conclusions of the study authors: dose-related improvements in ADHD-RSIV scores that exceeded those of placebo were observed in patients treated with methylphenidate-MLR. No new safety signals were noted
	Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no

Wiguna 2012

Methods	12-week open, prospective, non-randomised trial using a pre-test and post-test design
Participants	Number of participants screened: not stated Number of participants included: not stated Number of participants followed up: 21 Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV/ICD-10 (subtype: combined (71.4%), inattentive (28.6%)) Age: mean 8.52, 7-10 years old IQ: mean 110.14 Sex: 17 males, 4 females Methylphenidate-naïve: 100% Ethnicity: Indonesian Comorbidity: none Comedication: none Sociodemographics: low to average socioeconomic status *Inclusion criteria* 1. Between the ages of 7-10 years 2. Newly diagnosed with ADHD 3. Drug-naïve 4. Normal intelligence 5. Right handed *Exclusion criteria* 1. Any comorbidity or chronic illness
Interventions	Participants were assessed before and after methylphenidate-treatment Methylphenidate type: long acting Methylphenidate dosage: 20 mg Administration schedule: daily Duration of intervention: 12 weeks Treatment compliance: not stated
Outcomes	Weight, height, pulse, blood pressure and interim history: every 2 weeks

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Wiguna 2012 *(Continued)*

Notes	Sample calculation: yes Ethics approval: yes Funding: not stated Vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: findings of this pilot study are important in that it demonstrated, with stimulant treatment, significant neurochemical changes - thought to reflect functional improvement and improved neuroplasticity - in the prefrontal cortices of children with ADHD

Wilens 2005

Methods	A multicentre, open-label, cohort study of methylphenidate osmotic release oral system (OROS) use for 24 months
Participants	Number of participants screened: 436 Number of participants included: 407 Number of participants followed up: 289 (12 months), 229 (24 months) Number of withdrawals: 118 (12 months), 178 (24 moths) Diagnosis of ADHD: DSM-IV (subtype: combined (75.5%), hyperactive-impulsive (5.9%), inattentive (18.4%), not determined (0.2%)) Age: mean 9.2, range 6-13 years old IQ: not stated Sex: 338 males, 69 females Methylphenidate-naïve: none Ethnicity: white: 86%, African American: 5.7%, Asian: 0.7%, Hispanic:4.4%, others: 3.2% Country: USA Comorbidity: tics (11.8%) Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. ADHD diagnosis, as defined in Pelham 2001; Swanson 2003; Wolraich 2001, e.g. DSM-IV 2. Had participated in previous efficacy or pharmacokinetic studies of OROS methylphenidate 3. Only children who had been receiving methylphenidate either with a positive response or without having experienced a significant adverse event based on parent or physician reports; ADHD; normal urinalysis, haematology, and blood chemistry values; parents/caregivers and school teachers had to be willing to complete all assessments 4. Participants agreed to take the supplied study drug as their only medication for ADHD *Exclusion criteria* 1. Clinically significant gastrointestinal problems 2. History of hypertension, known hypersensitivity to methylphenidate, or a coexisting medical condition or concurrent medication likely to interfere with the safe administration of MPH

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Wilens 2005 *(Continued)*

3. Tourette syndrome, an ongoing seizure disorder, or a psychotic disorder
4. Girls who had reached menarche
5. Participants who were already receiving specific behavioural interventions for ADHD on an ongoing basis were permitted to enter the study, but new behavioural interventions could not be initiated during the study
6. Any participants who developed systolic or diastolic blood pressure ≥ 95th percentile for age or sex or who had a blood pressure measurement ≥ 150 mmHg (systolic) or ≥ 100 mmHg (diastolic) were discontinued

Interventions	Methylphenidate type: extended release (OROS) Methylphenidate dosage: 18 mg/day, 36 mg/day, or 54 mg/day Mean methylphenidate dosage: 35 mg at study entry, 41 mg at the end of 12 months, and 44.2 mg at month 21/24 Administration schedule: once daily Duration of intervention: 21 to 24 months Treatment compliance: 86.4%
Outcomes	*Non-serious adverse events* Growth (weight, height), rated objectively by observer at monthly visits for the first 12 months and then at 15, 18, 21, and 24 months Cardiac (heart rate, blood pressure), rated objectively by observer at monthly visits for the first 12 months and then at 15, 18, 21, and 24 months Sleep quality, tics, rated subjectively by parents at monthly visits for the first 12 months and then at 15, 18, 21, and 24 months Laboratory tests (urinalysis, haematology/complete blood counts, electrolytes, and liver function tests) were performed at baseline, at 6 and 12 months, and at the end of the study (21/24 months) At 12 months, 28 (6.9%) discontinued study medication prematurely because of adverse events. At 21/24 months, 38 discontinued study medication prematurely because of adverse events. From final: there was a 26% increase in mean daily dose over the study period, with most of the increase occurring during year 1. In general, treatment was well tolerated, with 31 (7.6%) participants discontinuing because of adverse events. Comparison of the baseline characteristics of participants discontinuing the study compared with those continuing with treatment for 21/24 months did not reveal any significant differences between the 2 groups for ADHD subtype, teacher and parent/caregiver IOWA Conners inattention/overactivity and oppositional/defiant baseline scores, previous stimulant exposure, presence of comorbidity, specific comorbidity, race, sex, or type of school classroom
Notes	Sample calculation: no Ethics approval: reviewed and approved by the institutional review board of participating centres prior to initiation of the study Funding: supported by McNeil Consumer & Specialty Pharmaceuticals Vested interests/authors' affiliations: all authors work for different medical companies *Key conclusions of the study authors*: sustained effectiveness of OROS methylphenidate was maintained for up to 24 months with minimal effects on growth, tics, vital signs, or laboratory test values, as demonstrated by stable IOWA Conners ratings and sustained improvements in peer interaction and Global Assessment Scale scores *Comments from the study authors*: the prospective trial was terminated by the sponsor (concomitant with US FDA approval) between 21 and 24 months of participation for administrative reasons that were

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Wilens 2005 *(Continued)*

	not related to safety or effectiveness. Therefore, although data were available for a minority of participants at 24 months (n = 56), we refer to the final end point as 21/24 months *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes. Included children had participated in previous controlled studies and were methylphenidate responders

Wilens 2006

Methods	A 2-week randomised, double-blind, 15-centre, parallel trial with 2 arms: 1. Methylphenidate osmotic release oral system (OROS) 2. Placebo Preceded by a 4 week open-label dose titration phase and followed by a 8 week open-label follow-up
Participants	Number of participants screened: not stated Number of participants included: 220 in the 4 week dose titration phase Number of participants randomised to methylphenidate: 87 and placebo: 90 Number followed up in the methylphenidate group: 71 Number of withdrawals in methylphenidate group: 16 Number followed up: 171 (total) Number completed follow-up: 135 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean: 14.6 years old (range 13-18) IQ: not stated Sex: 142 males, 35 females Methylphenidate-naïve: not stated, but ADHD treatment naïve (n = 24) Ethnicity: white (75.1%), African American (13.6%), others (11.3%) Country: USA Comorbidity: no Comedication: none Sociodemographics: not stated *Inclusion criteria*: 1. Diagnosis of ADHD as defined by DSM-IV 2. Children's Global Assessment Scale rating of 41-70 at baseline (Screening Phase) 3. Age between 8-13 years *Exclusion criteria*: 1. Participants who are known to not respond to methylphenidate 2. Have had adverse experiences from methylphenidate or hypersensitivity to CONCERTA or its components 3. Have marked anxiety, tension or agitation

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Wilens 2006 *(Continued)*

	4. A psychiatric co-morbidity requiring additional or different medication 5. Have glaucoma, ongoing seizure disorder, psychotic disorder, Tourette disorder or family history of Tourette disorder, bipolar disorder, an eating disorder 6. Treatment with theophylline, coumarin, anticonvulsants 7. Severe gastrointestinal narrowing 8. Systolic or diastolic blood pressures at the 95th percentile or greater for age, sex and height at screening
Interventions	Participants were randomly assigned to OROS-methylphenidate or placebo Mean methylphenidate dosage: 0.84 mg/kg Administration schedule: once daily Duration of intervention: 2 weeks Titration period: 4 weeks initiated before randomisation. All participants initiated therapy at 18 mg/day, and clinical response was measured after 1 week. If response to treatment was inadequate, as per the a priori study definition, the dose was titrated upward (in 18 mg increments) at 1 week intervals for up to 4 weeks, with the maximum dose being 72 mg/day Treatment compliance: not stated 8-week open-label follow-up on individualised dosage
Outcomes	*ADHD symptoms* ADHD-RS, clinician and parent rated, completed at baseline and weekly during double blind phase *Serious adverse events* Serious adverse events were reported in only 1 participant during the open-label dose titration phase of the study. While being treated with OROS, 18 mg/daily, a 16-year-old female participant with a history of depression and suicidal ideation threatened suicide on the third day of medication use after an argument with her mother. A decision was made to discontinue study medication, and the symptoms resolved No serious adverse events were reported during the double-blind phase *Non-serious adverse events* Heart rate and blood pressure, recorded by a clinician weekly throughout whole study ECG at screening and at the end of the double-blind phase of the study Spontaneous reports to the investigator of adverse events were recorded at weekly visits Safety assessments made at monthly visit and every 2 weeks between monthly visits during the follow-up Height and weight were assessed at baseline and at weeks 4 and 8 in the follow-up study No participants experienced clinically important effects on ECG-indexes, heart rate or blood pressure during the study
Notes	Sample calculation: yes Ethics approval: yes, approval of the study design was obtained from the institutional review boards for all participating centres before initiation of the study *Key conclusions of the study authors*: in adolescents, once-daily OROS methylphenidate significantly reduced ADHD symptoms and was well tolerated using dosages up to 72 mg/daily. Adolescents required, on average, a higher absolute dose but a lower weight-adjusted dose (mg/kg) of OROS than was previously reported in children. The incidence of adverse events was not related to dose

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Wilens 2006 *(Continued)*

	Comments from the study authors: participants were titrated to their individualised dosage before the double-blind phase of the study may have biased the results toward a positive response in the double-blind phase. The short duration of the double-blind phase also may have decreased the likelihood of detecting potential rare adverse events. The rates of adverse events reported for OROS have been underestimated, because participants entering this study phase were already stabilised on an affective tolerated dosage of medication *Supplemental information* requested through email correspondence with the authors in December 2013 and January 2014. No reply

Wilens 2008

Methods	An open-label, 5-week, dose optimisation period followed by a randomised, double-blind, 8-centre, 3-way, 3-week, cross-over trial with 2 interventions: 1. Methylphenidate transdermal system (MTS) 2. Placebo
Participants	Number of participants screened: 148 Number included in open-label dose-titration: 128 Number randomly assigned to 1 of 3 possible drug orders: 120 Number followed up for safety: 127 and for efficacy: 117 Number of withdrawals: 2 **Characteristics of the 127 followed up for safety** Diagnosis of ADHD: DSM-IV (combined or hyperactive-impulsive (92,1%)) Age: mean 8.8 (SD 1.84), range 6-12 years old IQ: above 80 Sex: 84 males, 43 females Methylphenidate-naïve: not stated Ethnicity: white (62.2%/63.2%), African American (not stated/15.4%), Asian (not stated) Country: USA Comorbidity: not allowed Comedication: not stated Sociodemographics: not stated **Characteristics of the 117 followed up for efficacy** Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: 8.8 (SD 0.2), range 6-12 years old IQ: above 80 Sex: 75 males, 42 females Methylphenidate-naïve: not stated Ethnicity: white (63.2%), African American (15.4%), Asian (0%), others (21.4%)

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Wilens 2008 *(Continued)*

	Country: USA Comorbidity: not allowed Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. Diagnosed with ADHD according to DSM-IV-T 2. Minimum IQ score of 80 *Exclusion criteria*: 1. Conduct disorder or comorbid illnesses that contraindicated or could confound MTS treatment 2. History of failing to respond to psychostimulant treatme 3. Taken another investigational product within 30 days of screening or to participate in other research trials involving drug treatment during the course of the study
Interventions	Participants were randomly assigned to 1 of 3 possible drug orders of (4 and 6 hours) methylphenidate and placebo Mean methylphenidate dosage: 10 mg patch (n = 15), 15 mg patch (n = 34), 20 mg patch (n = 32), and 30 mg patch (n = 36) Administration schedule: once daily in the morning, patch worn for 9 h daily, and 4 or 6 h for the cross-over assessments Duration of each medication condition: 1 day Washout: none Titration period: 5 weeks before randomisation Treatment compliance: not stated
Outcomes	*ADHD symptoms* SKAMP, teacher, rated at randomisation (week 5) and 2 hrs after patch application end of treatment (week 6, 7, and 8) *Quality of life* ADHD Impact Module-Child (AIM-C) - Child Impact Scale and Family Impact Scale, rated at baseline and randomisation (week 5) and end of study (week 8) *Non-serious adverse events* Vital signs were evaluated at screening, baseline, and on weeks 1 to 8 (erythema, oedema, papules, and vesicles, discomfort, haematology, urinalysis, and electrocardiographic measures were completed at screening, baseline, and weeks 5 and 8) No clinically meaningful changes from baseline were observed in vital signs, ECG, urinalysis, and haematological results, or physical examinations Adverse events were recorded from the time informed consent was signed until 30 days (week 12) after the last drug treatment
Notes	Sample calculation: yes Ethics approval: yes, institutional review board at each site approved the study

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Wilens 2008 *(Continued)*

Comments from the study authors: important to note that participants who failed to respond to psychostimulants in the past and those with conduct disorder were excluded from the study. The results of this study therefore should not be extrapolated to these patient populations.

From Manos: the lack of placebo comparison has the potential to confound the findings of this study. The relatively short study duration (about 2 months) may not be enough time to capture some emerging changes in HRQoL

Key conclusions from study authors: all of the efficacy measures indicated that 4- and 6-hour wear times improved ADHD symptoms

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: yes, participants with a history of failing to respond to psychostimulant treatment were also excluded

Supplemental information requested from the authors twice in August 2014. No reply

Williams 2008

Methods	A cohort study of methylphenidate use for 4 weeks
Participants	Number of participants screened: not stated Number of participants included: 51 Number of participants followed up: 33 Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (subtype: combined: 58.8%, inattentive: 37.3%, hyperactive-impulsive: 3.9%). Age: mean 13.79 (SD 2.33, range 8-17) years old IQ: above 80 Sex: 51 males Methylphenidate-naïve: 51% Ethnicity: not stated Country: Australia Comorbidity: not stated C-medication: no participant was taking concurrent medications known to affect the CNS Sociodemographics: not stated *Inclusion criteria* 1. DSM-IV ADHD diagnosis 2. IQ ≥ 80 *Exclusion criteria* 1. Physical brain injury 2. Neurological disorder 3. Other serious medical or genetic condition 4. Drug or alcohol dependence

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Williams 2008 *(Continued)*

Interventions	Methylphenidate type: immediate release Mean methylphenidate dosage: 24.1 mg/day (range 10-60 mg/day). 26 medication naïve titrated to maximum effective dose (0.4-1.3 mg/kg) in a week with 10 mg increments then kept on a stable dose for a week. 25 had 3 day washout then resumed optimal methylphenidate dose after baseline testing Administration schedule: methylphenidate given 60 minutes before testing Duration of intervention: 4 weeks Treatment compliance: not stated
Outcomes	No adverse events were reported
Notes	Sample calculation: not stated Ethics approval: not stated Funding: an Australia Research Council (ARC) Linkage Grant with industry partner Brain Resource Company (BRC) (Grant no. LP0349079) supported this work. LMW holds a competitive, peer-reviewed Pfizer Senior Research Fellowship. We acknowledge the support of the Brain Resource International Database (under the auspices of the Brain Resource Company) for data acquisition and processing. All scientific decisions are made independent of any BRC commercial decisions via the independently operated scientific division, BRAINnet Vested interests/authors' affiliations: DP, HK, and SC have no conflicts of interest to declare. As an industry partner on the ARC-linkage grant that supported this research (Grant no. LP0349079), BRC contributed to the salary of DFH as research officer on this grant for 2003-2005. MK uses BRC computerised cognitive tests in private practice. LMW and CRC hold a few private shares in BRC (1% of the company value), and CRC holds a number of share options in the BRC. EG is the chief executive officer of BRC. However, scientific decisions are made independent of the BRC operations, and access to the Brain Resource International Database for scientific purposes is coordinated via an independent scientific network BRAINnet *Key conclusions of the study authors*: methylphenidate normalised neural activity and produced some improvement of emotion recognition but had no impact on negative mood. Disruptions to emotional brain function may be improved with methylphenidate *Supplemental information* received through personal email correspondence with the authors in August 2014 (Williams 2014 [pers comm])

Williamson 2011

Methods	2 patient reports of resolution of enuresis when treated with methylphenidate
Participants	**Case 1** Diagnosis of ADHD: DSM-IV (subtype: combined) Age: 9 years old IQ: normal Sex: female Ethnicity: not stated Country: USA

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Williamson 2011 *(Continued)*

	Comorbidity: primary nocturnal enuresis Comedication: no Sociodemographics: not stated **Case 2** Diagnosis of ADHD: DSM-IV (subtype: inattentive) Age: 11 years old IQ: normal Sex: male Ethnicity: not stated Country: USA Comorbidity: primary nocturnal enuresis Comedication: no Sociodemographics: not stated
Interventions	**Case 1** Methylphenidate type: extended release (Concerta) Methylphenidate dosage: 54 mg Administration schedule: once daily Duration of intervention: not stated Treatment compliance: not stated **Case 2** Methylphenidate type: extended release dexmethylphenidate (Focalin XR) Methylphenidate dosage: 10 mg Administration schedule: once daily Duration of intervention: not stated Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: **Case 1** Cessation of enuresis occurred immediately after initiating the stimulant **Case 2** On days taking stimulant, no enuresis occurred. On days when not taking stimulant, enuresis did occur
Notes	*Key conclusions of study authors*: our patient series add to the existing literature of associations between ADHD and enuresis *Comments from the study authors*: information was gathered only from parents. We did not obtain collateral information from teachers or any other sources

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Williamson 2011 *(Continued)*

	Funding/vested interests/authors' affiliations: this work was supported by the University of Alabama's Research Grants Committee. The authors report no conflicts of interest

Winsberg 1982

Methods	A non-randomised, double-blind cross-over trial with fixed doses of methylphenidate given twice a day for a week each in the following schedule: 1. Placebo 2. 0.25 mg/kg 3. 0.50 mg/kg 4. 1.0 mg/kg 5. Placebo
Participants	Number of participants screened: not stated Number of participants included: 25 Participants were administered successive 5 1-week treatment conditions of fixed oral dose given twice daily Number of participants followed up: 20 Number of withdrawals: 5 Diagnosis of ADHD: DSM-III (subtype: not stated) Age: mean 9.27, range 6.7-12.1 IQ: mean 98.2 (14.2) Sex: 25 males Methylphenidate-naïve: not stated Ethnicity: not stated Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. ADHD according to DSM-II criteria 2. Rating by teacher of ≥ 2.5 on either the hyperactivity or aggressivity factor of the Conners Teacher Rating Scale (TRS) *Exclusion criteria* 1. Rating by the teacher < 2.5 during the placebo period 1 on the TRS (exclusion of placebo responders)
Interventions	Participants were administered successive 5 1-week treatment conditions of fixed oral doses given twice daily according to the following order: placebo 1; 0.25 mg/kg; 0.50 mg/kg; 1.00 mg/kg; placebo 2 Methylphenidate type: not stated Duration of intervention: 5 weeks

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Winsberg 1982 *(Continued)*

	Washout: not stated Titration period: none Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Treatment-emergent side effects, weight, blood pressure measured at the end of each treatment period (after 1 week intervention). Blood pressures were obtained 2 hours following the administration of the oral dose
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interests/authors' affiliations: not stated *Key conclusions from study authors*: teacher and parents ratings showed increased improvement in social behaviour as a function of methylphenidate dose. No drug effects were obtained on cognitive performance. Methylpenidate plasma concentrations were significantly associated with oral dose and with measures of social behaviour. No relationship was found with cognitive behaviour. Side effects at the largest dose were severe enough to require discontinuation of treatment for 5 children, but were relatively mild for the rest of the children *Supplemental information* requested through personal email correspondence with authors in September 2013. Not able to get supplemental information regarding data on side effects, and therefore we cannot use the data in the meta-analyses but only report them as part of a weighted mean (Hungund 2013 [pers comm])

Winterstein 2009

Methods	A 10 year retrospective cohort design evaluating the cardiac safety of methylphenidate and amphetamine salts
Participants	Number of participants screened: 2,131,953 Number of participants included: 30,576 Number of participants included in methylphenidate arm: 18,238 Number of participants followed up: 18,238 Number of withdrawals: 0 Diagnosis of ADHD: ICD-9 (subtype: not stated) Age: mean 8.5-9.2, range: 3-20 years old IQ: not stated Sex: 13332 males, 4906 females Methylphenidate-naïve: 100% Ethnicity: white: 44-48.2%, African American: 31.6-34.7%, Hispanic: 14.4-15.5% Country: USA Comorbidity: circulatory disease (3.5%) Comedication: bronchodilators 15.5-16.3%, antidepressants 14-16.4%, antipsychotics 8.2%

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Winterstein 2009 *(Continued)*

	Sociodemographics: not stated *Inclusion criteria* 1. Between 3-20 years 2. ≥ 1 inpatient or outpatient claim for ADHD defined by ICD-9 3. Newly started on methylphenidate or amphetamine salts *Exclusion criteria* 1. Eligibility ending 2. Diagnosis of malignant neoplasm 3. Turning 21 years 4. Switching from 1 drug class to the other 5. Starting to use drugs from both categories concomitantly 6. When outcome of interest has occurred
Interventions	Methylphenidate type: not stated Methylphenidate dosage: not stated Administration schedule: not stated Duration of intervention: not stated Treatment compliance: not stated
Outcomes	*Serious adverse events*: Data assembled from the Florida Medicaid fee-for-service programme Cardiac event defined as a first emergency department (ED) visit for cardiac disease or symptoms: myocardial infarction, stroke, hypertensive disease (excluding malignant causes), angina, aortic or thoracic aneurysm, arrhythmias, syncope, or tachycardia or palpitation ED visits were chosen as clinical end point because they occur more frequently than hospital admissions or cardiac death and provided the best power to detect even subtle difference between drugs
Notes	Sample calculation: no Ethics approval: not stated Funding: funded in part by the Florida Department of Health, Agency for Healthcare Administration Vested interests/authors' affiliations: Dr Gerhard was in part funded by a grant from the Agency for Healthcare Research and Quality *Key conclusions of the study authors*: exposure to methylphenidate and amphetamines salts showed similar risk for cardiac ED visits *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* requested through personal email correspondence with the authors in January 2014 with no reply

Witt 2008

Methods	Open-label parallel design study of methylphenidate or dexamphetamine use for 3 months

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Witt 2008 *(Continued)*

Participants	Number of participants screened: 84 Number of participants included: 63 Number of participants randomised to methylphenidate: 34 Number of participants followed up in the methylphenidate group: 25 Number of withdrawals: 9 Diagnosis of ADHD: DSM-IV (subtype: combined (48%), hyperactive-impulsive (4%), inattentive (44%), not specified (4%)) Age: mean 8.9 (SD 1.9), range 6-12 years old IQ: not stated Sex: 16 males, 9 females Methylphenidate-naïve: 100% Ethnicity: white: 64%, African American: 32%, Hispanic: 4% Country: USA Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Meet full DSM-IV ADHD criteria (any subtype) 2. Has not previously been treated with stimulant medications 3. All participants had to, in the opinion of the clinical team, be good candidates for stimulant treatment *Exclusion criteria* 1. Received an x-ray of any sort in the previous 3 months (excluding routine dental x-rays) 2. Had comorbid conditions that would contraindicate treatment with stimulant medication 3. Had clinically significant electrocardiogram readings 4. Reached menarche (for females)
Interventions	Methylphenidate type: Concerta (n = 24), Ritalin LA (n = 1) Methylphenidate dosage: n = 3, 8 mg Concerta/day; n = 11, 27 mg Concerta /day; n = 7, 36 mg Concerta/day; n = 3, 54 mg Concerta/day; n = 1, 30 mg Ritalin LA/day Administration schedule: first 4 weeks comprised weekly dose titration assessment with clinician using standardised parent/teacher rating scales to ensure adequate dose given. Thereafter, monthly reviews of medication, with adjustment of dose, as needed time points: once daily dose Duration of intervention: 90 days Treatment compliance: 96%
Outcomes	*Serious adverse events*: Cytotoxic damage to cells cultured from blood samples *Non-serious adverse events*:

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Witt 2008 *(Continued)*

	Other adverse events have been recorded, but the data are not available. AEs recorded include insomnia, syncope, loss of appetite, and a worsening of ADHD symptoms
Notes	Sample calculation: the target enrollment of 30 participants in each group was based on the projected number of participants needed to detect a doubling of any of the cytogenetic endpoints with ≥ 90% power at a 0.05 level of significance. Posthoc power analyses with actual sample sizes confirmed that, even with less-than-target enrollment, the power was ≥ 90% for detecting a doubling of each of the 3 cytogenetic endpoints within each treatment group because the variability of each endpoint was smaller than anticipated Ethics approval: this study protocol was reviewed and approved by the institutional review boards of both Duke University Medical Center and the National Institute of Environmental Health Sciences Funding/vested interests/authors' affiliations: Dr Kollins received research support and/or honoraria/consulting fees from the following sources during the conduct of this study: Athenagen, Eli Lilly, Psychogenics, Pfizer, New River Pharmaceuticals, Shire Pharmaceuticals, National Institute on Drug Abuse, National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, and Environmental Protection Agency. Dr Chrisman received honoraria and was on the speakers' bureaus of Shire Pharmaceuticals and McNeil-PPC. The other authors report no conflicts of interest *Key conclusions of the study authors*: the present study found no evidence of changes in any of the 3 cytogenetic endpoints examined in the lymphocytes of children treated with methylphenidate or mixed amphetamine salts based products continuously for 3 months. Our results add to a growing body of evidence that therapeutic levels of methylphenidate do not induce chromosomal damage in humans *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no, only methylphenidate-naïve patients included *Supplemental data* on adverse events requested from the study authors. Answer received in July 2014: data are not available (Witt 2014 [pers comm])

Woolley 2003

Methods	A patient report of obsessive-compulsive disorder (OCD) emerging during methylphenidate treatment
Participants	Diagnosis of ADHD: ICD-10 (subtype: not stated) Age: 11 years old IQ: normal Sex: male Ethnicity: not stated Country: UK Comorbidity: obsessive-compulsive disorder Comedication: Risperidone (1 mg/day) Sociodemographics: not stated
Interventions	Methylphenidate type: immediate release Methylphenidate dosage: 40 mg/day Administration schedule: not stated Duration of treatment: more than 15 months Treatment compliance: not stated

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Woolley 2003 *(Continued)*

Outcomes	*Non-serious adverse events*: Obsessions and compulsions with anxiety (DSM-IV diagnosis of OCD). Washing his hands excessively, accompanied by checking rituals, reassurance seeking, and emetophobia. When methylphenidate was withdrawn the OCD symptoms decreased rapidly but increased when methylphenidate was reintroduced
Notes	*Key conclusions of the study authors*: obsessive-compulsive disorder (OCD) may emerge with stimulant treatment for attention deficit hyperactivity disorder (ADHD). We report a case of OCD worsening with methylphenidate treatment but not with dexamphetamine Funding/vested interest/authors affiliation: not stated *Supplemental information* regarding ADHD diagnosis and IQ received through personal email correspondence with the authors in October 2013 (Heyman 2013 [pers comm])

Yalcin 2012

Methods	2 patient reports of methylphenidate use and development of dysphonic symptoms
Participants	**Case 1** Diagnosis of ADHD: DSM-IV Age: 10 years old IQ: normal Sex: male Country: Turkey Comorbidity: none Comedication: none Sociodemographics: living in metropolitan area with high school student mother who doesn't work and university graduate father who works as sergeant in the army, and older sister **Case 2** Diagnosis of ADHD: DSM-IV Age: 11 years old IQ: normal Sex: male Country: Turkey Comorbidity: specific learning disorder and social anxiety Comedication: not stated Sociodemographics: fourth child of high school graduate father who works as official and elementary school graduate mother
Interventions	**Case 1** Immediate release methylphenidate dosage: 5 mg

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Yalcin 2012 *(Continued)*

	Administration schedule: twice a day Duration of intervention: 2 weeks Treatment compliance: not stated **Case 2** OROS methylphenidate dosage: 18 mg/day Administration schedule: morning Duration of intervention: 2 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: **Case 1** Disturbance of voice quality, hoarseness and bifurcation-strain and over vibration of voice observed by teacher and family. The symptoms began on the first day of methylphenidate treatment. Hoarseness and reduction in the voice amplitude was evident during the first psychiatric control Drug-free days: no symptoms observed by parents or during the psychiatric control. Methylphenidate administration in the clinic: hoarseness. 3 hours after ingestion: voice quality returned to normal. Physical and endoscopic examination: laryngitis or other organic conditions causing hoarseness were not observed Discontinuation of methylphenidate and administration of atomoxetine: no important side effects **Case 2** Significant appetite loss, drowsiness, disturbance of voice and hoarseness. Disturbance of voice and hoarseness occurred every day since the first day on the medication. The symptoms started shortly after the single morning dose and decreased gradually until dinner time and disappeared before bedtime Drug-free days: no symptoms. Otolaryngology consultation: no organic pathology was detected with respect to clinical and endoscopic observation Discontinuation of methylphenidate and prescription of atomoxetine: no symptom of hoarseness or disturbance of voice quality
Notes	Funding/vested interest/authors' affiliations: the authors reported no conflict of interest related to this article *Key conclusions of the study authors*: 2 male children developed disturbances in voice quality and hoarseness associated with MPH use, which required drug discontinuation *Comments from the study authors*: according to the Naranjo 1981 classification, +5 point was calculated (+5-8 possibly related side effect) for the hoarseness and impairment of voice quality associated with methylphenidate for these patients *Supplemental information* regarding IQ and ADHD diagnostic criteria received through personal email correspondence with the authors in March 2013 (Yalcin 2013 [pers comm])

Yalcin 2014

Methods	A cohort study of osmotic release oral system (OROS) methylphenidate use for 60 days
Participants	Number of participants screened: not stated

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Yalcin 2014 *(Continued)*

	Number of participants included: 40 Number of participants followed up: 33 Number of withdrawals: 7 Diagnosis of ADHD: DSM-IV (subtype: combined (54.54%), hyperactive-impulsive (18.18%), inattentive (27.27%) Age: mean 9.20 years (range 6-12) IQ: not stated Sex: 33 males Methylphenidate-naïve: 100% Ethnicity: not stated Country: Turkey Comorbidity: oppositional defiant disorder: 9.09%; enuresis: 6.06% Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. Being a prepubertal male child 2. Meeting the DSM-IV criteria for ADHD 3. No usage of methylphenidate or any other psychiatric drug treatment before the trial 4. Having no depression or psychotic disorder at the time of the trial 5. No history of autism, mental retardation, developmental delay, any other neurological, endocrinological, metabolic or infectious disease or cardiac, liver or kidney dysfunction and no routine use of any drugs *Exclusion criteria* 1. Female patients
Interventions	Methylphenidate type: osmotic release oral system (OROS) Methylphenidate dosage: 18 mg Administration schedule: fixed daily dose (no titration) Duration of intervention: 60 days Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Weight and height before and after methylphenidate. Mothers rated severity of methylphenidate associated adverse reactions (sleep problems, headache, tics, loss of appetite,abdominal pain, weight loss, sadness, mouth dryness, nausea, vomiting, fears, irritability, skin eruption and others): 0, not a problem; 1, mild; 2, moderate; 3, severe. Before and after medication appetite status of the children was rated by the mothers
Notes	Sample calculation: not stated Ethics approval: Gazi University Medical Faculty, Ethics Committee Funding/vested interests: this research was not supported by university funds or any drug company

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Yalcin 2014 *(Continued)*

	Key conclusions of the study authors: this is the first study which directly aims to determine methylphenidate's effect on serum active ghrelin levels. Further research with higher methylphenidate doses and/or other stimulants such as atomoxetine and amphetamine should be done as ghrelin is also associated with obesity, alcohol and drug addiction and reward system pathologies, which are also closely related to attention deficit hyperactivity disorder
	Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: no, 100% were methylphenidate-naïve

Yang 2004

Methods	A 16 week, open-label methylphenidate treatment study
Participants	Number of participants screened: not stated Number of participants included: 25 Number of participants followed up: 19 Number of withdrawals: 6 Diagnosis of ADHD: DSM-IV (subtype: combined (100%)) Age: mean 8.7 (SD 1.7) years (range: 6 years and 4 months - 11 years and 10 months) IQ: full intelligence quotients available from 10 participants (mean 100, range 86-129). The other 9 participants were estimated to be normal Sex: 14 males, 5 females Methylphenidate-naïve: not stated Ethnicity: 100% Asian Country: Taiwan Comorbidity: none Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. 6-12 years old 2. Confirmed ADHD diagnosis, combined subtype (DSM-IV) 3. Maternal report of developmental history consistent with ADHD 4. Absence of gross neurological, sensory, or motor impairment determined by paediatric examinations 5. Attending public elementary school 6. IQ above 70 *Exclusion criteria* 1. Conduct disorder, oppositional defiant disorder, anxiety disorder, bipolar disorder, depressive disorder, dyslexia, autistic disorder, psychosis or Tourette syndrome
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 10 mg/day (starting dose, bodyweight < 30kg) or 20 mg/day (starting dose, bodyweight ≥ 30 kg)

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Yang 2004 *(Continued)*

	Mean methylphenidate dosage: 18.95 (SD 7.56, range 10-35) mg/day, equivalent to 0.61 mg/kg of body-weight (SD 0.15, range 0.38-0.87 mg/kg) Administration schedule: twice daily, mornings before school and at 1 pm Titration period: 3 weeks Duration of intervention: 16 weeks Treatment compliance: 4 noncompliant
Outcomes	The study does not mention any measuring of adverse events. However it is reported, that 2 participants dropped out due to intolerable medication side effects
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interests: not stated Authors' affiliations: Department of Psychiatry, Kaohsiung Medical University Hospital and Department of Psychiatry, Chung Shan Medical University Hospital, Taiwan *Key conclusions of the study authors*: the methylphenidate treatment demonstrated improvement in domains of classroom/home behaviours and academic performance, but showed minimal change on neuropsychological functioning in Taiwanese ADHD children. The finding of academic gain was unexpected, which might be due to the greater interest in achievement and better compliance to cultural expectations by Taiwanese versus Western students, which translated into more rapid improvement in academic performance *Comments from the study authors*: limitations of the study: the present study was conducted in a naturalistic manner, without a placebo controlled or contrast group and without blinding. The diagnoses were made by clinicians, without the benefit of standardised diagnostic instruments administered by a blind clinician. The exclusion criterion dyslexia was not tested *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no

Yang 2012

Methods	A single-blind (rater blinded) randomised parallel trial comparing: 1. Osmotic release oral system (OROS) methylphenidate 2. Atomoxetine 3. A (non-diagnosed) control group receiving no intervention
Participants	Number of participants screened: not stated Number of participants included: 262 Number of participants randomised to methylphenidate: 130 Number of participants followed up: 85 Number of withdrawals: 39 Diagnosis of ADHD: DSM-IV (subtype: inattentive (42%), combined (56.5%), hyperactive/impulsive (1.2%) Age: mean 9.64 (SD 1.95), range 7-14 years old

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Yang 2012 *(Continued)*

	IQ: above 70, mean 102.99 (15.01) Sex: 129 males, 23 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: China Comorbidity: oppositional defiant disorder (n = 44), conduct disorder (n = 2) Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. ADHD criteria by clinical and structured interview 2. Unmedicated or successfully medicated with methylphenidate but had not received methylphenidate during the last 6 months *Exclusion criteria* 1. History of no response or intolerance to methylphenidate or atomoxetine 2. Diagnosis of bipolar I or II, psychosis, anxiety disorder, depression, tic disorder or pervasive developmental disorder 3. Mental retardation (IQ below 70) 4. Seizure disorder or abnormal EEG associated with epilepsy 5. Currently taking anticonvulsive drugs 6. Some medical conditions not appropriate to receive medications such as narrow-angle glaucoma, cardiovascular diseases, or any diseases which may deteriorate when pulse or blood pressure is increased, including hypertension or those taking anti-hypertensive drugs 7. Taking other psychotropic drugs including health food with CNS activity during the prior 30 days or during the study
Interventions	Methylphenidate type: osmotic release oral system (OROS) Methylphenidate dosage: started at 18 mg/daily and could be increased each week to 36 mg/daily and then 54 mg/daily according to the patients response Mean methylphenidate dosage: not stated Administration schedule: not stated Duration of intervention: titration + 4-6 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: 15 dropped out of the methylphenidate group due to adverse events
Notes	Sample calculation: yes Ethics approval: yes Funding: Xian-Janssen Pharmaceutical Ltd. Vested interests/authors' affiliations: Xian-Janssen, Eli Lilly *Key conclusions of the study authors*: the results imply that both OROS-methylphenidate and atomoxetine could improve EF in ADHD children

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Yang 2012 *(Continued)*

Comments from the study authors: there are a number of methodological limitations in the current study. First, we did not include a group that received placebo; therefore, there might have been a bias in the results for the potential placebo effect when we estimated the effect of each medication. The relatively small sample size in the atomoxetine group may have underestimated its therapeutic effect. Further, the slight differential effect between OROS-methylphenidate and atomoxetine treatment groups might also have been a type I error. We excluded youths with significant current psychiatric co-morbidity, restricting the generalisation the findings to more co-morbid, clinically relevant populations

Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate: yes

Supplemental information requested from the study authors in May 2014. No reply

Yatsuga 2014

Methods	A cohort study of methylphenidate use for 3 months
Participants	Number of participants screened: not stated Number of participants included:, 50 Number of participants followed up: 50 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV TR (subtype not stated) Age: mean 9.7 years (SD 2 years 8 months) (range: 6-16) IQ: mean 93.15 Sex: 50 males Methylphenidate-naïve: 100% Ethnicity: not stated Country: Japan Comorbidity: none Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. Diagnosis of ADHD confirmed diagnosis by semi-structured interviews using ADHD behaviour module of Japanese version of the KSADS-PL-J 2. Male, aged 6-16 years *Exclusion criteria* 1. Lifetime diagnosis of any psychiatric disorder, head trauma with loss of consciousness 2. Lifetime substance abuse 3. Any history of epilepsy 4. Significant fetal exposure to alcohol or drugs 5. Perinatal complications 6. Female 7. Use of psychopharmacological components prior to study

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Yatsuga 2014 *(Continued)*

Interventions	Methylphenidate type: osmotic release oral system (OROS) Methylphenidate dosage: 18/27 mg (0.5-1.2 mg/kg/day) Administration schedule: not stated Duration of intervention: 3 months Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: In all, 7 children reported some kind of adverse effect: 2 children reported headache, 3 children had appetite loss, 3 children had sleeplessness and 1 child reported appetite loss and sleeplessness
Notes	Sample calculation: not stated Ethics approval: ethics committee of Graduate School of Medical Sciences, Kumamoto University Funding/vested interests/authors' affiliations: Grant-in-Aid for Scientific Research (B) and Challenging Exploratory Sports, Science and Technology (MEXT) of Japan (KAKENHI:grant number 24300149 and 23650223 to A.T). Partially supported by Grant in Aid for Scientific Research from Japan-U.S. Brain Research Cooperation Program (grant number 210201 to A.T) as well as the Research Grants from the University of Fukui to AT. The funding organisations had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or in preparation, review or approval of the manuscript. No authors have financial or personal relations that could pose a conflict of interest Any withdrawals due to adverse events: none *Key conclusions of the study authors*: this study showed no relation between the COMT genotype and methylphenidate adverse effects *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: none indicated

Yildiz 2010

Methods	An 8-week, open-label, prospective, parallel study with 2 arms: 1. Osmotic release oral system-methylphenidate HCL (OROS-MPH) 2. Immediate-release methylphenidate (IR-MPH)
Participants	Number of participants screened: not stated Number of participants included: 90 Number of participants randomised: OROS-MPH: 50 and IR-MPH: 40 Number of participants followed up: OROS-MPH: 47 and IR-MPH: 36 Number of withdrawals: OROS-MPH: 3 and IR-MPH: 4 Diagnosis of ADHD: DSM-IV (subtype: combined (IR-MPH: 75.0%, OROS-MPH: 80.9%), inattentive (IR-MPH: 25.0%, OROS-MPH: 19.1%)) Age: mean 9.7 SD 1.8, range 7-15 years old (IR-MPH: 9.3 SD 1.3 and OROS-MPH: 10.0 SD 2.1) IQ: above 80. WISC-R total IQ: IR-MPH: 99.9 SD 14.2 and OROS-MPH: 99.5 SD 10.9 Sex: IR-MPH: 28 males, 8 females. OROS-MPH: 41 males, 6 females Methylphenidate-naïve: not stated Ethnicity: not stated

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Yildiz 2010 *(Continued)*

	Country: Turkey Comorbidity: specific learning difficulties (IR-MPH: 22.2%, OROS-MPH: 23.4%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. 7-14 years old 2. Diagnosed with ADHD based on DSM-IV clinical interviews 3. Psychostimulant treatment initiation 4. Parents signed written consent form *Exclusion criteria* 1. Previous unresponsiveness to psychostimulant treatment 2. Especially drug sensitivity to psychotropic drugs 3. Having other disruptive behaviour disorders, and specific learning difficulties 4. Serious gastrointestinal, cardiovascular and haematological diseases history of epilepsy, and severe head trauma 5. IQ below 80 according to the WISC-R test intelligence quotient of children and adolescents
Interventions	Dosage the first 4 weeks: IR-MPH: 10 mg/day. OROS-MPH: 18 mg/day After the fourth week: IR-MPH: 10 mg/day (n = 16) or 20 mg/day (n = 20) and OROS-MPH: 18 mg/day (n = 22) or 36 mg/day (n = 25) Duration of intervention: 60 days Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Based on Side Effects of Stimulant Medications for Screening Scale developed by Turgay, there are 16 side effects for psychostimulants. Parents filled out the form for each side effects based on a 4-point Likert scale (0: none, 1: rare, 2: moderate, 3: severe) in 4th and 8th week
Notes	Sample calculation: not stated Ethics approval: yes Funding/vested interests: not stated *Key conclusions of the study authors*: OROS-methylphenidate was found to be as effective as IR-methylphenidate in the treatment of behavioural symptoms in Turkish children with ADHD. These results demonstrated that both drugs were effective and well tolerated in the treatment of Turkish children with ADHD *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes

Yildiz 2011

Methods	A 14-week parallel, randomised, open-label trial (first 2 weeks screening phase) with 2 arms: 1. Atomoxetine 2. Osmotic release oral system (OROS) methylphenidate

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Yildiz 2011 *(Continued)*

Participants	Number of participants screened: not stated Number of participants included: 12 Number of participants followed up: 11 Number of withdrawals: 1 Diagnsosis of ADHD: DSM-IV-TR (subtype: combined (66.7%), inattentive (33.3%)). Age: mean 10.16, range 8-14 years old IQ: none with mental retardation Sex: not stated Methylphenidate-naïve: not stated Ethnicity: not stated Country: Turkey Comorbidity: oppositional defiant disorder: 7, learning disorder: 6 Comedication: participants taking concomitant psychoactive medications were excluded from the study Sociodemographics: not stated *Inclusion criteria* 1. Met diagnostic criteria for ADHD as defined by DSM-IV-TR 2. Symptom severity at entry ≥ 4 points or above as assessed by the CGI-S *Exclusion criteria* 1. Seizures, bipolar disorder, psychotic illness, mental retardation, pervasive developmental disorder 2. Taking concomitant psychoactive medications 3. Anxiety and tic disorders
Interventions	Methylphenidate type: osmotic release oral system (OROS) Mean methylphenidate dosage: 1.07 mg/kg/day Administration schedule: morning dose, once daily Duration of intervention: 12 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Weight, height, pulse, systolic, diastolic blood pressure, AST, ALT, EEG, ECG, observer, beginning and end point (12 weeks) Self-reported medication related adverse events 18 item list, parent/children, at 4, 8 and 12 weeks 1 child discontinued the study due to chest pain and palpitations
Notes	Sample calculation: no Ethics approval: approved by the Local Independent Ethics Committee Funding/vested interests: not stated

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Yildiz 2011 *(Continued)*

	Authors' affiliations: Department of Child and Adolescent Psychiatry, Kocaeli University, Izmit, Turkey *Key conclusions of the study authors*: treatment responses were not significantly different between the 2 study groups. OROS-methylphenidate led to a significantly greater reduction in teacher T-DSM-IV-S scores. OROS-methylphenidate was more effective than atomoxetine on Stoop-5 time and number of corrections. Significant decrease in the percentage of perseverative errors on WCST in the OROS-methylphenidate group was seen. In the OROS-methylphenidate group, patients most frequently reported anorexia, nervousness, insomnia, headache, nausea and weight loss. When all the results are considered, although both drugs can be considered effective in ADHD treatment, more remarkable improvement is provided by OROS-methylphenidate based on the rates across informant and neuropsychological evaluation

Yilmaz 2013

Methods	A patient report of methylphenidate-induced acute orofacial and extremity limb dyskinesia
Participants	Diagnosis of ADHD: DSM-IV Age: 7 years old IQ: above 70 Sex: male Ethnicity: Turkish Country: Turkey Comorbidity: epilepsy Comedication: sodium valproate Sociodemographics: not stated
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 18 mg Administration schedule: once daily in the morning Duration of treatment: 1 dose Treatment compliance: good
Outcomes	*Serious adverse events*: Involuntary movements started about 5 hours after taking methylphenidate. Lip-licking, lip-smacking and tongue-rolling movements. Dyskinetic tongue movements inside and outside the mouth and involuntary bilateral arm swinging while sitting and standing. Opening and closing his fingers without complete extension. Occasional repetitive movements of the feet, such as beating them against each other while sitting. About 15 hours after methylphenidate intake both hand-mouth movements and excessive mobility had significantly resolved. Dyskinetic symptoms had completely disappeared on the second day of hospitalisation, and the patient was discharged
Notes	Funding/vested interest/authors' affiliations: authors declare that there are no potential conflicts of interest *Key conclusions of the study authors:* this case is reported to emphasise the potential side effects of methylphenidate, individual differences in drug sensitivities, and drug-receptor interactions via different mechanisms

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Yilmaz 2013 *(Continued)*

	*Comments from the study authors: a*ntiepileptic therapy may increase the sensitivity to the side effects of methylphenidate *Supplemental data* received through personal email correspondence with the authors in December 2013 (Yilmaz 2013 [pers comm])

Yu 2010

Methods	A patient report of 4 boys with attention-deficit/hyperactivity disorder who developed vasculopathy during treatment with psychostimulants. 3 received treatment with methylphenidate
Participants	Diagnosis of ADHD: ICD-9/ICD-10 (subtype: not stated) Age: 11, 12, 16 years old (mean: 13) IQ: no mentally retarded Sex: 3 males Ethnicity: white Country: USA Comorbidity: case 2 (suspected bipolar disorder) Comedication: case 1 (Adderall); case 2 (Abilify and Lamictal, later on they were discontinued and Seroquel was added) Sociodemographics: not stated
Interventions	**Case 1** *First methylphenidate attempt*: Extended release methylphenidate dosage: 54 mg/daily (Concerta). Comedication: Adderall. Administration schedule: not stated. Duration of treatment: 2 years. Treatment compliance: not stated *Second methylphenidate attempt*: Immediate release-/dex- and extended release-methylphenidate dosage: Concerta 90 mg/daily and Focalin 20 mg/daily. Administration schedule: not stated. Duration of treatment: 9 months. Treatment compliance: not stated Total duration of psychostimulant treatment: 9 years **Case 2** Immediate- and extended release methylphenidate dosage: long acting Ritalin: 30 mg/daily and Focalin 2.5 mg/daily Administration schedule: not stated Duration of current treatment: 4 years Total duration of psychostimulant treatment: 5 years Treatment compliance: not stated **Case 4** Extended release/dex- and immediate release/dex methylphenidate dosage: Focalin XR 20 mg/daily, Focalin IR 10 mg/daily

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Yu 2010 *(Continued)*

	Administration schedule: twice daily, XR in the morning, and IR in the afternoon Duration of treatment: 1 year Total duration of psychostimulant treatment: 7 years Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: **Case 1** Tachycardia at age 11 while taking Concerta, 54 mg/daily Vasculopathy at age 16. Hands and feet were a continuous blue color which increased in frequency in cold weather. Diagnosed with decreased circulation but not Raynaud's syndrome. Occured when the Concerta dose was increased from 54 mg/daily to 90 mg/daily in 3 months with the same Focalin dose (10 mg/daily) **Case 2** Vasculopathy. First diagnosed with Raynaud's syndrome with finger pain and colour changes during a neurology consultation at age 10. At age 12 had diffuse erythema of both earlobes, the fingers of both hands, and the toes of the left foot Tics at age 10 - not clear if these were present prior to ADHD treatment **Case 4** Vasculopathy. After taking Focalin for a year, he developed persistent curling of the toes of both feet. In addition, he had reddish and purple colour changes in his hands and feet with cold exposure that lasted for 20 min. No associated pain and only rare paresthesia. At age 10 toes 2, 3, and 4 of both feet were held in a flexed position ('curled toes'), and there was skin discoloration and excoriation
Notes	Funding/vested interest: none Authors' affiliations: Drs Ronald and Elizabeth Weller are co-owners of the Children's Interview for Psychiatric Syndromes (and the parent's version) and have received annual royalties from copyright ownership of this diagnostic interview. Dr Elizabeth Weller was the principal investigator for a grant from GlaxoSmithKline to investigate the tolerability and efficacy of lamotrigine in children and adolescents diagnosed with bipolar disorder *Key conclusions of the study authors*: these patient reports raise the concern that adverse effects in the peripheral vascular system of children and adolescents may be associated with psychostimulant treatment *Comments from the review authors:* none of the patients had their psychostimulants decreased or discontinued. Due to the severe nature of their ADHD symptoms, these patient could not stop or reduce their psychostimulant treatment to determine whether their vascular symptoms would improve *Supplemental information* received through personal email correspondence with the authors in October 2013 (Yu 2013 [pers comm])

Zarinara 2010

Methods	A 6-week double-blind, parallel-group randomised clinical trial with 2 arms: 1. Methylphenidate 2. Venlafaxine No control/no-intervention group

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Zarinara 2010 *(Continued)*

Participants	Number of participants screened: 60 Number of participants included: 38 Number randomised to methylphenidate: 19 Number of participants followed up in the methylphenidate group: 18 Number of withdrawals in the methylphenidate group: 1 **MPH group** Diagnosis of ADHD: DSM-IV-TR (subtype: combined (100%)) Age: mean 9.57 years old (range 6-13) IQ: above 70 Sex: 13 males, 6 females Methylphenidate-naïve: 100% (newly diagnosed) Ethnicity: Persian (100%) Country: Iran Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. 6-13 years old 2. Diagnosis of ADHD according to DSM-IV-TR 3. Total or subscale scores (or both) on ADHD-RS-IV: School Version of ≥ 1.5 SD above norms for patient's age and gender 4. To participate, parents and children had to be willing to comply with all requirements of the study *Exclusion criteria*: 1. A history or current diagnosis of pervasive developmental disorders, schizophrenia, or other psychiatric disorders (DSM-IV axis I) 2. Any current psychiatric comorbidity that required pharmacotherapy 3. Any evidence of suicide risk and mental retardation (IQ below 70) 4. A clinically significant chronic medical condition, including organic brain disorder, seizures, or current abuse or dependence on drugs the last 6 months 5. Hypertension or hypotension
Interventions	Methylphenidate type: not stated Methylphenidate dosage: 20-30 mg/day depending on weight (20 mg/day for < 30 kg and 30 mg/day for > 30 kg) Methylphenidate titration: 3 weeks (week 1: 10 mg/day twice daily; week 2: 20 mg/day twice daily; and week 3: 30 mg/day for children > 30 kg 3 times daily) Duration of intervention: 6 weeks inclusive titration Treatment compliance: not stated

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Zarinara 2010 *(Continued)*

Outcomes	Adverse effects checklist (20 possible adverse events), rated by a child psychiatrist on days 7, 21, 42. Body weight and vital signs assessed at baseline, week 1, 2, 4, 6. 12-lead ECG and physical examination at baseline and week 6
Notes	Sample calculation: not stated Ethics approval: yes Funding/vested interests/authors' affiliations: this study was supported by a grant from Tehran University of Medical Sciences *Key conclusions of the study authors*: the results suggest that venlafaxine may be useful for the treatment of ADHD. In addition, a tolerable side-effect profile is one of the advantages of venlafaxine in the treatment of ADHD *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* regarding data requested through personal communication with the authors in August 2013. No reply

Zelnik 2015

Methods	A naturalistic study of osmotic release oral system (OROS) methylphenidate use for ≥ 1 year
Participants	Number of participants included: 128 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean: not stated (range 7-17) IQ: patients with intellectual disabilities were excluded Sex: 83 males, 40 females Methylphenidate-naïve: not stated, but all were newly diagnosed Ethnicity: not stated Country: Israel Comorbidity: anxiety 27.2-46.8%, depression 1.2-9.7%, all psychiatric comorbidities 48.1%-74.5% Comedication: no Sociodemographics: not stated *Inclusion criteria*: 1. Diagnosis of ADHD evaluated at the Clalit Health Services ADHD neuropaediatric clinic in Haifa with DSM IV-TR criteria *Exclusion criteria*: 1. Excluded were patients with autism spectrum disorder, intellectual disabilities, static encephalopathy (such as cerebral palsy) and children with severe psychiatric conditions that required chronic medication with anti-psychotic drugs 2. Patients who were referred to our clinic for second opinion and/or were already diagnosed with ADHD were also excluded
Interventions	Methylphenidate type: group I: lower dose OROS + short acting formulation; group II: OROS

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Zelnik 2015 *(Continued)*

	Mean methylphenidate dosage: group I: 0.83 SD 0.21 mg/kg; group II: 1.06 SD 0.29 mg/kg Administration schedule: group I: not stated; group II: OROS once daily Duration of intervention: ≥ 1 year Treatment compliance: not stated
Outcomes	In the present study data were retrospectively collected of all the patients that were treated with OROS methylphenidate and characterised the clinical characteristics of those who tolerated it well in comparison with those that better tolerated lower doses of OROS methylphenidate together with shorter acting methylphenidate, offering them a more potent level during school hours while lessening the effect during the afternoon and evening hours
Notes	Sample calculation: not stated Ethics approval: yes Funding/vested interest: no Authors' affiliations: none *Key conclusions of the study authors*: while OROS methylphenidate and other long-acting methylphenidate formulations prove beneficial for most children and adolescents with ADHD, some patients (mostly those with psychiatric comorbidities) might sometimes better tolerate a lower OROS methylphenidate dose combined with short-acting methylphenidate formulation. Additional larger-scale prospective studies are required to validate our preliminary observation *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated

Zeni 2007

Methods	A cohort study of methylphenidate use for 1 month
Participants	Number of participants screened: 111 Number of participants included:106 Number of participants followed up: not stated Number of withdrawals: 5 Diagnosis of ADHD: DSM-IV (subtype: combined (58.5%), hyperactive-impulsive (7.5%), inattentive (26.4%)) Age: mean 10.26, range 4-17 years old IQ: not stated Sex: 82 males, 24 females Methylphenidate-naïve: 100% Ethnicity: 100% European-Brazilian Country: Brazil Setting: outpatient clinic Comorbidity: conduct disorder (16%), oppositional defiant disorder (51.9%), mood disorders (9,4%), anxiety disorders (23.8%)

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Zeni 2007 *(Continued)*

	Comedication: none Sociodemographics: not stated *Inclusion criteria* 1. ADHD diagnosis according to DSM-IV 2. Age between 4 and 17 years old 3. European-Brazilian ethnicity 4. Drug naïve for methylphenidate 5. Prescribed dose of methylphenidate of 0.3 mg/kg/day
Interventions	Methylphenidate type: short acting Mean methylphenidate dosage: 0.5 mg/kg/day Administration schedule: not stated Duration of intervention: 1 month Treatment compliance: 2 patients excluded due to irregular use of methylphenidate
Outcomes	*Non-serious adverse events* Barkley SERS: 1. Sleep (insomnia): absent: 77 (72.6%); present: 21 (19.8%); information missing: 8 (7.5%) 2. Decreased appetite: absent: 44 (41.5%); present: 53 (50%); information missing: 9 (8.5%)
Notes	Sample calculation: no Ethics approval: yes Funding/vested interest: governmental agencies: Conselho Nacional de Desenvolvimento Cientıfico e Tecnologico (CNPq, Brazil); Grant number: 471761/03-6; Grant sponsor: Programa de Apoio a Nucleos de Excelencia (PRONEX, Brazil); Grant sponsor: Hospital de Clınicas de Porto Alegre *Key conclusions of the study authors*: no significant association was detected between polymorphisms of dopaminergic (DRD4, DAT1) and serotonergic genes (HTR1B, HTR2A, and 5-HTT) on the response nor side effects to the treatment with methylphenidate *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no, 100% were methylphenidate-naïve *Supplemental information* received through personal email correspondence with the authors in September 2016 (Zeni 2016 [pers comm])

Zhang 2010

Methods	A case-control study of methylphenidate use for 2-4 years
Participants	Number of participants screened: not stated Number of participants included: 175 Number included as cases: methylphenidate 126; controls (no intervention) 29 Number followed up in each arm: methylphenidate 46; controls 2 Number of withdrawals in each arm: methylphenidate 98; controls 27

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Zhang 2010 *(Continued)*

	Diagnosis of ADHD: DSM-IV (subtype: combined (74.65%), hyperactive-impulsive (8.9%), inattentive (16.43%)) Age: mean 7.42 years old (range 6-9.8) IQ: not stated Sex: 126 males, 20 females Methylphenidate-naïve: not stated Ethnicity: not stated Country: China Comorbidity: oppositional defiant disorder (39.73%), conduct disorder (4.79%), learning disorder (8.22%), tics (4.79%) Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. ADHD 2. Pubertal stage before Tanner's II *Exclusion criteria*: 1. All participants have been excluded from diagnoses of pervasive developmental disorder, schizophrenia, emotional disorders, epilepsy and other organic diseases
Interventions	Methylphenidate type: immediate release Mean methylphenidate dosage: 0.27-0.64 mg/kg Administration schedule: 2 time points (mornings and afternoons) Duration of intervention: 2-4.8 years Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: Height Weight BMI
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interest: not stated Authors' affiliations: Department of Paediatrics, First Affiliated Hospital, Sun Yat-sen University, Guangzhou, P. R. China *Key conclusions of the study authors*: methylphenidate inhibits linear growth of children, but it is correlated to methylphenidate treatment length; there was no influence on weight; there was no differences on BMI *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: not stated

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Zhang 2010 *(Continued)*

	Supplemental information requested through personal email correspondence with the authors in June 2014. Email sent twice but no answer received

Zheng 2011

Methods	A 6-week multicentre, prospective, naturalistic, open-label, pilot study evaluating the effectiveness and safety of osmotic release oral system (OROS) methylphenidate
Participants	Number of participants screened: not stated Number of participants included: 1447 Number of participants followed up: 1154 Number of withdrawals: 293 Diagnosis of ADHD: DSM-IV (subtype: combined (56.8%), hyperactive-impulsive (9.8%), inattentive (28.5%), unidentified type (3.4%)) Age: 9.53 (SD 2.35) years old (range 6-16) IQ: not stated Sex: 1219 males, 228 females Methylphenidate-naïve: not stated (no current methylphenidate treatment: 1304 (90%)) Ethnicity: Asian (97.8%), others (2.2%) Country: China Comorbidity: no Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. ADHD according to DSM-IV 2. Willing to take OROS methylphenidate as the only medicine for ADHD 3. Written informed content from parents/guardians *Exclusion criteria*: 1. Anxiety disorder, mood disorder, general development disorder, serious depression, schizophrenia 2. Known to be allergic to methylphenidate or other ingredients of the study drug 3. Glaucoma 4. Family history or diagnosed as Tourette syndrome 5. Taking or having taken monoamine oxidase inhibitor in the past 14 days 6. Taking the following drugs such as clonidine, other alpha-2 adrenergic receptor agonist, tricyclic antidepressants, theocine, bishydroxycoumarin and so on 7. Participating in clinical trials of other drugs 8. Cardiovascular diseases including moderate to severe hypertension, hyperthyroidism 9. History of drug dependence or alcohol dependence 10. Participants with serious gastrointestinal stenosis, dysphagia and other serious somatic diseases During the 6-week treatment period, participants would be excluded if the following conditions occurred:

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Zheng 2011 *(Continued)*

	1. Unwilling to keep receiving OROS methylphenidate therapy due to poor therapeutic effect, intolerance of adverse events, etc. 2. Serious adverse events related to OROS methylphenidate 3. Violating the study protocol by taking ADHD drugs which are not allowed 4. Other serious somatic diseases judged by investigators occur (the condition that the child is in danger based on the BP measurement at any time was also included) 5. Tic symptoms increase or new serious tic symptoms appear 6. Pregnancy
Interventions	Methylphenidate type: osmotic release oral system (OROS) Methylphenidate dosage: 18, 36 or 54 mg once daily at the discretion of investigators. However, the recommended dosing strategy is: methylphenidate-naïve: 18 mg; currently receiving 5 mg immediate release methylphenidate 2-3 times a day: 18 mg OROS methylphenidate; currently receiving 10 mg immediate release methylphenidate 2-3 times a day or a total daily dose of 40 mg immediate release methylphenidate: 36 mg OROS methylphenidate; and currently receiving 15 mg immediate release methylphenidate 2-3 times a day or a total daily dose of > 45-60 mg: 54 mg OROS methylphenidate Doses of OROS methylphenidate could be adjusted between a total daily dose range of 18 and 54 mg after 14 days of treatment by the investigator on the basis of safety and efficacy. At the end of the study 96.8% participants received an OROS methylphenidate dose of 18 mg, 3.1% 36 mg and 0.1% 54 mg Duration of intervention: 6 weeks Treatment compliance: 93.4% of the patients showed good compliance (defined as more than 80% adherence to the prescribed regimen)
Outcomes	*Non-serious adverse events* Blood pressure, pulse rate measurement, adverse event review were conducted by the investigator at baseline, week 2, 4 and 6 Parents rated the participant's sleep quality and were asked about the presence of motor and/or verbal tics at baseline, week 2, 4 and 6
Notes	Sample calculation: not stated Ethics approval: not stated Funding: funded by Xi'an Jassen Pharmaceutical Ltd, China *Key conclusions of the study authors*: this open-label, naturalistic study provides further evidence of effectiveness and safety of OROS methylphenidate in school-aged children under routine practice *Comments from the study authors*: since the patients in this study only received 6-weeks OROS methylphenidate treatment, the long-term adverse events such as influence on growth and weight can not be observed. This is a limitation of this study because ADHD patients need long-term treatment *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: yes *Supplemental information* requested through email correspondence with the first author in September 2013. No reply

Zheng 2015

Methods	A 12-week, prospective, multicentre, open-label, self-controlled clinical study of methylphenidate use for 12 weeks

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Zheng 2015 *(Continued)*

Participants	Number of participants screened: not stated Number of participants included: 153 Number of participants followed up: 123 Number of withdrawals: 30 Diagnosis of ADHD: DSM-IV (subtype: not stated) Age: mean 9.2 (SD 1.5) years old (range 6-12) IQ: 85 or more Sex: 108 males, 20 females Methylphenidate-naïve: 90.4% Ethnicity: Han (96.9%), others (3.1%) Country: China Comorbidity: not stated Comedication: none Sociodemographics: not stated *Inclusion criteria*: 1. Boys and girls between 6 and 12 years of age 2. Normal intelligence (IQ of 85 or more) 3. A documented diagnosis of ADHD according to DSM-IV 4. Weight 20-60 kg 5. Academic performance of the previous term 6. Children having no history of taking psychotropic drugs in the last 6 months 7. Currently taking effective MPH-IR (≤ 60 mg/d) *Exclusion criteria*: 1. Evidence of any bipolar I or II affective disorder, anxiety disorder, general development disorder, schizophrenia, glaucoma, Tourette syndrome, hypertension and cardiovascular disease 2. Any physical disease that can significantly reinforce the activity of the sympathetic nervous systems, serious gastrointestinal stenosis, dysphagia, and other serious somatic diseases 3. Not being able to coordinate with the cognitive examination 4. Highly sensitive to methylphenidate 5. Had taken or taking sympathomimetic agents such as β-adrenoreceptor blocking drugs, received or receiving monoamine oxidase inhibitor drugs such as clonidine, other α-2 adrenergic receptor agonist, tricyclic antidepressants, theophylline, or bishydroxycoumarin in the past 30 days 6. History of drug or alcohol dependence
Interventions	Methylphenidate type: osmotic release oral system (OROS) Methylphenidate dosage: during the optimised treatment phase (weeks 3-12), 73.5% children received OROS methylphenidate 18 mg once daily and 26.5% received 36 mg once daily (weeks 7-12) Administration schedule: once daily Duration of intervention: 12 weeks Treatment compliance: the mean course of OROS methylphenidate treatment was 80.1 days and total compliance was 93.6%

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Zheng 2015 *(Continued)*

Outcomes	Children had a general physical and blood examination (if required) before initiating OROS methylphenidate. Blood pressure, pulse rate, concomitant medications, adverse events (AEs), and treatment review were conducted at baseline and at each visit. A total of 149 patients were included in the safety analysis set
Notes	Sample calculation: not stated Ethics approval: yes Funding/vested interest: the study presented in this report was supported by Xi'an Janssen Pharmaceutical Ltd. Authors' affiliations: Ms. Jian-Min Zhuo and Dr Sheng-Nan Xie are full-time salaried employees of Xi'an-Janssen Pharmaceutical Ltd. Drs. Yi Zheng, Hong-Yun Gao, Zhi-Wei Yang, Fu-Jun Jia, Fang Fang, and Rong Li have served on advisory boards of Xi'an Janssen Pharmaceutical Ltd., and Eli Lilly and Company *Key conclusions of the study authors*: in conclusion, this open-label study suggests that the OROS methylphenidate improves academic and cognitive performance in Chinese school-aged children with ADHD. The treatment was safe and generally well-tolerated over the period of 12 weeks *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: see exclusion criteria 4

Çetin 2015

Methods	A randomised, open-label parallel study of methylphenidate or atomoxetine use for 6 months
Participants	Number of participants screened: not stated Number of participants included: 145 Number of participants randomised to methylphenidate: 73 Number of participants followed up on methylphenidate: 61 Number of withdrawals: 12 Diagnosis of ADHD: DSM-IV-TR (subtype: combined (91.8%), inattentive (8.2%)) Age mean: 9.47 (SD 2.32) years old IQ: above 90 Sex: 9 males (86.9%), 8 females (13.1%) Methylphenidate-naïve: 100% Ethnicity: not stated Country: Turkey Comorbidity: none Comedication: not stated Sociodemographics: not stated *Inclusion criteria*: 1. Diagnosis of ADHD 2. 7-16 years old *Exclusion criteria*: 1. IQ > 90

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Çetin 2015 *(Continued)*

	2. Presence of a central nervous system disease 3. Organic problems 4. Comorbid psychopathologies 5. Previous treatment with the diagnosis of ADHD
Interventions	Methylphenidate type: osmotic release oral system Mean methylphenidate dosage: 0.73 (SD 0.22) mg/kg/day Administration schedule: not stated Duration of intervention: 6 months Treatment compliance: not stated
Outcomes	The adverse effects and tolerability of medications were evaluated using a questionnaire including 12 questions about anorexia, insomnia, stomachache, nervousness, headache, weight loss, rash, obsessions, sedation, epistaxis, tics and others, in addition to open ended questions The rate of adverse effects observed was 31.1% (n = 19) in the OROS-methylphenidate group Treatment was stopped in 5 patients because of the adverse effects *Non-serious adverse events*: 1. Allergic reactions: 2 2. Loss of appetite and weight loss > 10%: 2 3. Tachycardia: 1
Notes	Sample calculation: not stated Ethics approval: yes, the study protocol was approved by local Ethics Committee Funding/vested interests/authors' affiliations: not stated *Key conclusions of the study authors*: OROS-methylphenidate and atomoxetine had similar efficacies and adverse effect profiles in the treatment of ADHD *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: all participants were methylphenidate-naïve

Özcan 2004

Methods	A cohort study comparing time domain heart rate variability in non-ADHD controls and ADHD cases treated with methylphenidate for 12 weeks
Participants	Number of participants screened: not stated Number of participants included: 73 Number included as cases (ADHD): 42 Number included as controls (non-ADHD): 31 **ADHD group** Number of participants followed up: 42 Number of withdrawals: 0 Diagnosis of ADHD: DSM-IV (subtype: not stated)

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Özcan 2004 *(Continued)*

	Age: mean 11.1 years old (range 6-15) Sex: 34 males, 8 females IQ: above 70 Country: Turkey Setting: Ethnicity: not stated Methylphenidate-naïve: not stated Comorbidity: not stated Comedication: no Sociodemographics: not stated *Inclusion criteria*: 1. ADHD based on DSM-IV 2. Age 6-15 years old *Exclusion criteria*: 1. Psychotic disorder, autistic disorder, hearing and visual problems and mental retardation
Interventions	Methylphenidate type: not stated Mean methylphenidate dosage: 10 mg (2 x 5 mg) Administration schedule: not stated Duration of treatment: 12 weeks Treatment compliance: not stated
Outcomes	*Non-serious adverse events*: heart rate variability
Notes	Sample calculation: not stated Ethics approval: yes Funding/vested interests: not stated Authors' affiliations: no affiliations to pharmaceutical companies stated *Key conclusions of the study authors*: methylphenidate decreased the time domain HRV parameters in ADHD group. Therefore, close cardiac follow-up is necessary for the detection of side effects of methylphenidate especially in patients who are under risk for developing cardiac arrhythmias and in patients using methylphenidate together with drugs affecting central nervous system *Exclusion of methylphenidate non-responders/children who have previously experienced adverse events on methylphenidate*: no *Supplemental information* regarding IQ has not been possible to receive through personal email correspondence with the authors. Emails sent twice to several of the authors

ADD: attention deficit disorder; **ADD-H**: attention deficit disorder with hyperactivity; **ADHD**: attention deficit hyperactivity disorder; **AE**: adverse event;**bpm**: beats per minute; **CGI-S**: Clinical Global Impression-Severity; **CI**: confidence interval; **CK**: cytokine; **CNS**: central nervous system; **C-SSRS**: Columbia Suicide Severity Rating Scale; **DBP**: diastolic blood pressure; **DSM-III-R**: *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*, Revised; **DSM-IV**: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; **DSM-IV-TR**: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; **DSM-5**: *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition;* **ECG**: electrocardiogram; **ED**: emergency department; **EEG**: electroencephalogram; **EF**: ejection fraction;

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EKG: electrocardiogram; **FDA**: Food and Drug Administration; **ER**: extended release; **HCL**: hydrochloride; **HRQoL**: health-related quality of life; **ICD**: International Classification of Diseases; **IQ**: intelligence quotient; **IQR**: interquartile range; **IR**: immediate release; **IRR**: interrater reliability;**ITT**: intention-to-treat; **LLC**: limited liability company; **LOCF**: last observation carried forward; **LTFU**: loss to follow-up; **MAOI**: monoamine oxidase inhibitors; **MedDRA**: Medical Dictionary for Regulatory Activities; **MPH**: methylphenidate; **MPT**: methylphenidate trial; **MRI**: magnetic resonance imaging; **MTA**: Multimodal Treatment Study of Children With ADHD; **MTS**: methylphenidate transdermal system; **NICE**: National Institute for health and Care Excellence; **NNTB**: number needed to treat for an additional beneficial outcome; **OCD**: obsessive compulsive disorder; **ODD**: oppositional defiant disorder; **OROS**: osmotic Release Oral System; **PDD**: pervasive developmental disorder; **PTS**: placebo transdermal system; **PTSD**: post-traumatic stress disorder; **RCT**: randomised controlled trial; **SD**: standard deviation; **SERS**: Side Effects Rating Scale; **SBP**: systolic blood pressure; **SODAS**: spheroidal oral drug absorption system; **SSRI**: selective serotonin reuptake inhibitors; **WISC**: Wechsler Intelligence Scale for Children.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bart 2010	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Beauchaine 2003	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Becker 2011	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Beery 1994	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Benamor 2014	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Biederman 1999	Not possible to obtain the disaggregated data for the methylphenidate group
Biederman 2009	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Bohane 2010	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Brossard-Racine 2012	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Byrne 1998	No data on adverse events
Casat 1995	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Cavadas 2007	No data on adverse events
Chambers 2012	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Chavez 1999	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Chelonis 2010	Lack of relevant outcome measures
Chelonis 2011	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Clarke 2003	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Conzelmann 2014	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Cooper 2011	Unable to obtain the disaggregated data on children receiving methylphenidate, either from the publication or through personal email correspondence with the study authors
De Zeeuw 2012	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
DeVito 2009	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events

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Study	Reason for exclusion
Drtílková 1990	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Epstein 2010	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Faraone 2007b	No data on adverse events
Fegert 2006	No data on adverse events
Foodman 1996	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Frank 1993	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Funk 1993	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Gau 2009	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Gimpel 2005	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Glenngård 2013	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Gormez 2012	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Gould 2009	No ADHD diagnosis
Gualtieri 1985	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Guimarães 2009	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Gurkan 2011	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Hautmann 2013	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Hawcutt 2012	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Hawk 2003	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Heiser 2004	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Hidas 2011	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Hood 2005	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Hoza 1992	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Hwang 2012	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Jonkman 1999	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Kerdar 2007	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Kereszturi 2008	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Keulers 2007	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events
Klein 2002	No relevant outcomes (experimental, neurocognitive or functional). No data on adverse events

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Study	Reason for exclusion
Kramer 2001	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Lajoie 2005	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Lawrence 2005	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Matier 1992	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Mayes 1993	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Miller 1994	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Miller 1996	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Miranda 2006	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Monden 2012a	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Monden 2012b	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Nahshoni 2012	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Neef 2005	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Negrao 2011	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Nigg 1996	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Nikles 2005	No relevant outcome measures (experimental, neurocognitive or functional). The paper investigates the patients' satisfaction with N-of-1 trials
Nolan 1999	Unable to obtain the disaggregated data for the methylphenidate group
Ohashi 2010	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Orgill 1996	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Overcash 2005	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Ozdag 2004	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Palomino 2012	Unable to obtain the disaggregated data for the methylphenidate group
Park 2012	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Pelham 1986	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Pelham 2011	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Perera 2012	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Pierce 2008	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Poulton 2013	Unable to obtain the disaggregated data for the methylphenidate group

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Study	Reason for exclusion
Prehn-Kristensen 2011	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Rapport 1985	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Rhodes 2004	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Rhodes 2006	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Roman 2002	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Rubia 2009	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Rubia 2009a	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Rubio 2011	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Schecklmann 2011	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Scheres 2003	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Scheres 2006	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Schmiedeler 2009	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Shafritz 2004	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Shaywitz 1982	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Sheppard 1999	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Snyder 2008	Unable to obtain the disaggregated data for the methylphenidate group
Solanto 1989	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Spivak 2001	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Stein 1999	Unable to obtain the disaggregated data for the methylphenidate group
Syrigou-Papavasiliou 1988	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Tabori-Kraft 2007	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Tamm 2007	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Tillery 1998	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Trenque 2009	Unable to obtain the disaggregated data for the methylphenidate group
Van der Meere 2009	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Van der Oord 2012	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Vance 1999	Unable to obtain the disaggregated data for the methylphenidate group
Vickers 2002	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events

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Study	Reason for exclusion
Vogt 2011	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Winterstein 2007	Unable to obtain the disaggregated data for the methylphenidate group
Winterstein 2012	Unable to obtain the disaggregated data for the methylphenidate group
Wong 2012	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Yeh 2012	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Zachor 2006	Unable to obtain the disaggregated data for the methylphenidate group
Zalsman 2003	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events
Zang 2005	No relevant outcome (experimental, neurocognitive or functional). No data on adverse events

ADHD: attention deficit hyperactivity disorder.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Arnold-Von 2000

Methods	Non-randomised study of 2 cases
Participants	ADHD diagnosis according to DSM-III-R
Interventions	Type of methylphenidate not stated
Outcomes	Not stated
Notes	The article is written in Dutch, and we have not yet been able to obtain a translation

Dalsgaard 2011

Methods	A longitudinal, prospective cohort study of the cardiovascular safety of stimulants
Participants	All children born in Denmark between 1990 and 1999; children with ADHD were identified from within this cohort
Interventions	Type of methylphenidate not stated
Outcomes	Cardiovascular adverse events
Notes	Found too late in the review process to include

Flapper 1989

Methods	Non-randomised study of 8 cases
Participants	Children with a diagnosis of ADHD as well as Minimal Brain Dysfunction (MBD) according to DSM-III

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Flapper 1989 *(Continued)*

Interventions	Type methylphenidate not found
Outcomes	Effects and adverse events
Notes	The article is written in Dutch and we have not yet been able to obtain a translation

Husár 2006

Methods	Case-study
Participants	14-year-old boy with priapism
Interventions	Olanzapine and methylphenidate (diazepam and metamisolum)
Outcomes	Priapism occurrence
Notes	The article is written in Czech and we have not yet been able to obtain a translation

Ince 2015

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Uncelar
Notes	Not able to retrieve article

Ishizaki 2001

Methods	Observational study
Participants	Unclear
Interventions	Unclear
Outcomes	Serious adverse events
Notes	The article is written in Japanese, and we have not yet been able to obtain a translation

Laezer 2015

Methods	Not retrieved
Participants	Not retrieved

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Laezer 2015 *(Continued)*

Interventions	Not retrieved
Outcomes	Not retrieved
Notes	We were not able to find the paper

Mulas 2014

Methods	Review of patient records
Participants	23 participants, 5-16 years' old with epilepsy
Interventions	Methylphenidate, type unclear
Outcomes	Clinical course
Notes	The article is written in Spanish, and we have not yet been able to obtain a translation

Ptáček 2008

Methods	Case-control study
Participants	Group of boys (n = 46) diagnosed with ADHD
Interventions	Methylphenidate, type not stated
Outcomes	Various unspecified anthropometric characteristics
Notes	The article is written in Czech, and we have not yet been able to obtain a translation

Radziuk 2015

Methods	Open-label, non-controlled trial
Participants	30 children and adolescents with epilepsy and comorbid ADHD
Interventions	Methylphenidate, type not stated
Outcomes	Tolerability to methylphenidate, quality of life, seizure frequency
Notes	—

Socanski 2015

Methods	Prospective study on children with ADHD
Participants	517 children diagnosed with ADHD (82% male), age 5-14 years

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Socanski 2015 *(Continued)*

Interventions	Methylphenidate, type not stated
Outcomes	Initial positive response to methylphenidate after 4-6 weeks titration, and the use of methylphenidate at 1-year follow-up
Notes	Conference abstract. Could not retrieve full-text report

Sugama 2009

Methods	Cases with ADHD
Participants	181 participants with ADHD
Interventions	Switched medication from conventional immediate-release preparations of methylphenidate to extended-release tablets (OROS)
Outcomes	Types of developmental disorders, drug dosages, efficacy, adverse events, concomitant medication, other relevant problems, and so on, prior to switching the medications
Notes	The article is written in Japanese, and we have not yet been able to obtain a translation

TOSCA 2011

Methods	A 4-site, phase 2, parallel-group RCT: 1. 3-week open-label titration of methylphenidate 2. 6-week double-blind RCT with 2 arms: a. methylphenidate + parent training programme + placebo b. methylphenidate + parent training programme + risperidone 3. 12-week double-blinded extension 4. 1-year follow-up
Participants	Sample size: 160 patients included Age range: 6-12 years' old (inclusive) ADHD diagnosis: DSM-IV Comorbidity: disruptive behaviour disorder (conduct disorder or oppositional defiant disorder 100%), significant aggressive behaviour Country: USA Baseline demographics: no supplemental data Inclusion criteria: 1. DSM-IV diagnosis of ADHD, any subtype 2. DSM-IV diagnosis of a disruptive behaviour disorder, including conduct disorder or oppositional defiant disorder 3. 6-12 years' old 4. Evidence of serious physical aggression, as rated on the Overt Aggression Scale-Modified (score of 3 or more), and as determined by parent or guardian ratings on the Nisonger Child Behavior Rating Form (NCBRF) D-Total Score (score > 26, > 90th percentile). In addition, the blinded clinician must assign a clinical global impressions' severity score of 4 or greater for aggression

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TOSCA 2011 *(Continued)*

	5. Prior to random assignment, participants must be free of all psychotropic medicines for 2 weeks for most drugs (such as most antidepressants, alpha agonists, beta blockers, anxiolytics, mood stabilisers, and antihistamines), and 4 weeks for depot antipsychotics and fluoxetine Exclusion criteria: 1. Full-scale IQ below 71 2. Pregnancy or a history of seizure disorder or other neurological or medical disorders for which medication may present a considerable risk 3. Abnormal liver function 4. Pervasive developmental disorder, schizophrenia or other psychotic disorders, or eating disorders 5. Currently taking other psychotropic medications from which discontinuation would present a significant risk. Participants may not have discontinued a satisfactory medication to participate 6. Presence or history of major depressive disorder 7. Diagnosis of bipolar disorder 8. A hypomanic/biphasic score of 36 or greater as rated by child's parent on the General Behavior Inventory and confirmed by clinician as indication of mood disorder 9. Active substance abuse disorder or lack of control of substance use that does not allow for safe medication administration 10. Evidence of current child abuse or neglect 11. History of suicide attempt in the past year or current suicidal ideation with plan or intent, or both 12. Family history of type II diabetes in ≥ 2 first-degree relatives, defined as biological parents or full biological siblings, or both
Interventions	At baseline, participants were randomised to OROS-methylphenidate + placebo or OROS-methylphenidate + risperidone. OROS methylphenidate was initiated at 18 mg each morning and titrated up to a limit of 54 mg or 72 mg (depending on weight: < 25 kg and > 25 kg, respectively) by week 2. If participants did not demonstrate sufficient improvement on methylphenidate by end of week 3 (defined as normative value + 0.5 SD on the NCBRF D-Total score and the Clinical Global Impressions Scale (CGI-I) of 1, parent training or risperidone was added. However, if the second drug was not needed at week 3 and the child's behaviour subsequently deteriorated on the optimal stimulant dose, the prescriber was able to add the second medication through the sixth week of the study. At end of week 9, participants were classified as clinical responders (CGI-I = 1-2 and NCBRF D-Total reduced by 25% relative to baseline). Responders were followed on their originally assigned conditions for 12 weeks of double-blinded extension. Non-responders were treated clinically, as appropriate, based on the study team's best judgment. 1-year follow-up assessment Treatment compliance: no information Although the stimulant of first choice in this trial was OROS methylphenidate, owing primarily to its extended duration of action, it was not mandated in the protocol so as not to exclude children who had prior poor response or who had difficulty swallowing pills. It was required that the substituted medication be a stimulant and that the dosage was matched in potency to the OROS methylphenidate
Outcomes	Screen and endpoint: ECG Week 0, 1-2, 3, 4-8, 9, 13-17, 21, 52: heart rate, blood pressure, height, weight, and hip-waist ratio, extrapyramidal symptoms, appetite, sleep patterns Parent-rated adverse event scale specific to stimulants or teacher rated stimulant adverse events Treatment-induced motor disturbances: clinician rated Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Rating Scale, Barnes Akathisia Scale
Notes	Comment: design article regarding the TOSCA study Sample calculation: yes Ethics approval: yes Funding: National Institute of Mental Health (NIMH)

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TOSCA 2011 *(Continued)*

	Adverse event data regarding the open-label phase and the placebo + methylphenidate + PT group in the parallel phase, extension phase and follow-up are usable according to the inclusion criteria for this review Personal correspondence with the authors in June 2013: distribution of adverse event data are not possible until after publication (Aman 2013 [pers comm])

Waldon 2016

Methods	Unclear
Participants	Unclear
Interventions	Unclear
Outcomes	Unclear
Notes	Not able to retrIeve full-text report

Yusufoglu 2014

Methods	A patient report of acneiform eruptions and dermatitis during methylphenidate treatment
Participants	12-year-old boy with a diagnosis of ADHD
Interventions	Methylphenidate, type not stated
Outcomes	Non-serious adverse events
Notes	Conference abstract. Not able to retrieve additional data

ADHD: attention deficit hyperactivity disorder; **DSM-III**: *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*; **DSM-III-R**: *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*; **DSM-IV**: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; **ECG**: electrocardiogram; **IQ**: intelligence quotient; **OROS**: osmotic controlled-release delivery system; **RCT**: randomised clinical trial.

Characteristics of ongoing studies *[ordered by study ID]*

Beau 2009

Trial name or title	Spontaneous report safety signals profile and comparative Bayesian analysis of ADHD medication in children in the UK
Methods	Examines safety signal profiles in the UK Yellow Card database
Participants	Children under 16 years' old using methylphenidate and atomoxetine
Interventions	Methylphenidate and atomoxetine
Outcomes	Psychiatric adverse events. White blood cell count, tics, alopecia, arrhythmia, suicidal ideation, depressed mood, aggression and appetite

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Beau 2009 *(Continued)*

Starting date	October 2008
Contact information	Liam.smeeth Email: liam.smeeth@lshtm.ac.uk
Notes	Correspondence with authors October 2013. The paper will not be published in a foreseeable future (Smeeth 2013 [pers comm])

Bottelier 2014

Trial name or title	The effects of psychotropic drugs on developing brain (ePOD) study: methods and design
Methods	Double-blind, placebo-controlled trial
Participants	Boys aged 10-12 years and adults aged 23-40 years for methylphenidate treatment 50 children and 50 adult male patients, diagnosed with ADHD (all subtypes), and in need of pharmacological therapy
Interventions	Methylphenidate, type not specified
Outcomes	Adverse events, disruptive behaviours, functioning, depression, anxiety, among others
Starting date	Not stated
Contact information	Liesbeth Reneman Email: L.Reneman@amc.uva.nl
Notes	Ongoing study. Protocol published

Dahlgren 2012

Trial name or title	Overweight and obese children with diagnosed attention deficit hyperactivity disorder have a favourable weight loss with methylphenidate 1-year data
Methods	Retrospectively investigated records of children with ADHD
Participants	100 children with ADHD, 24 of whom (14 females and 10 males, age range 5.9-16.8 years) were overweight (BMI z score < 1.5 SD)
Interventions	Methylphenidate (dose range 10-54 mg). Type not specified
Outcomes	BMI, height
Starting date	Not stated
Contact information	jovanna.dahlgren@vgregion.se
Notes	Correspondence with Jovanna Dahlgren in August 2013 revealed that a paper is in preparation (Dahlgren 2013 [pers comm])

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Djurkovic-Lazic 2009

Trial name or title	School children with ADHD - effects of once-daily OROS methylphenidate treatment ADHD symptoms included improvement academic functioning
Methods	An ongoing cohort study of children and adolescents aged 7 to 14 years with ADHD treated with OROS-methylphenidate
Participants	Number of participants screened: not stated Number of participants included: 32 Number of participants followed up: not stated Number of withdrawals: not stated Diagnosis of ADHD: DSM-IV (subtype not stated) Age: range 7-14 years' old IQ: not stated Sex: not stated Methylphenidate-naïve: not stated Ethnicity: not stated Country: Serbia Comorbidity: not stated Comedication: not stated Sociodemographics: not stated *Inclusion criteria* 1. Children with ADHD symptoms, team-diagnosed by a psychiatrist, psychologist and neurologist
Interventions	Methylphenidate type: OROS Methylphenidate dosage: 18-54 mg Administration schedule: once daily Duration of intervention: not stated Treatment compliance: not stated
Outcomes	Adverse events, vital signs, EEG (no further data)
Starting date	—
Contact information	J Djurkovic-Lazic, Institute for Psychophisiological and Speach Pathology, Belgrade
Notes	Sample calculation: not stated Ethics approval: not stated Funding/vested interests: not stated Authors' affiliations: not stated

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Djurkovic-Lazic 2009 *(Continued)*

	Key conclusions of the study authors: (PRELIMINARY) "Besides our expecting on reduction of ADHD symptoms with minimal effects on vital sings, values on growth, tick, laboratory test, it considers too, better academic functioning social relationship with continual therapy" *Comments from the review authors*: we have not been able to obtain the full-text report. Therefore, the data are incomplete.

Díez-Suárez 2015

Trial name or title	Long-term effects of medication for ADHD in weight and height in children and adolescents
Methods	A longitudinal, naturalistic follow-up study of 497 children with ADHD
Participants	ADHD diagnosis, type not stated. Mean age 10.66 (SD 3.84) years. 79.9% males
Interventions	Methylphenidate, type not stated
Outcomes	Weight, height
Starting date	Not stated
Contact information	Azucena Diez-Suarez. www.linkedin.com/in/azucena-d%C3%ADez-su%C3%A1rez-10b14245 atpacientecun@unav.es
Notes	Personal email correspondence with the authors in June 2016: awaiting the full publication (Castro-Manglano 2016 [pers comm])

Gau 2010

Trial name or title	The influence of using methylphenidate on the coming up of psychiatric disorders in children with ADHD
Methods	Database study of children with new onset ADHD between 1999 and 2003 and age- and sex-matched healthy controls
Participants	2109 children (aged > 18 years) with onset of ADHD. Type of ADHD not stated. Mean onset age of 7.3 years, 79.8% were males
Interventions	Methylphenidate, type not stated
Outcomes	Incidence of other comorbid psychiatric disorders (i.e. depression, bipolar disorder, dysthymia, anxiety, conduct disorder and oppositional defiant disorder)
Starting date	Not found
Contact information	Dr Churn-Shiouh Gau Email: csgau206@cde.org.tw
Notes	Correspondence with authors in October 2013: no publications yet (Gau 2013b [pers comm])

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Houmann 2011

Trial name or title	Individualised methylphenidate therapy based on pharmacogenetics: focus on carboxylesterase1 (CES1)
Methods	Multicentre study on CES1 genotype response in ADHD children
Participants	200 drug-naïve children with ADHD
Interventions	Methylphenidate, type not specified
Outcomes	CES1 genotype response, adverse reaction, discontinuation of treatment, treatment failure
Starting date	2011, otherwise not specified
Contact information	Tine Bodil Houmann Email: Tine.Houmann@regionh.dk
Notes	Personal email correspondence with the first author in September 2013 revealed the study is ongoing (Houmann 2013 [pers comm])

Yook 2012

Trial name or title	Obesity is associated with non-response to prolonged-release methylphenidate treatment in ADHD
Methods	8-week, open-label trial
Participants	90 children and adolescents, aged 6-15 years' old, diagnosed with ADHD (types not specified)
Interventions	Up to 54 mg of OROS-methylphenidate
Outcomes	ADHD symptoms, functioning, Barkley Stimulant Side Effect Rating Scale
Starting date	Not stated
Contact information	Ki-Hwan Yook Email: cha99@cha.ac.kr
Notes	Correspondence with first author in August 2013: no publications yet (Yook 2013 [pers comm])

ADHD: attention deficit hyperactivity disorder; **BMI**: body mass index; **DSM-IV**: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;* **OROS**: osmotic controlled-release delivery system; **SD**: standard deviation.

DATA AND ANALYSES

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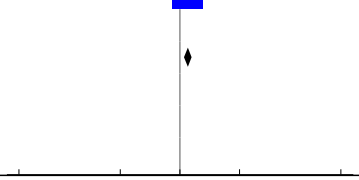
Comparison 1. Comparative studies: number of serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any serious adverse events	2	72005	Risk Ratio (IV, Random, 95% CI)	1.36 [1.17, 1.57]
2 Central nervous system	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1 Seizures	1	234	Risk Ratio (IV, Random, 95% CI)	1.31 [0.07, 23.74]
2.2 Psychotic disorder	1	71771	Risk Ratio (IV, Random, 95% CI)	1.36 [1.17, 1.57]
3 Cardiovascular and respiratory system			Other data	No numeric data
3.1 Arrhythmias			Other data	No numeric data
3.2 Hypertension			Other data	No numeric data
3.3 Myocardial infarction			Other data	No numeric data
3.4 Ischaemic stroke			Other data	No numeric data
3.5 Heart failure			Other data	No numeric data

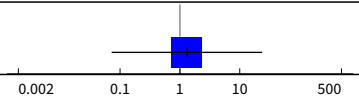
Analysis 1.1. Comparison 1 Comparative studies: number of serious adverse events, Outcome 1 Any serious adverse events.

Study or subgroup	Methylphenidate n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Hemmer 2001	4/205	0/29		0.25%	1.31[0.07,23.74]
Shyu 2015	856/52646	229/19125		99.75%	1.36[1.17,1.57]
Total (95% CI)	**52851**	**19154**		**100%**	**1.36[1.17,1.57]**
Total events: 860 (Methylphenidate), 229 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.98); I^2=0%					
Test for overall effect: Z=4.14(P<0.0001)					



Analysis 1.2. Comparison 1 Comparative studies: number of serious adverse events, Outcome 2 Central nervous system.

Study or subgroup	Methylphenidate n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 Seizures					
Hemmer 2001	4/205	0/29		100%	1.31[0.07,23.74]



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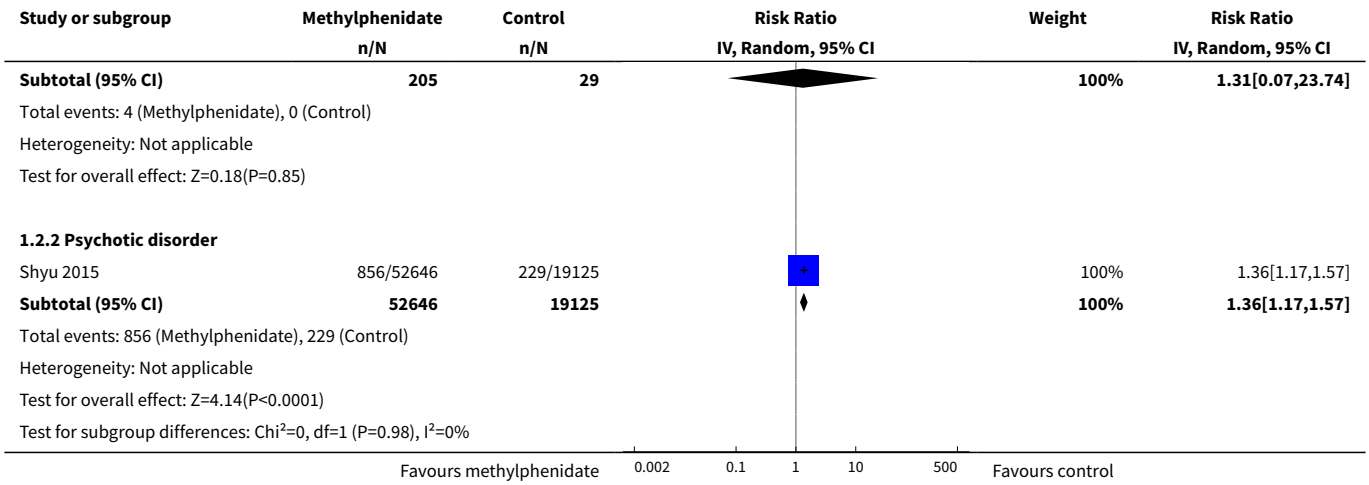

Analysis 1.3. Comparison 1 Comparative studies: number of serious adverse events, Outcome 3 Cardiovascular and respiratory system.

Study	Cardiovascular and respiratory system
Arrhythmias	
Shin 2016	RR 1.61 (95% CI 1.48 to 1.74)
Hypertension	
Shin 2016	RR 1.07 (95% CI 0.94 to 1.22)
Myocardial infarction	
Shin 2016	RR 1.33 (95% CI 0.90 to 1.98)
Ischaemic stroke	
Shin 2016	RR 0.70 (95% CI 0.49 to 1.01)
Heart failure	
Shin 2016	RR 0.54 (95% CI 0.30 to 0.96)

Comparison 2. Comparative studies: number of participants with non-serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Central nervous system: sleep-related adverse events	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Insomnia and sleep problems	3	425	Risk Ratio (IV, Random, 95% CI)	2.58 [1.24, 5.34]
1.2 Nightmares	1	23	Risk Ratio (IV, Random, 95% CI)	1.15 [0.41, 3.21]
1.3 Snoring	1	23	Risk Ratio (IV, Random, 95% CI)	4.62 [0.25, 86.72]
1.4 Non-breathing or gasping while sleeping	1	23	Risk Ratio (IV, Random, 95% CI)	2.77 [0.12, 61.65]
1.5 Sleepwalking	1	23	Risk Ratio (IV, Random, 95% CI)	2.75 [0.33, 22.69]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Various sleep positions	1	23	Risk Ratio (IV, Random, 95% CI)	2.77 [0.12, 61.65]
1.7 Enuresis	1	23	Risk Ratio (IV, Random, 95% CI)	4.62 [0.25, 86.72]
1.8 Talking in sleep	1	23	Risk Ratio (IV, Random, 95% CI)	0.46 [0.05, 4.38]
2 Central nervous system: other specific sleep-related adverse events	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Number of hours sleep	1	10	Mean Difference (IV, Random, 95% CI)	-0.65 [-1.32, 0.02]
2.2 Number of nocturnal movements	1	10	Mean Difference (IV, Random, 95% CI)	-27.84 [-57.90, 2.22]
2.3 Sleep quality	1	10	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.74, 0.34]
3 Central nervous system: other specific adverse events	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1 Headache	1	235	Risk Ratio (IV, Random, 95% CI)	8.13 [0.48, 137.74]
3.2 Dizziness	1	335	Risk Ratio (IV, Random, 95% CI)	4.00 [0.23, 69.27]
4 Cardiovascular and respiratory system	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Systolic blood pressure	1	43	Mean Difference (IV, Random, 95% CI)	0.10 [-6.27, 6.47]
4.2 Diastolic blood pressure	1	43	Mean Difference (IV, Random, 95% CI)	3.50 [-1.42, 8.42]
4.3 Pulse rate	1	43	Mean Difference (IV, Random, 95% CI)	0.60 [-7.95, 9.15]
5 Gastrointestinal system	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1 Nausea	1	335	Risk Ratio (IV, Random, 95% CI)	2.64 [0.34, 20.29]
5.2 Abdominal pain	1	335	Risk Ratio (IV, Random, 95% CI)	0.79 [0.16, 3.84]
5.3 Decreased appetite	1	335	Risk Ratio (IV, Random, 95% CI)	15.06 [2.12, 106.83]
6 Musculoskeletal system	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Height	2	93	Std. Mean Difference (IV, Random, 95% CI)	-0.93 [-2.61, 0.75]
6.2 Weight	2	93	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-1.16, 0.62]

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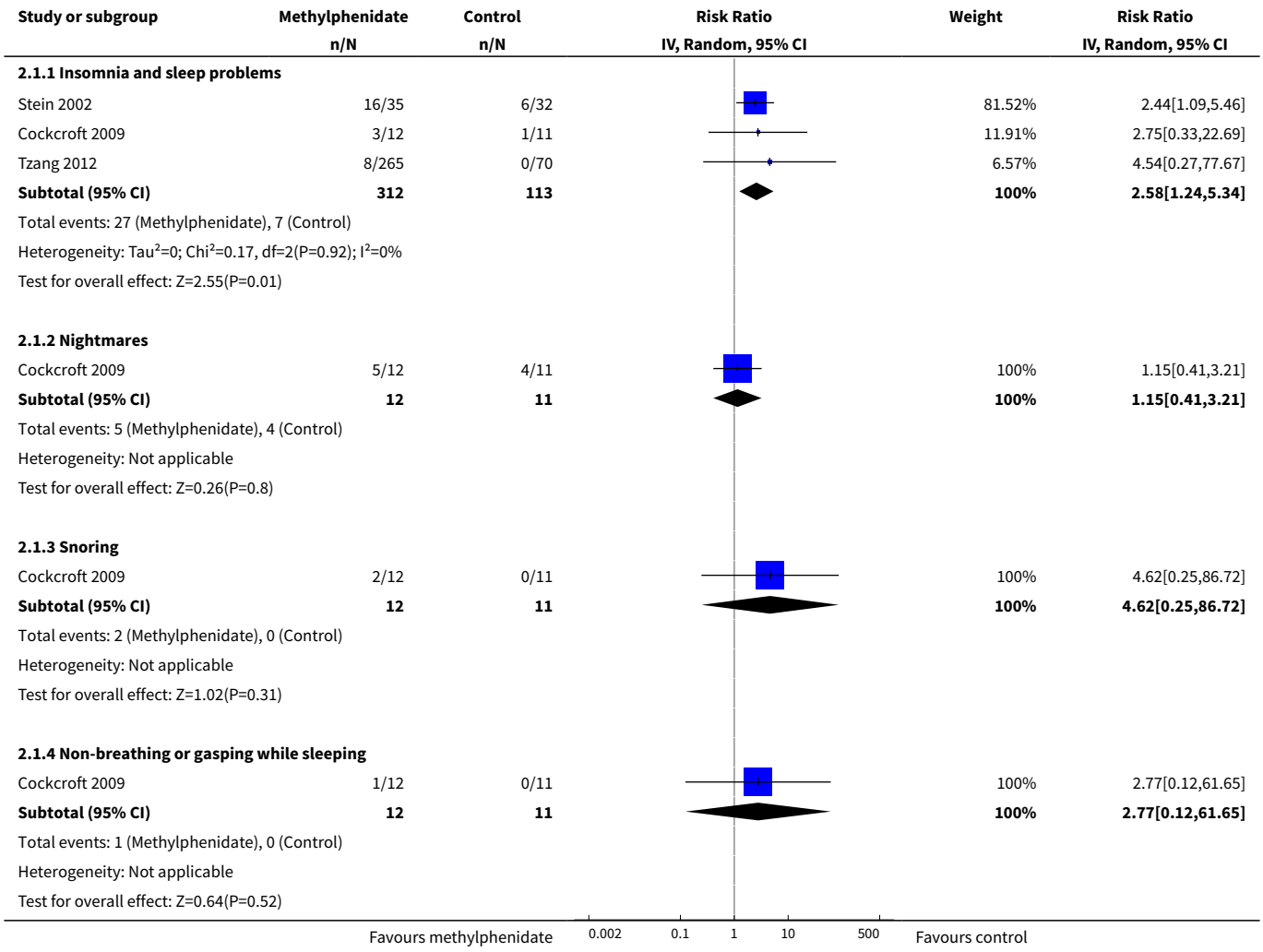
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Musculoskeletal system: body mass index (BMI)	1	43	Mean Difference (IV, Random, 95% CI)	-1.60 [-2.96, -0.24]
8 Musculoskeletal system: z scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Height z score	1	275	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.43, 0.05]
8.2 Weight z score	1	275	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.30, 0.16]
8.3 BMI z score	1	275	Mean Difference (IV, Random, 95% CI)	0.01 [-0.22, 0.24]

Analysis 2.1. Comparison 2 Comparative studies: number of participants with non-serious adverse events, Outcome 1 Central nervous system: sleep-related adverse events.



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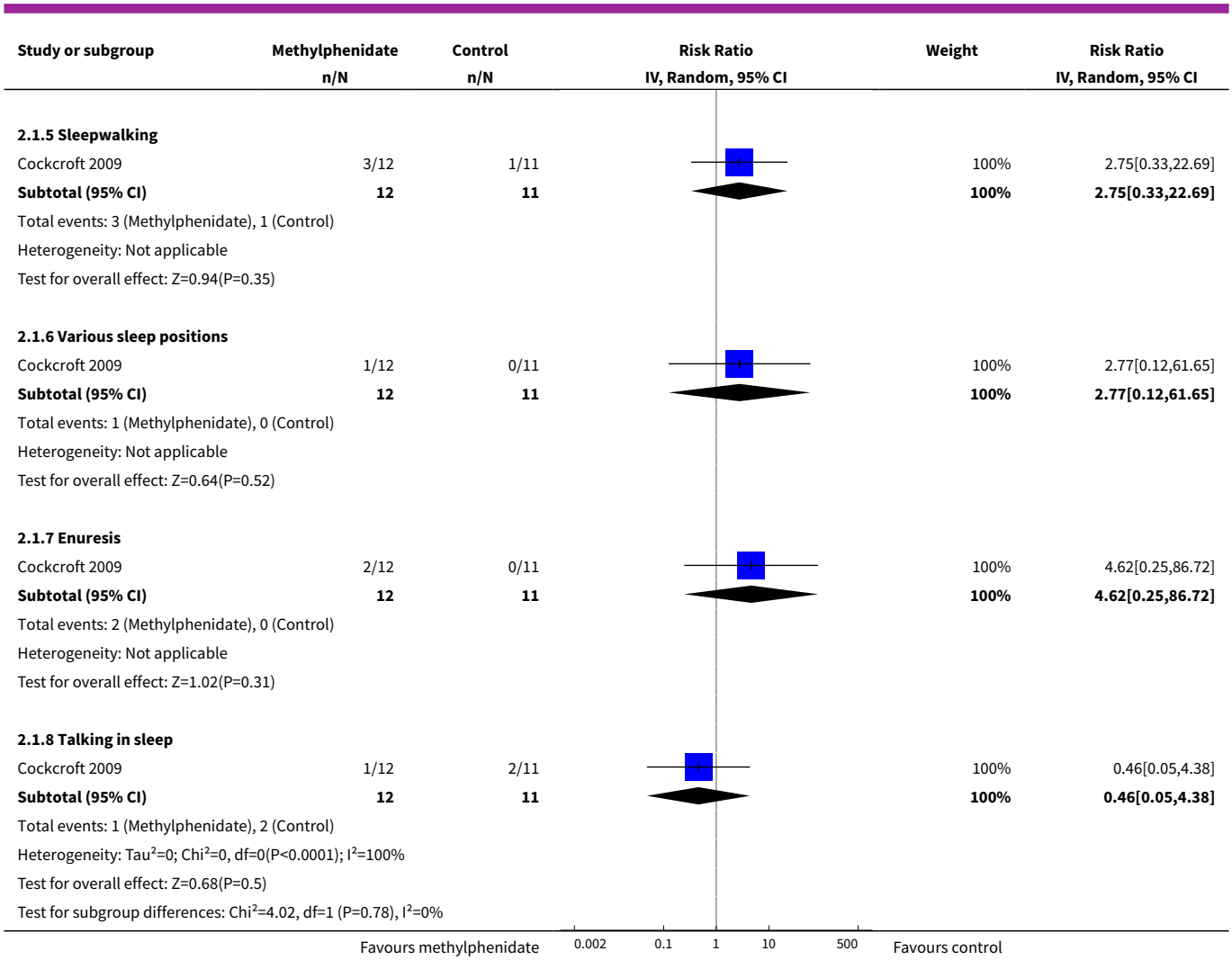
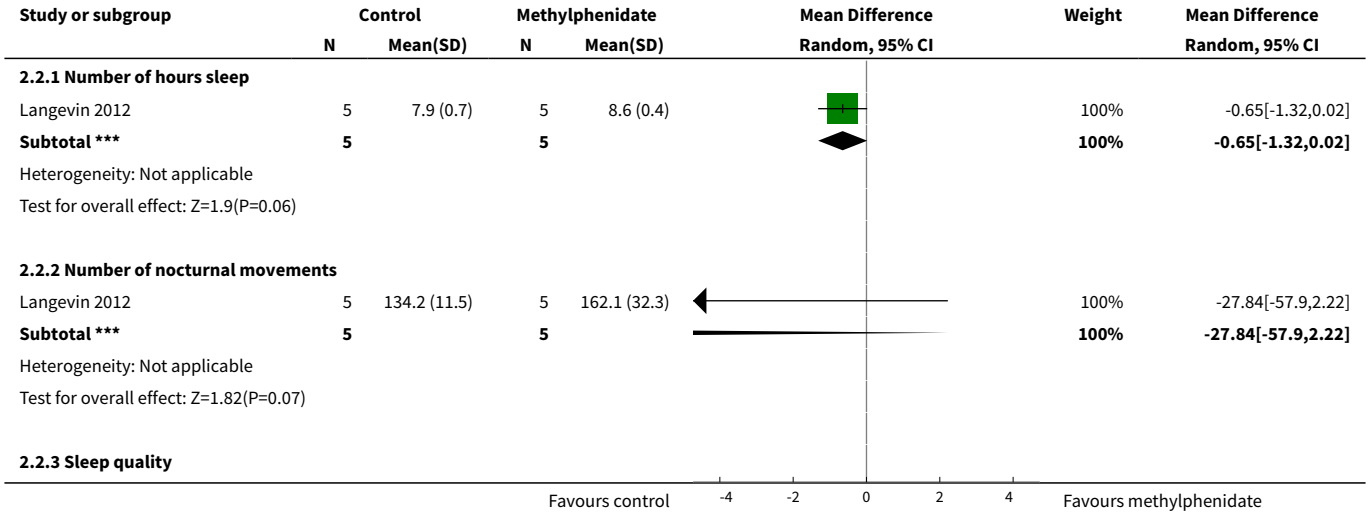


Analysis 2.2. Comparison 2 Comparative studies: number of participants with non-serious adverse events, Outcome 2 Central nervous system: other specific sleep-related adverse events.



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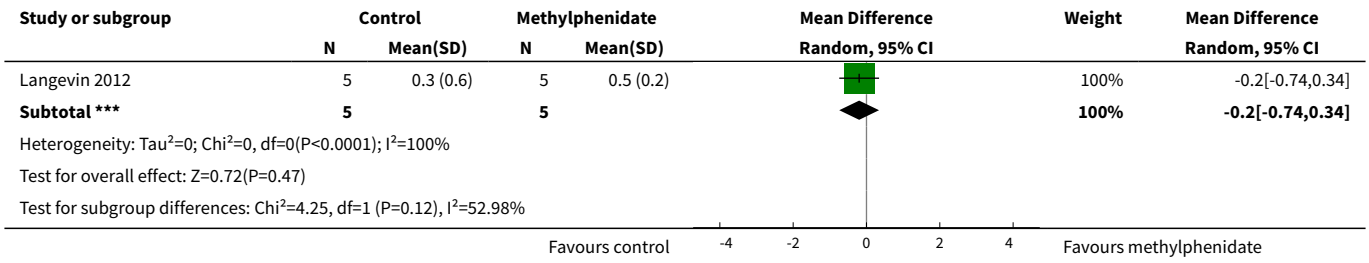
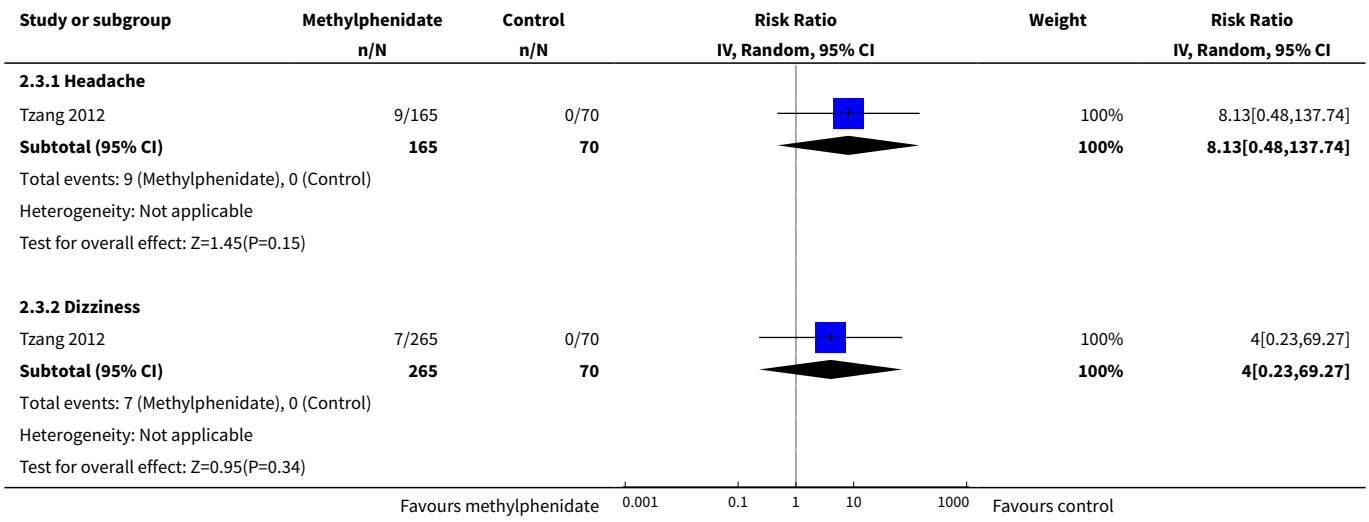
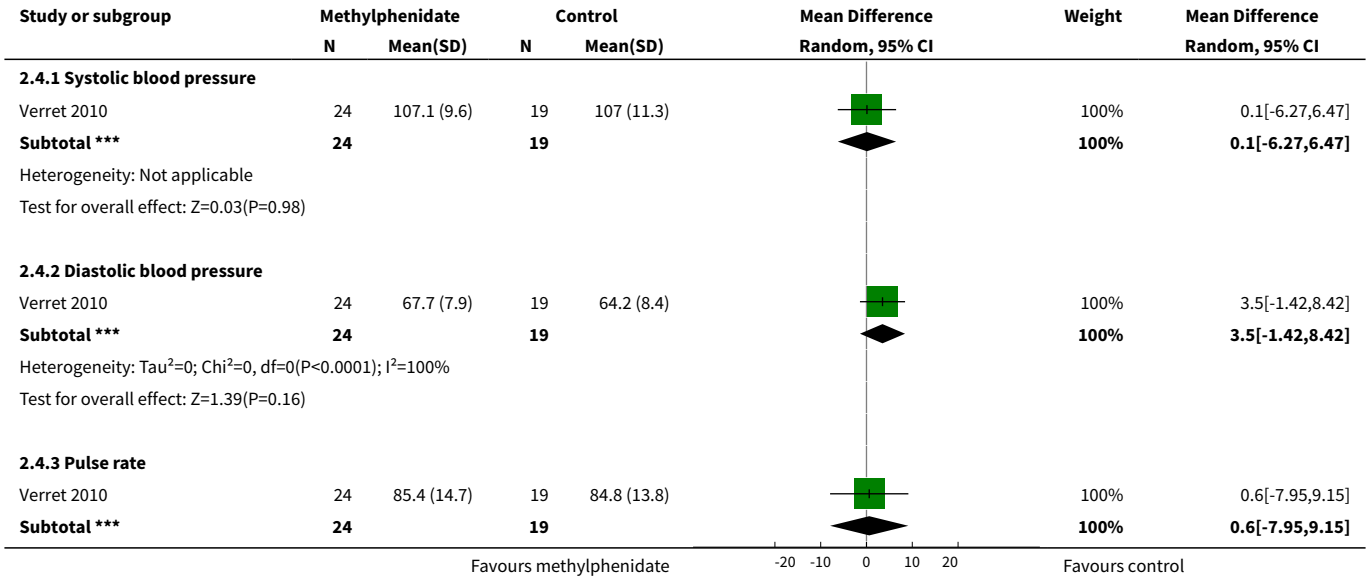


Analysis 2.3. Comparison 2 Comparative studies: number of participants with non-serious adverse events, Outcome 3 Central nervous system: other specific adverse events.



Analysis 2.4. Comparison 2 Comparative studies: number of participants with non-serious adverse events, Outcome 4 Cardiovascular and respiratory system.



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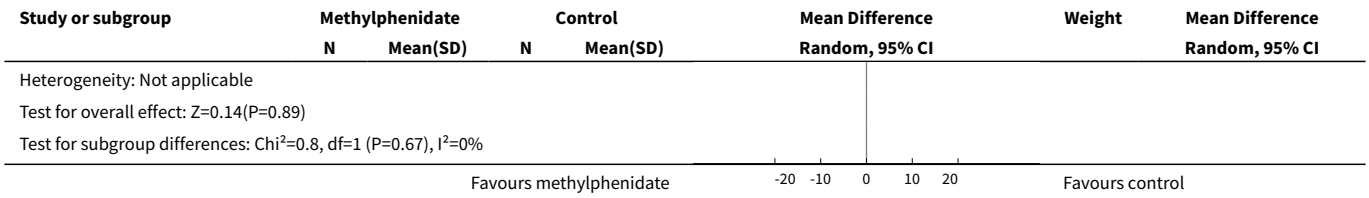
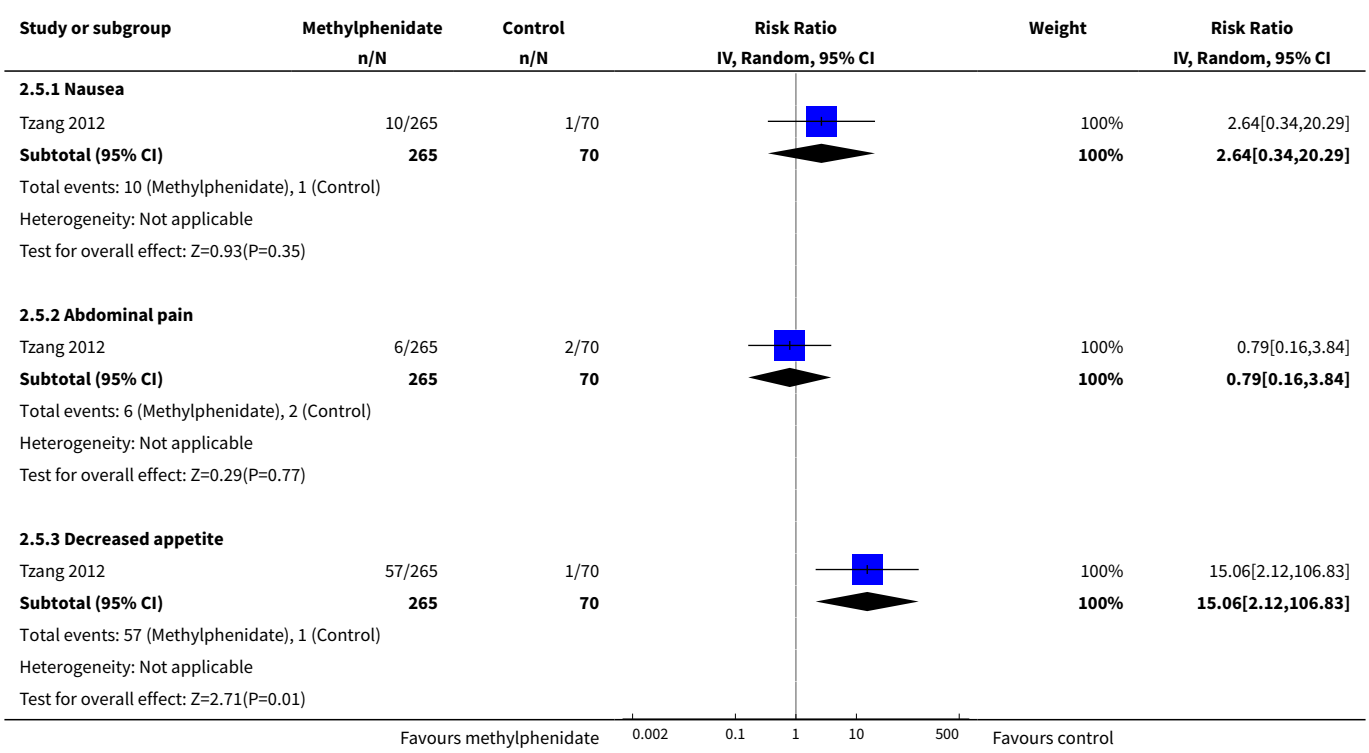
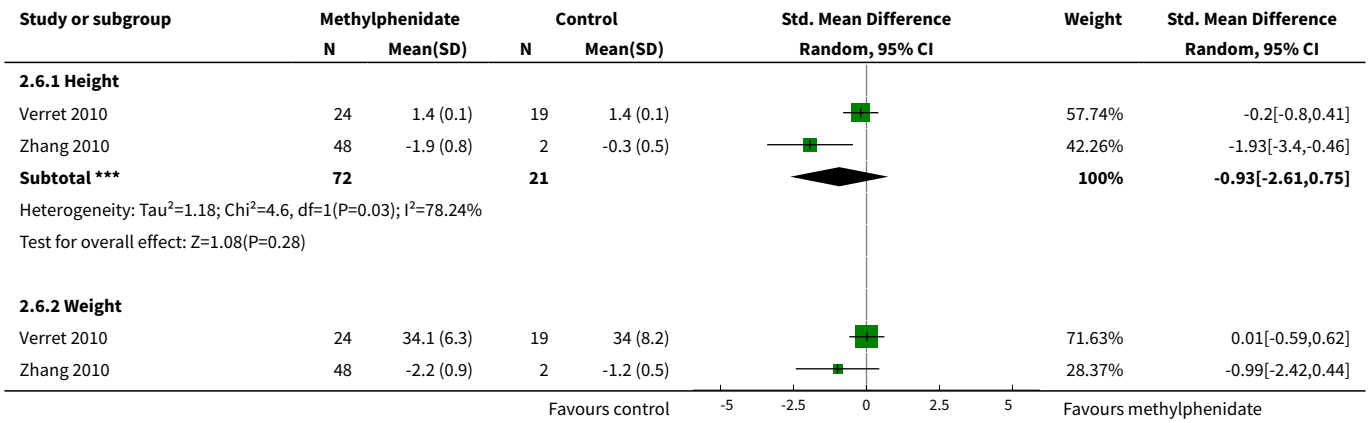


Analysis 2.5. Comparison 2 Comparative studies: number of participants with non-serious adverse events, Outcome 5 Gastrointestinal system.



Analysis 2.6. Comparison 2 Comparative studies: number of participants with non-serious adverse events, Outcome 6 Musculoskeletal system.



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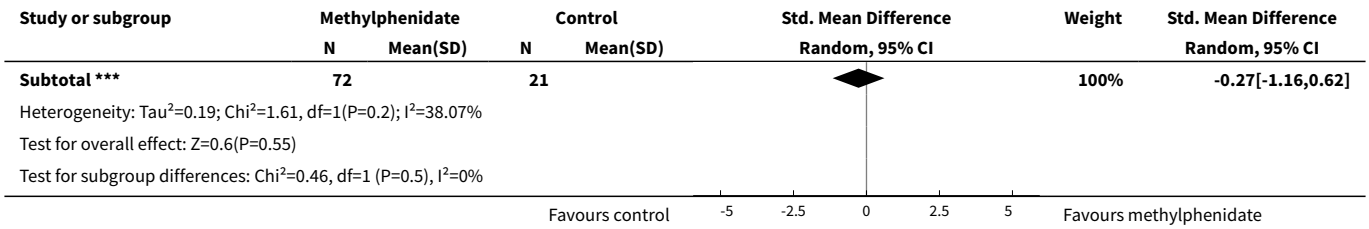
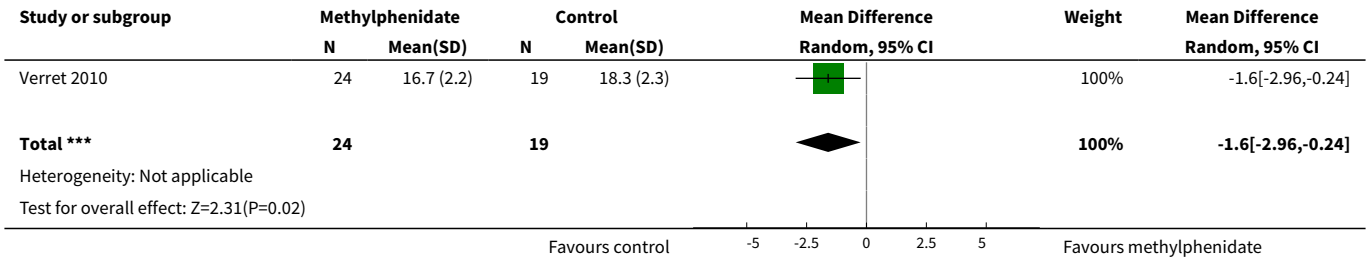
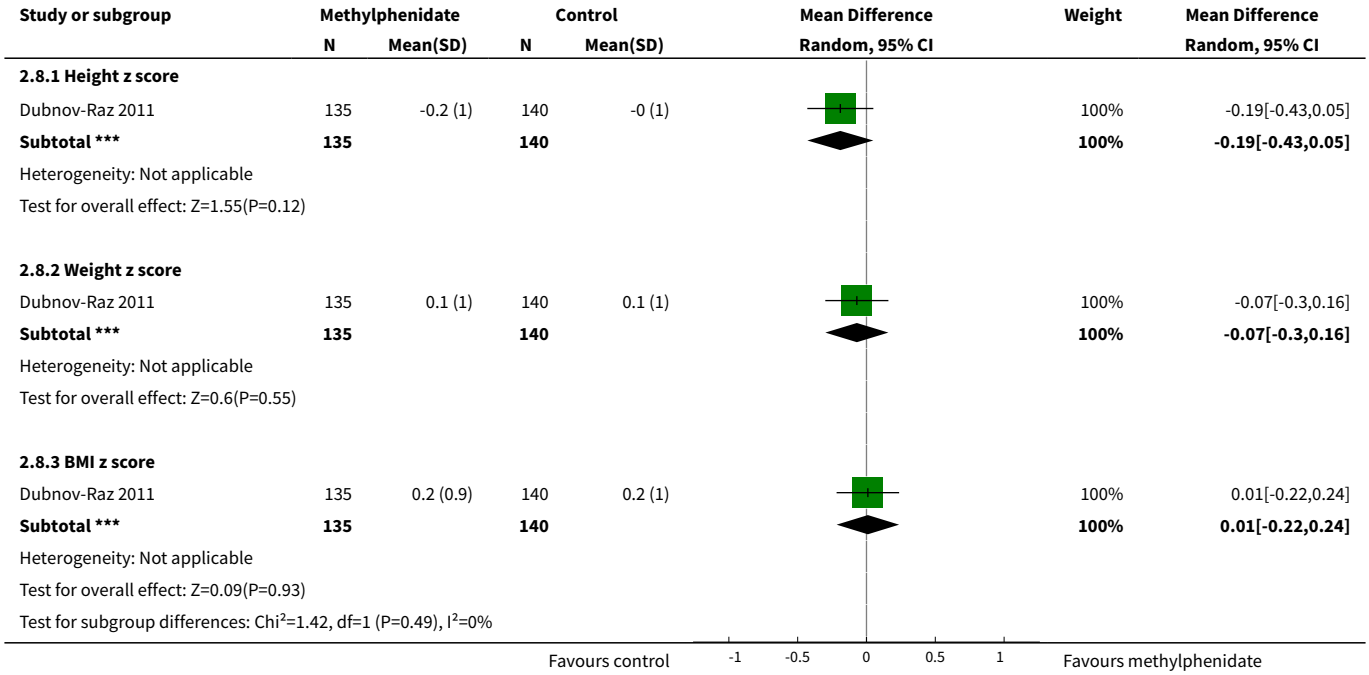


Analysis 2.7. Comparison 2 Comparative studies: number of participants with non-serious adverse events, Outcome 7 Musculoskeletal system: body mass index (BMI).



Analysis 2.8. Comparison 2 Comparative studies: number of participants with non-serious adverse events, Outcome 8 Musculoskeletal system: z scores.



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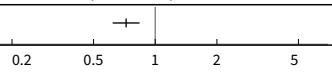
Comparison 3. Comparative studies: number of participants withdrawn from methylphenidate treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants withdrawn from methylphenidate for unknown reasons	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Comparative studies: number of participants withdrawn from methylphenidate treatment, Outcome 1 Proportion of participants withdrawn from methylphenidate for unknown reasons.

Study or subgroup	Methylphenidate n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Zhang 2010	98/146	27/29		0.72[0.62,0.84]



Comparison 4. Non-comparative studies: proportion of participants with serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any serious adverse event			Other data	No numeric data
2 Central nervous system			Other data	No numeric data
2.1 Sudden death			Other data	No numeric data
2.2 Suicide			Other data	No numeric data
2.3 Suicide attempt			Other data	No numeric data
2.4 Suicide thoughts			Other data	No numeric data
2.5 Psychotic symptoms			Other data	No numeric data
2.6 Seizure			Other data	No numeric data
2.7 Syncope			Other data	No numeric data
2.8 Tremor			Other data	No numeric data
2.9 Psychiatric problems			Other data	No numeric data
2.10 Severe depression			Other data	No numeric data
2.11 Overdose			Other data	No numeric data
2.12 Eating disorder			Other data	No numeric data
2.13 Aphasia			Other data	No numeric data
2.14 Headache			Other data	No numeric data

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.15 Neurological disorder			Other data	No numeric data
2.16 Sleep disorder			Other data	No numeric data
2.17 Mood disorder			Other data	No numeric data
2.18 Loss of consciousness			Other data	No numeric data
2.19 Family stress			Other data	No numeric data
2.20 Impotence			Other data	No numeric data
2.21 Severe aggression			Other data	No numeric data
2.22 Severe anorexia			Other data	No numeric data
2.23 Amphetamine intoxication			Other data	No numeric data
3 Cardiovascular and respiratory system			Other data	No numeric data
3.1 Respiratory, thoracic and mediastinal disorders			Other data	No numeric data
3.2 Cardiac problems			Other data	No numeric data
3.3 Tachycardia			Other data	No numeric data
3.4 Severe hypertension			Other data	No numeric data
3.5 Epistaxsis			Other data	No numeric data
3.6 Viral illness			Other data	No numeric data
4 Gastrointestinal system			Other data	No numeric data
4.1 Gastrointestinal disease			Other data	No numeric data
4.2 Liver disease			Other data	No numeric data
5 Musculoskeletal system: fractures			Other data	No numeric data
6 Immune system: autoimmune disease			Other data	No numeric data

Analysis 4.1. Comparison 4 Non-comparative studies: proportion of participants with serious adverse events, Outcome 1 Any serious adverse event.

	Any serious adverse event	
Study	Symptoms	Adverse events/total number of participants
Altin 2013	No patients experienced any serious adverse events	0/221
Arabgol 2015	Severe anorexia	1/18

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Any serious adverse event		
Study	**Symptoms**	**Adverse events/total number of participants**
Ardic 2014	Serious adverse events	0/101
Arnold 2004	Serious adverse events	3/89
Arnold 2010	Acute depression and suicide attempt	1/150
Ashkenasi 2011	Hallucinations	1/26
Berek 2011	Serious adverse events	4/822
Cherland 1999	Serious adverse events	13/98
Chou 2012b	Serious adverse events	0/230
Cortese 2015	Serious adverse events	64/1426
Davari-Ashtiani 2010	Serious adverse events	0/16
Dittmann 2014	Serious adverse events	0/247
Döpfner 2011a, OBSEER	Serious adverse events	21/777
Döpfner 2011b	Serious adverse events	38/822
Findling 2009	Serious adverse events	3/157
Germinario 2013	Serious adverse events	7/1098
Gerwe 2009	Serious adverse events	2/263
Haertling 2015	Serious adverse events	3/239
Hammerness 2009	Participants affected or at risk	5/57
Hammerness 2012	Serious adverse events	0/10
Hulvershorn 2012	Serious adverse events	0/25
Jafarinia 2012	Serious adverse events	0/20
Jensen 1999 (MTA)	Serious adverse events	1/245
Kemner 2005 (FOCUS)	Sudden death	0/850
Kim 2011	Serious adverse events	0/97
Lakic 2012	Strong depressive symptoms	1/68
Lee 2014	Serious adverse events	542/4055
Li 2011	Serious adverse events	0/36
Maayan 2009	Serious adverse events	0/8
McCarthy 2009	Sudden death	5/5351
McCracken 2016	Serious adverse events	0/61
Mohammadi 2004	Serious adverse events	3/116
Pierce 2010	Serious adverse events	0/71
Remschmidt 2005	Serious adverse events	4/89
Schmidt 2002	Generalized tonic-clonic seizure	1/124
Schulz 2010	Serious adverse events	0/145
Shin 2016	Serious adverse events	1224/123,636
Sobanski 2013	Serious adverse events	8/347
Steele 2006	Serious adverse events	0/73
Su 2015	Serious adverse events	0/239
Valdizán Usón 2013	Serious adverse events	0/689
Warshaw 2010	Serious adverse events	0/260
Weiss 2007	Serious adverse events	0/79
Wigal 2011	Serious adverse events	0/31
Wigal 2013	Serious adverse events	0/39
Wigal 2015	Serious adverse events	1/200
Wilens 2006	Serious adverse events	1/87
Wilens 2008	Serious adverse events	0/127
Winterstein 2009	Serious adverse events	171/18,238
Zheng 2015	Serious adverse events	0/149

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Analysis 4.2. Comparison 4 Non-comparative studies: proportion of participants with serious adverse events, Outcome 2 Central nervous system.

Central nervous system		
Study	**Symptom**	**Adverse events/total number of participants**
	Sudden death	
Kemner 2005 (FOCUS)	Sudden death	0/850
Lee 2014	Sudden death	7/100
McCarthy 2009	Sudden death	1/5351
	Suicide	
Jensen 1999 (MTA)	Suicide	1/245
McCarthy 2009	Suicide	4/5351
	Suicide attempt	
Arnold 2010	Acute depression and suicide attempt	1/150
Lee 2014	Suicide attempt	6/100
Remschmidt 2005	Suicide attempt	1/89
	Suicide thoughts	
Remschmidt 2005	Depressive, suicidal thoughts	1/89
Wilens 2006	Serious adverse events were reported in only 1 participant during the open-label, dose-titration phase of the study	1/87
	Psychotic symptoms	
Cherland 1999	Psychotic symptoms	7/96
Cortese 2015	Hallucinations	2/1426
Findling 2009	Paranoid behavior disorder	3/157
Green 2011	Hallucinations	0/22
Mohammadi 2004	Hallucinations	0/11
Na 2013	Hallucinations	0/55
Remschmidt 2005	Delusions	1/89
Shyu 2015	Psychotic disorders	856/52,646
Su 2015	Hallucinations	1/239
Wilens 2005	Hallucinations	0/369
	Seizure	
Cortese 2015	Seizures	3/1426
Schmidt 2002	Generalized tonic-clonic seizure	1/124
	Syncope	
Findling 2009	Syncope	1/327
Germinario 2013	Vasovagal syncope	1/1098
	Tremor	
Arnold 2004	Tremor	1/89
Gerwe 2009	Tremor	1/306
	Psychiatric problems	
Arnold 2004	Rambling speech	1/89
Cortese 2015	Psychiatric disorder	5/1426
Germinario 2013	Psychiatric problems	5/1098
	Severe depression	
Cherland 1999	Severe depression	1/98
Lakic 2012	Strong depressive symptoms	1/68
	Overdose	
Lee 2014	Overdose	6/100
	Eating disorder	
Cortese 2015	Eating disorder	1/1426
	Aphasia	
Cortese 2015	Aphasia	1/1426
	Headache	
Cortese 2015	Headache	3/1426
	Neurological disorder	
Cortese 2015	Neurologicaol disorder	2/1426

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Central nervous system		
Study	**Symptom**	**Adverse events/total number of participants**
	Sleep disorder	
Cortese 2015	Sleep disorder	1/1426
	Mood disorder	
Cortese 2015	Mood disorder	1/1426
	Loss of consciousness	
Gerwe 2009	Short loss of consciousness	1/306
	Family stress	
Gerwe 2009	Family stress	1/306
	Impotence	
Germinario 2013	Impotence	1/1098
	Severe aggression	
Remschmidt 2005	Severe aggression	1/89
	Severe anorexia	
Arabgol 2015	Severe anorexia	1/18
	Amphetamine intoxication	
Cherland 1999	Amphetamine intoxication	3/98

Analysis 4.3. Comparison 4 Non-comparative studies: proportion of participants with serious adverse events, Outcome 3 Cardiovascular and respiratory system.

Cardiovascular and respiratory system		
Study	**Symptom**	**Adverse events/total number of participants**
	Respiratory, thoracic and mediastinal disorders	
Germinario 2013	Aortic embolism	1/1098
Hammerness 2009	Spontaneous pneumothorax	1/57
	Cardiac problems	
Arman 2013	Cardiac rhythm abnormalities	0/15
Germinario 2013	Cardiovascular problems	2/1098
Winterstein 2009	Serious cardiac problems	171/18,238
	Tachycardia	
Cortese 2015	Tachycardia	2/1426
Germinario 2013	Tachycardia	2/1098
	Severe hypertension	
Cortese 2015	Severe hypertension	2/1426
	Epistaxsis	
Cortese 2015	Epistaxsis	1/1426
	Viral illness	
Hammerness 2009	Participants affected by viral illness	1/57

Analysis 4.4. Comparison 4 Non-comparative studies: proportion of participants with serious adverse events, Outcome 4 Gastrointestinal system.

Gastrointestinal system		
Study	**Symptom**	**Adverse events/total number of participants**
	Gastrointestinal disease	
Cortese 2015	Gastrointestinal disease	6/1426
	Liver disease	
Cortese 2015	Hyperbilrubinemia	1/1426

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Analysis 4.5. Comparison 4 Non-comparative studies: proportion of participants with serious adverse events, Outcome 5 Musculoskeletal system: fractures.

Musculoskeletal system: fractures		
Study	**Symptom**	**Adverse events/total number of participants**
Findling 2009	Ankle fracture	1/327
Hammerness 2009	Leg fracture	2/57

Analysis 4.6. Comparison 4 Non-comparative studies: proportion of participants with serious adverse events, Outcome 6 Immune system: autoimmune disease.

Immune system: autoimmune disease		
Study	**Symptom**	**Adverse events/total number of participants**
Cortese 2015	Autoimmune disease	1/1426

Comparison 5. Non-comparative studies: proportion of participants withdrawn from methylphenidate treatment due to serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants withdrawn from methylphenidate treatment due to serious adverse events			Other data	No numeric data
1.1 Serious adverse events			Other data	No numeric data
1.2 Hallucinations			Other data	No numeric data
1.3 Severe anorexia			Other data	No numeric data
1.4 Suicide attempt			Other data	No numeric data
2 Proportion of participants withdrawn from methylphenidate treatment due to adverse events of unknown severity			Other data	No numeric data

Analysis 5.1. Comparison 5 Non-comparative studies: proportion of participants withdrawn from methylphenidate treatment due to serious adverse events, Outcome 1 Proportion of participants withdrawn from methylphenidate treatment due to serious adverse events.

Proportion of participants withdrawn from methylphenidate treatment due to serious adverse events	
Study	
	Serious adverse events
Arabgol 2015	1/18
Arnold 2010	1/171
Ashkenasi 2011	1/26
Faraone 2007a	3/268
Findling 2010	2/162
Na 2013	1/121
Wilens 2005	1/407
	Hallucinations

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Proportion of participants withdrawn from methylphenidate treatment due to serious adverse events	
Study	
Ashkenasi 2011	1/26
Na 2013	1/121
Wilens 2005	1/407
Severe anorexia	
Arabgol 2015	1/18
Suicide attempt	
Arnold 2010	1/171

Analysis 5.2. Comparison 5 Non-comparative studies: proportion of participants withdrawn from methylphenidate treatment due to serious adverse events, Outcome 2 Proportion of participants withdrawn from methylphenidate treatment due to adverse events of unknown severity.

Proportion of participants withdrawn from methylphenidate treatment due to adverse events of unknown severity	
Study	
Altin 2013	4/204
Arnold 2004	4/89
Arnold 2010	4/171
Atzori 2009	17/189
Chou 2012b	15/296
Dodangi 2011	2/15
Döpfner 2011a, OBSEER	26/822
Findling 2009	51/326
Kim 2015b	8/143
Kordon 2011	53/598
Kratochvil 2002	5/44
Lee 2009	28/144
Lee 2012	1/93
Maia 2008	3/39
Mayes 1994	2/69
McCracken 2016	1/69
Mohammadi 2009	6/30
Remschmidt 2005	16/89
Steele 2006	6/73
Yang 2004	2/25
Yang 2012	15/130
Yildiz 2010	3/50

Comparison 6. Non-comparative studies: proportion of participants with adverse events of unknown severity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with adverse events of unknown severity			Other data	No numeric data

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Analysis 6.1. Comparison 6 Non-comparative studies: proportion of participants with adverse events of unknown severity, Outcome 1 Proportion of participants with adverse events of unknown severity.

	Proportion of participants with adverse events of unknown severity	
Study	**Symptom**	**Adverse events/total number of participants**
Barbaresi 2006	Adverse events of unknown seriousness	63/251

Comparison 7. Non-comparative studies: proportion of participants with non-serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-serious adverse events			Other data	No numeric data
2 Central nervous system			Other data	No numeric data
2.1 Affect lability			Other data	No numeric data
2.2 Aggression			Other data	No numeric data
2.3 Anorexia			Other data	No numeric data
2.4 Anxiety			Other data	No numeric data
2.5 Fingernail biting			Other data	No numeric data
2.6 Daydreams			Other data	No numeric data
2.7 Difficulty falling asleep			Other data	No numeric data
2.8 Depression			Other data	No numeric data
2.9 Disturbed sleep			Other data	No numeric data
2.10 Dizziness			Other data	No numeric data
2.11 Drowsiness			Other data	No numeric data
2.12 Dysthymia			Other data	No numeric data
2.13 Emotional lability			Other data	No numeric data
2.14 Euphoria/hypomania			Other data	No numeric data
2.15 Asthenia and fatigue			Other data	No numeric data
2.16 Headache			Other data	No numeric data
2.17 Increased need to sleep			Other data	No numeric data
2.18 Involuntary movements			Other data	No numeric data
2.19 Irritability			Other data	No numeric data
2.20 Nervousness			Other data	No numeric data

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.21 Nightmares			Other data	No numeric data
2.22 Restlessness and agitation			Other data	No numeric data
2.23 Sadness			Other data	No numeric data
2.24 Stares			Other data	No numeric data
2.25 Excessive talking			Other data	No numeric data
2.26 Taciturnity ('talking too little')			Other data	No numeric data
2.27 Tics			Other data	No numeric data
2.28 Isolation and lack of interest in others			Other data	No numeric data
2.29 'Zombie like' demeanour			Other data	No numeric data
2.30 Somnolence			Other data	No numeric data
2.31 Obsession			Other data	No numeric data
2.32 Mood disorder			Other data	No numeric data
2.33 Confusional state			Other data	No numeric data
2.34 Sleep disorder			Other data	No numeric data
2.35 Propensity to cry			Other data	No numeric data
2.36 Sedation			Other data	No numeric data
2.37 Daytime sleepiness			Other data	No numeric data
2.38 Dysphoria			Other data	No numeric data
2.39 Logorrhoea			Other data	No numeric data
2.40 Impaired concentration			Other data	No numeric data
2.41 Difficulty waking up			Other data	No numeric data
2.42 Urinary incontinence			Other data	No numeric data
2.43 Paralysis			Other data	No numeric data
2.44 Affective disorder			Other data	No numeric data
2.45 Jumbled thoughts			Other data	No numeric data
2.46 Bulimia			Other data	No numeric data
2.47 Sleep late			Other data	No numeric data

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.48 Tooth grinding			Other data	No numeric data
2.49 Tremor			Other data	No numeric data
2.50 Stuttering			Other data	No numeric data
2.51 Flushing			Other data	No numeric data
2.52 Apathy			Other data	No numeric data
2.53 Abnormal behaviour			Other data	No numeric data
2.54 Stereotypies			Other data	No numeric data
2.55 Quietness			Other data	No numeric data
2.56 EEG changes			Other data	No numeric data
2.57 Did not like themselves			Other data	No numeric data
2.58 Sleep walking			Other data	No numeric data
2.59 Personality and behaviour disorders			Other data	No numeric data
2.60 Vertigo			Other data	No numeric data
3 Cardiovascular and respiratory system			Other data	No numeric data
3.1 Cough			Other data	No numeric data
3.2 Pharyngolaryngeal pain			Other data	No numeric data
3.3 Upper respiratory tract infection			Other data	No numeric data
3.4 Tachycardia			Other data	No numeric data
3.5 Abnormal ECG			Other data	No numeric data
3.6 Nasal congestion			Other data	No numeric data
3.7 Palpitation			Other data	No numeric data
3.8 Systolic blood pressure			Other data	No numeric data
3.9 Diastolic blood pressure			Other data	No numeric data
3.10 Pulse rate			Other data	No numeric data
3.11 ECG-QT			Other data	No numeric data
3.12 Cold fingers			Other data	No numeric data

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.13 Sweating			Other data	No numeric data
3.14 Hypertension			Other data	No numeric data
3.15 Hypotension			Other data	No numeric data
3.16 Respiratory, thoracic and mediastinal disorders			Other data	No numeric data
3.17 Proportion of patients with micro-nucleated (Mn) peripheral lymphocytes			Other data	No numeric data
4 Gastrointestinal system			Other data	No numeric data
4.1 Abdominal pain			Other data	No numeric data
4.2 Constipation			Other data	No numeric data
4.3 Decreased appetite			Other data	No numeric data
4.4 Decreased weight			Other data	No numeric data
4.5 Diarrhoea			Other data	No numeric data
4.6 Dry mouth			Other data	No numeric data
4.7 Gastrointestinal adverse events			Other data	No numeric data
4.8 Nausea			Other data	No numeric data
4.9 Upset stomach			Other data	No numeric data
4.10 Vomiting			Other data	No numeric data
4.11 Dyspepsia			Other data	No numeric data
4.12 Gastroenteritis			Other data	No numeric data
4.13 Increased appetite			Other data	No numeric data
4.14 Xerostomia			Other data	No numeric data
5 Musculoskeletal system			Other data	No numeric data
5.1 Chest pain			Other data	No numeric data
5.2 Height			Other data	No numeric data
5.3 Weight			Other data	No numeric data
5.4 BMI			Other data	No numeric data
5.5 Height z score			Other data	No numeric data

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.6 Weight z score			Other data	No numeric data
5.7 BMI z score			Other data	No numeric data
5.8 Increased mobility			Other data	No numeric data
5.9 Bone mineral density			Other data	No numeric data
6 Immune system			Other data	No numeric data
6.1 Nasopharyngitis			Other data	No numeric data
6.2 Pyrexia			Other data	No numeric data
6.3 Allergies			Other data	No numeric data
6.4 Cold symptoms			Other data	No numeric data
6.5 Pharyngitis			Other data	No numeric data
6.6 Viral infection			Other data	No numeric data
6.7 Rash			Other data	No numeric data
6.8 Rhinitis			Other data	No numeric data
6.9 Ear disorders			Other data	No numeric data
6.10 Fever			Other data	No numeric data
6.11 Infections			Other data	No numeric data
7 Urogenital system: enuresis			Other data	No numeric data
8 Other body systems			Other data	No numeric data
8.1 Hair loss			Other data	No numeric data
8.2 Skin problems			Other data	No numeric data
8.3 Accidental injury			Other data	No numeric data
8.4 Voice frequency			Other data	No numeric data
8.5 Hypersalivation			Other data	No numeric data
8.6 Nasal bleeding			Other data	No numeric data
8.7 Chromosomal aberration			Other data	No numeric data

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Analysis 7.1. Comparison 7 Non-comparative studies: proportion of participants with non-serious adverse events, Outcome 1 Non-serious adverse events.

	Non-serious adverse events	
Study	**Symptom**	**Adverse events/total number of participants**
Altin 2013	Total adverse events	21/142
Ardic 2014	Any adverse event (with OROS (osmotic controlled release oral delivery system) methylphenidate)	52/122
Arnold 2004	Any adverse event	76/76
Atzori 2009	Total number of patients who experience adverse events	54/134
Barrickman 1995	Total adverse events	5/15
Berek 2011	Total adverse events	195/762
Chou 2012b	Total adverse events	95/230
Cortese 2015	Total adverse events	369/1426
Dirksen 2002	Total adverse events	78/287
Dittmann 2014	Total adverse events	25/195
Döpfner 2011a, OBSEER	Total adverse events	209/822
Döpfner 2011b	Total adverse events	40/106
Findling 2010	Total adverse events	68/88
Garg 2014	Total adverse events	18/27
Gau 2008	Total adverse events	180/607
Gerwe 2009	Total adverse events	160/263
Goez 2012	Total adverse events	7/28
Green 2011	Total adverse events	14/14
Greenberg 1987	Total adverse events	8/49
Greenhill 1983	Total adverse events	5/7
Gucuyener 2003	Total adverse events	26/119
Haertling 2015	Total adverse events	27/239
Hammerness 2009	Total adverse events	45/57
Hammerness 2012	Total adverse events	0/27
Haubold 2010	Total adverse events	32/103
Jensen 1999 (MTA)	Total adverse events	150/245
Karabekiroglu 2008	Total adverse events	28/90
Khajehpiri 2014	At least one adverse drug reaction	71/71
Kim 2015b	Total adverse events	8/116
Kordon 2011	Total adverse events	172/541
Lee 2014	Total adverse events	3513/4055
Lyon 2010	Total adverse events	7/10
Mayes 1994	Total adverse events	35/63
McCracken 2016	Total adverse events	58/60
Na 2013	Total number of patients who experienced adverse events	98/103
Remschmidt 2005	Total adverse events	76/89
Schulz 2010	Total adverse events	36/145
Sobanski 2013	Total adverse events	26/347
Song 2012	Total adverse events	116/116
Su 2015	Total adverse events	101/205
Tasdelen 2015	Total adverse events	12/17
Valdizán Usón 2013	Total adverse events	177/689
Warshaw 2010	Total adverse events	242/260
Weiss 2007	Total adverse events	64/79
Wigal 2013	Total adverse events	42/45
Wilens 2005	Total adverse events	344/407
Wilens 2006	Total adverse events	96/135
Yatsuga 2014	Total adverse events	7/50
Zheng 2015	Total adverse events	24/123

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Analysis 7.2. Comparison 7 Non-comparative studies: proportion of participants with non-serious adverse events, Outcome 2 Central nervous system.

	Central nervous system	
Study	**Symptom**	**Adverse events/total number of participants**
	Affect lability	
Sahin 2014	Moodiness	10/30
Wigal 2013	Affect lability	12/44
	Aggression	
Barrickman 1995	Anger	1/15
Berek 2011	Aggressive reaction	13/762
Davari-Ashtiani 2010	Aggression	1/16
Dittmann 2014	Aggression	0/195
Döpfner 2011a, OBSEER	Aggression	31/777
Döpfner 2011b	Aggression	2/113
Haertling 2015	Aggression	3/239
Kemner 2005 (FOCUS)	Aggression	10/850
Kordon 2011	Aggression	10/541
Lee 2014	Aggression	7/100
Mayes 1994	Aggression	1/69
Na 2013	Anger	6/103
Remschmidt 2005	Aggression	1/105
Wilens 2005	Hostility	8/407
	Anorexia	
Arabgol 2015	Anorexia	8/15
Arnold 2004	Anorexia	16/76
Arnold 2010	Anorexia	6/150
Berek 2011	Anorexia	35/762
Cortese 2015	Anorexia	9/1426
Döpfner 2011a, OBSEER	Anorexia	9/777
Döpfner 2011b	Anorexia	0/113
Gerwe 2009	Anorexia	20/263
Greenhill 1983	Anorexia	5/7
Haertling 2015	Anorexia	11/239
Khajehpiri 2014	Anorexia	45/71
Kordon 2011	Anorexia	23/541
Kratochvil 2002	Anorexia	6/25
Lee 2007	Anorexia	29/110
Na 2013	Anorexia	66/103
Song 2012	Anorexia	104/116
Wang 2007	Anorexia	42/166
Warshaw 2010	Anorexia	9/260
Weiss 2007	Anorexia	16/79
Wilens 2006	Anorexia	22/220
Yildiz 2011	Anorexia	9/11
Zelnik 2015	Anorexia	36/128
Çetin 2015	Anorexia	12/61
	Anxiety	
Abbasi 2011	Anxiety	9/20
Akhondzadeh 2003	Anxiety	3/10
Akhondzadeh 2004	Anxiety	3/20
Amiri 2008	Anxiety, nervousness	4/27
Barrickman 1995	Anxiety	1/15
Blader 2010	Anxiety or nervousness	12/65
Davari-Ashtiani 2010	Phobia & anxiety	2/16

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Study	Symptom	Adverse events/total number of participants
	Central nervous system	
Efron 1997	Anxiousness	76/123
El-Fiky 2014	Anxious	2/31
Gau 2006	Anxious	10/32
Ghanizadeh 2012	Anxiety	1/12
Green 2011	Anxiousness	4/14
Hammerness 2009	Anxiety	2/57
Hazell 2003	Anxious	6/10
Jafarinia 2012	Anxiety	5/20
Maia 2008	Anxious	12/31
Mohammadi 2004	Anxiety	0/11
Mohammadi 2010	Anxiety	9/19
Na 2013	Anxiety	9/103
Song 2012	Anxiety	12/116
Wilens 2005	Anxiety	9/407
Zelnik 2015	Anxiety	21/128
	Fingernail biting	
Blader 2010	Bites fingernails	9/65
Efron 1997	Biting fingernails	56/123
El-Fiky 2014	Bites fingers	0/31
Gau 2006	Biting fingernails	8/32
Green 2011	Biting fingernails	3/14
Hazell 2003	Biting fingernails	2/10
Maia 2008	Bites fingernails	3/31
Sahin 2014	Nail biting	3/30
Shang 2015	Nail biting	1/66
	Daydreams	
Efron 1997	Daydreams	77/123
Gau 2006	Daydreams	10/32
Green 2011	Daydreams	3/14
Sahin 2014	Daydreams	7/30
	Difficulty falling asleep	
Akhondzadeh 2003	Difficulty falling asleep	4/10
Akhondzadeh 2004	Difficulty falling asleep	6/20
Altin 2013	Insomnia	5/71
Amiri 2008	Difficulty falling asleep	8/30
Ardic 2014	Insomnia	19/101
Arnold 2004	Insomnia	16/76
Arnold 2010	Insomnia	9/171
Atzori 2009	Insomnia	3/129
Barrickman 1995	Insomnia	1/15
Berek 2011	Insomnia	59/762
Blader 2010	Insomnia	21/65
Chou 2012b	Insomnia	25/230
Cortese 2015	Insomnia	31/1426
Coşkun 2010	Sleep problems	4/7
Davari-Ashtiani 2010	Sleep problems	7/16
Döpfner 2011a, OBSEER	Initial insomnia	11/777
Döpfner 2011b	Initial insomnia	3/113
Efron 1997	Trouble sleeping	79/123
El-Fiky 2014	Insomnia	2/31
Famularo 1987	Later sleep onset	1/10
Garg 2014	Insomnia	1/27
Gau 2006	Insomnia or trouble sleeping	15/32
Germinario 2013	Insomnia	1/9

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Study	Central nervous system Symptom	Adverse events/total number of participants
Gerwe 2009	Difficulty falling asleep	73/263
Grcevich 2001	Sleep problems	7/75
Green 2011	Trouble sleeping	7/34
Greenhill 1983	Insomnia	2/7
Gucuyener 2003	Difficulty falling asleep	19/119
Haertling 2015	Insomnia	3/239
Hazell 2003	Sleep problems	7/10
Işeri 2007	Sleep problems	5/20
Jafarinia 2012	Insomnia	10/20
Jensen 1999 (MTA)	Insomnia	12/245
Johnson 2013	Insomnia (new onset)	12/45
Jung 2007	Insomnia	16/83
Kemner 2005 (FOCUS)	Insomnia	53/850
Khajehpiri 2014	Insomnia	44/71
Kim 2010	Insomnia	6/24
Kordon 2011	Insomnia	46/541
Kratochvil 2002	Insomnia	7/25
Lee 2007	Insomnia	24110
Li 2011	Difficulty falling asleep	9/34
Maayan 2009	Trouble sleeping	3/8
Maia 2008	Insomnia	5/31
Mayes 1994	Insomnia	9/63
McCracken 2016	Insomnia	20/61
Miller-Horn 2008	Insomnia	2/23
Mohammadi 2004	Difficulty falling asleep	4/11
Mohammadi 2010	Trouble sleeping	9/19
Mohammadi 2012a	Difficulty falling asleep	8/23
Mohammadi 2012b	Insomnia	9/20
Montañés-Rada 2012	Insomnia	5/40
Na 2013	Trouble sleeping	37/103
Peyre 2012a	Insomnia	21/121
Remschmidt 2005	Insomnia	3/89
Sahin 2014	Difficulty falling asleep	16/30
Sangal 2006	Insomnia	21/79
Shang 2015	Insomnia	12/66
Song 2012	Insomnia	44/116
Steele 2006	Insomnia	12/60
Su 2015	Insomnia	20/205
Tasdelen 2015	Insomnia	1/17
Thorell 2009	Difficulties falling asleep	15/79
Tomás Vila 2010b	Difficulty falling asleep	45/114
Valdizán Usón 2004	Initial insomnia	11/155
Wang 2007	Insomnia	9/166
Warshaw 2010	Difficulty falling asleep	25/260
Weiss 2007	Insomnia	13/79
Wigal 2013	Insomnia	9/39
Wigal 2015	Insomnia	24/200
Wilens 2005	Insomnia	81/229
Wilens 2006	Insomnia	16/220
Wilens 2008	Insomnia	25/127
Yatsuga 2014	Insomnia	4/50
Yildiz 2010	Difficulty sleeping	15/47
Yildiz 2011	Insomnia	7/11
Zarinara 2010	Insomnia	10/18

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Study	Symptom	Adverse events/total number of participants
	Central nervous system	
Zelnik 2015	Insomnia	31/128
Zeni 2007	Insomnia	21/106
Zheng 2011	Insomnia	145/1154
Zheng 2015	Insomnia	3/123
Çetin 2015	Insomnia	5/61
	Depression	
Atzori 2009	Vegetative symptoms	4/134
Cherland 1999	Mood symptoms or mood-congruent psychotic symptoms	11/98
Döpfner 2011a, OBSEER	Depressed mood	13/777
Grcevich 2001	Depression	1/75
Haertling 2015	Depression	1/262
Kratochvil 2002	Depression	2/25
Na 2013	Depression	9/103
Song 2012	Depression	5/116
Valdizán Usón 2013	Depressive symptoms	7/689
Weiss 2007	Depression	5/79
Wilens 2005	Depression	6/407
Yildiz 2010	Depressive symptoms	4/47
Yildiz 2011	Depression	3/11
	Disturbed sleep	
Abbas 2006	Sleeping problems	4/90
Abbasi 2011	Trouble sleeping	10/20
Arabgol 2015	Disturbed sleep	4/15
Arnold 2010	Insomnia	9/150
Blader 2010	Early waking	6/65
Efron 1997	Trouble sleeping	79/123
Findling 2009	Insomnia	29/157
Galland 2010	Restless sleep	14/27
Gau 2008	Poor sleep quality	37/607
Haertling 2015	Sleep disorder	1/239
Hammerness 2009	Insomnia	7/57
Hazell 2003	Nightmares	8/10
Işeri 2007	Sleep problems	5/20
Kim 2010	Insomnia	6/27
Kim 2011	Poor sleep	8/97
Mohammadi 2004	Disturbed sleep	4/11
Montañés-Rada 2012	Insomnia	5/40
Perera 2010	Poor sleep	13/102
Remschmidt 2005	Delayed sleep	1/105
Steele 2006	Sleep disorder	3/60
Su 2015	Poor quality sleep	1/205
Valdizán Usón 2013	Sleep disorder	33/689
Yildiz 2011	Insomnia	7/11
Zheng 2015	Poor sleep quality	3/149
	Dizziness	
Abbasi 2011	Dizziness	8/20
Blader 2010	Dizzy	1/65
Chou 2012b	Dizziness	9/230
Cortese 2015	Dizziness	5/1426
Davari-Ashtiani 2010	Dizziness	0/16
Döpfner 2011b	Dizziness	1/113
Efron 1997	Dizziness	15/123
El-Fiky 2014	Dizziness	0/31
Green 2011	Dizziness	3/14

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Study	Symptom	Adverse events/total number of participants
	Central nervous system	
Haertling 2015	Dizziness	1/239
Hammerness 2009	Dizziness	4/57
Hazell 2003	Dizziness	7/9
Jafarinia 2012	Dizziness	1/20
Kemner 2005 (FOCUS)	Dizziness	7/850
Kim 2010	Dizziness	2/27
Lee 2007	Dizziness	5/110
Li 2011	Dizziness	4/34
Maia 2008	Dizziness	3/39
McCracken 2016	Dizziness	6/61
Mohammadi 2004	Dizziness	2/11
Mohammadi 2012b	Dizziness	2/20
Na 2013	Dizziness	11/103
Pierce 2010	Dizziness	2/71
Sahin 2014	Dizziness	6/30
Shang 2015	Dizziness	1/66
Song 2012	Dizziness	15/116
Wang 2007	Dizziness	12/166
Wilens 2005	Dizziness	7/407
Yildiz 2010	Dizziness	2/47
	Drowsiness	
Barrickman 1995	Drowsiness	1/15
Efron 1997	Drowsiness	22/123
El-Fiky 2014	Drowsiness	2/31
Garg 2014	Drowsiness	1/27
Gau 2006	Drowsiness	6/32
Germinario 2013	Drowsiness	1/9
Ghanizadeh 2012	Drowsiness	2/12
Green 2011	Drowsiness	2/14
Hazell 2003	Drowsiness	7/10
Kratochvil 2002	Somnolens	0/40
Lyon 2010	Drowsiness	2/10
Maia 2008	Drowsiness	1/39
Sahin 2014	Drowsiness	8/30
Song 2012	Somnolence	6/116
Wilens 2005	Somnolence	10/407
Wilens 2006	Somnolence	3/220
Yildiz 2011	Somnolence	1/11
	Dysthymia	
Haertling 2015	Dysphemia	1/239
Mohammadi 2004	Dysphemia	0/16
	Emotional lability	
Ardic 2014	Emotional change	22/101
Davari-Ashtiani 2010	Emotional lability	0/16
Findling 2009	Emotional lability	5/157
Hammerness 2009	Moody	2/57
Kemner 2005 (FOCUS)	Emotional disturbance	5/850
Kordon 2011	Emotional lability	8/598
Kratochvil 2002	Emotional lability	2/25
Maayan 2009	Emotional lability	2/8
McCracken 2016	Affect lability	14/61
Silva 2004	Emotional lability	4/22
Steele 2006	Emotional lability	9/60
Warshaw 2010	Affect lability	18/260

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Study	Symptom	Adverse events/total number of participants
	Central nervous system	
Weiss 2007	Emotional lability	3/79
Wigal 2013	Affect lability	10/39
Wilens 2005	Emotional lability	1/229
Yildiz 2010	Emotional lability	12/47
	Euphoria/hypomania	
Blader 2010	Unusually happy	12/65
El-Fiky 2014	Euphoria	0/31
Gau 2006	Euphoric	3/32
Grcevich 2001	Agitation	2/75
Green 2011	Unusually happy	0/14
Kim 2010	Euphoria	1/27
Maia 2008	Euphoric	2/39
Mohammadi 2004	Euphoria or hypomania	0/16
Sahin 2014	Ecstasy	8/30
	Asthenia and fatigue	
Abbasi 2011	Fatigue	13/20
Arnold 2004	Asthenia	7/76
Blader 2010	Tired + low energy	4/65
Davari-Ashtiani 2010	Tiredness	0/16
Dittmann 2014	Fatigue	0/195
Döpfner 2011b	Fatigue	0/113
Galland 2010	Daytime sleepiness	2/27
Garg 2014	Fatigue	2/27
Haertling 2015	Asthenia	1/239
Kemner 2005 (FOCUS)	Fatigue	3/850
Lee 2007	Fatigue	5/110
McCracken 2016	Fatigue	5/61
Mohammadi 2010	Fatigue	4/19
Na 2013	Fatigue	13/103
Pierce 2010	Fatigue	3/71
Sangal 2006	Fatigue	3/79
Steele 2006	Fatigue	7/60
Wang 2007	Fatigue	5/166
Wigal 2015	Fatigue	10/200
	Headache	
Abbas 2006	Headache	2/90
Abbasi 2011	Headache	12/20
Akhondzadeh 2003	Headache	6/10
Akhondzadeh 2004	Headache	9/20
Altin 2013	Headache	3/25
Amiri 2008	Headache	7/27
Ardic 2014	Headache	16/101
Arnold 2004	Headache	24/76
Arnold 2010	Headache	12/150
Atzori 2009	Headache	6/129
Barrickman 1995	Headache	1/15
Berek 2011	Headache	15/762
Blader 2010	Headache	1/65
Chou 2012b	Headache	7/230
Cortese 2015	Headache	62/1426
Dirksen 2002	Headache	17/287
Dittmann 2014	Headache	1/195
Döpfner 2011a, OBSEER	Headache	9/777
Döpfner 2011b	Headache	8/113

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Study	Central nervous system Symptom	Adverse events/total number of participants
Efron 1997	Headache	30/123
El-Fiky 2014	Headache	4/31
Findling 2009	Headache	54/157
Galland 2010	Morning headache	3/27
Garg 2014	Headache	4/27
Gau 2006	Headache	11/32
Gau 2008	Headache	21/607
Gerwe 2009	Headache	15/263
Goez 2012	Headache	4/28
Golubchik 2011	Headache	2/9
Green 2011	Headache	8/14
Greenberg 1987	Headache	1/49
Greenhill 1983	Headache	2/7
Gucuyener 2003	Headache	14/119
Guerreiro 1996	Headache	2/22
Haertling 2015	Headache	2/239
Hammerness 2009	Headache	14/57
Hazell 2003	Headache	8/10
Hulvershorn 2012	Headache	1/25
Işeri 2007	Headache	5/20
Jafarinia 2012	Headache	10/20
Jung 2007	Headache	8/83
Kemner 2005 (FOCUS)	Headache	33/850
Khajehpiri 2014	Headache	7/71
Kim 2010	Headache	3/27
Kordon 2011	Headache	14/541
Kratochvil 2002	Headache	13/25
Lee 2007	Headache	16/110
Lee 2014	Headache	6/100
Li 2011	Headache	3/34
Maayan 2009	Headache	1/11
Maia 2008	Headaches	4/39
Mayes 1994	Headache	3/63
McCracken 2016	Headache	23/61
Miller-Horn 2008	Headache	1/23
Mohammadi 2004	Headache	7/11
Mohammadi 2010	Headache	15/19
Mohammadi 2012a	Headache	4/23
Mohammadi 2012b	Headache	9/20
Na 2013	Headache	32/103
Perera 2010	Headache	13/102
Peyre 2012a	Headache	43/121
Pierce 2010	Headache	6/71
Remschmidt 2005	Headache	2/105
Sahin 2014	Headache	14/30
Sangal 2006	Headache	12/79
Schulz 2010	Headache	9/145
Shang 2015	Headache	14/66
Silva 2004	Headache	4/22
Song 2012	Headache	30/116
Steele 2006	Headache	14/60
Su 2015	Headache	4/205
Tasdelen 2015	Headache	1/17
Thorell 2009	Headache	6/79

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Study	Symptom	Adverse events/total number of participants
	Central nervous system	
Valdizán Usón 2004	Headache	2/155
Valdizán Usón 2013	Headache	11/689
Wang 2007	Headache	16/166
Warshaw 2010	Headache	23/260
Weiss 2007	Headache	10/79
Wigal 2013	Headache	7/39
Wigal 2015	Headache	35/200
Wilens 2005	Headache	123/229
Wilens 2006	Headache	25/220
Wilens 2008	Headache	27/127
Yatsuga 2014	Headache	7/50
Yildiz 2010	Headache	27/47
Yildiz 2011	Headache	3/11
Zarinara 2010	Headache	11/18
Zelnik 2015	Headache	107/128
Zheng 2011	Headache	143/1154
Çetin 2015	Headache	2/61
	Increased need to sleep	
Blader 2010	Trouble waking	1/65
Galland 2010	Hard to wake + difficult to wake	14/27
Mohammadi 2004	Increased need to sleep	5/11
Mohammadi 2012a	Sleepiness	4/23
Na 2013	Somnolence	8/103
Pierce 2010	Somnolence	2/71
Wang 2007	Somnolence	6/166
Zarinara 2010	Somnolence	3/19
	Involuntary movements	
Balázs 2011	Involuntary movements after methylphenidate treatment	9/34
Berek 2011	Muscle contractions, involuntary	34/762
Blader 2010	Shaking + tremor	4/65
Galland 2010	Restless legs	2/27
Kordon 2011	Muscle contraction, involuntary	13/541
Kratochvil 2002	Hyperkinesia	2/25
Lee 2014	Convulsion	4/100
	Irritability	
Abbasi 2011	Irritability	18/20
Amiri 2008	Irritability	6/27
Ardic 2014	Irritability	30/101
Atzori 2009	Irritability	9/129
Barrickman 1995	Irritability	1/15
Blader 2010	Irritability	16/65
Cortese 2015	Irritabillity	67/1426
Efron 1997	Irritable	100/123
El-Fiky 2014	Irritable	6/31
Findling 2009	Irritability	20/157
Garg 2014	Irritability	2/27
Gau 2006	Irritable	7/32
Green 2011	Irritability	2/14
Greenhill 1983	Irritability	4/7
Hazell 2003	Irritability	3/10
Işeri 2007	Irritability	3/20
Jensen 1999 (MTA)	Irritability	10/245
Johnson 2013	Irritability	23/45
Kemner 2005 (FOCUS)	Irritability	7/850

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Study	Symptom	Adverse events/total number of participants
	Central nervous system	
Khajehpiri 2014	Irritability	25/71
Maayan 2009	Irritability	1/8
Maia 2008	Irritability	10/39
Mayes 1994	Irritability	18/63
McCracken 2016	Irritability	12/61
Mohammadi 2012a	Irritability	10/23
Na 2013	Irritable	16/121
Sangal 2006	Irritability	12/79
Silva 2004	Irritability	3/22
Song 2012	Irritability	9/116
Tasdelen 2015	Irritability	5/17
Valdizán Usón 2004	Irritability	4/155
Wang 2007	Irritability	10/166
Warshaw 2010	Irritability	15/260
Wigal 2015	Irritability	11/200
Yildiz 2010	Irritability	16/47
	Nervousness	
Arabgol 2015	Nervousness	5/15
Berek 2011	Nervousness	17/762
Jafarinia 2012	Nervousness	5/20
Kordon 2011	Nervousness	13/541
Kratochvil 2002	Nervousness	4/25
Lee 2007	Nervousness	2/110
Mohammadi 2010	Nervousness	14/19
Na 2013	Nervousness	7/103
Song 2012	Nervousness	9/116
Steele 2006	Nervousness	9/60
Weiss 2007	Nervousness	14/79
Wilens 2006	Nervousness	6/220
Yildiz 2011	Nervousness	9/11
Çetin 2015	Nervousness	2/61
	Nightmares	
Blader 2010	Nightmares	2/65
El-Fiky 2014	Nightmares	1/31
Gau 2006	Nightmares	8/32
Green 2011	Nightmares	1/14
Khajehpiri 2014	Nightmares	3/71
Kim 2010	Nightmares	1/27
Maia 2008	Nightmares	1/31
Sahin 2014	Nightmares	4/30
Silva 2004	Nightmares	1/22
Song 2012	Nightmares	10/116
Tomás Vila 2010b	Nightmares	12/114
	Restlessness and agitation	
Blader 2010	Restlessness	3/65
Davari-Ashtiani 2010	Restlessness	4/16
Dittmann 2014	Agitation	1/195
Döpfner 2011b	Restlessness	1/113
Grcevich 2001	Agitation	2/75
Haertling 2015	Agitation	2/239
Khajehpiri 2014	Agitation	16/71
Lee 2014	Agitation	6/100
Mohammadi 2010	Restlessness	8/19
Perera 2010	Restlessness	5/102

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Study	Symptom	Adverse events/total number of participants
	Central nervous system	
Sahin 2014	Restlessness	9/30
Steele 2006	Agitation	8/60
Valdizán Usón 2013	Physical activity modifications	16/689
Zarinara 2010	Restlessness	5/19
	Sadness	
Abbasi 2011	Sadness	9/20
Amiri 2008	Sadness	6/27
Barrickman 1995	Low mood	1/15
Blader 2010	Crying + sadness	17/65
Davari-Ashtiani 2010	Sadness	3/16
Efron 1997	Sadness or unhappiness	69/123
El-Fiky 2014	Sad	3/31
Garg 2014	Sadness	0/27
Gau 2006	Sadness	14/32
Green 2011	Sadness	7/14
Hammerness 2009	Sad	1/57
Hazell 2003	Sad	5/10
Işeri 2007	Sadness	2/20
Jensen 1999 (MTA)	Tearfulness	6/245
Johnson 2013	Sadness	18/45
Kemner 2005 (FOCUS)	Crying	13/850
Maia 2008	Sad	4/31
Mohammadi 2010	Sadness	4/19
Mohammadi 2012a	Sadness	2/23
Perera 2010	Sadness	13/102
Sahin 2014	Sadness	9/30
	Stares	
Blader 2010	Stares into space	3/65
El-Fiky 2014	Stares a lot	8/31
Hazell 2003	Stares	6/10
Maia 2008	Stares a lot or daydreams	7/31
	Excessive talking	
Blader 2010	Overly talkative	8/65
Hazell 2003	Talks too much	5/10
Khajehpiri 2014	Speaking more	6/71
	Taciturnity ('talking too little')	
Blader 2010	Less talkative	4/65
El-Fiky 2014	Talk less	2/31
Green 2011	Talking little	6/14
Maia 2008	Talk less	9/31
	Tics	
Ardic 2014	Tics	3/101
Atzori 2009	Tics	2/129
Blader 2010	Tics	3/65
Cortese 2015	Tics	27/1426
Davari-Ashtiani 2010	Tics	1/16
Döpfner 2011a, OBSEER	Tics	100/777
Döpfner 2011b	Tics	1/113
Efron 1997	Tics	35/123
El-Fiky 2014	Tics or involuntary movements	0/31
Findling 2009	Tics	0/157
Gau 2006	Tics	6/32
Germinario 2013	Tics	1/9
Golubchik 2011	Motor tics exacerbation	1/9

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Study	Symptom	Adverse events/total number of participants
	Central nervous system	
Grcevich 2001	Motor tics	1/75
Green 2011	Tics	0/14
Gucuyener 2003	Motor tics	2/119
Işeri 2007	Tics	3/20
Johnson 2013	Tics (new onset)	1/45
Khajehpiri 2014	Tics	18/71
Kim 2010	Tics	3/27
Kim 2011	Tics	19/97
Lakic 2012	Tics	3/61
Lee 2007	Tics	6/110
Miller-Horn 2008	Tics	2/23
Mohammadi 2004	Tics	0/11
Mohammadi 2012a	Tics	1/23
Mohammadi 2012b	Tics	4/20
Remschmidt 2005	Tics	7/89
Sahin 2014	Tics	2/30
Shang 2015	Tics	1/66
Song 2012	Tics	7/116
Su 2015	Tourette disorder	6/205
Tasdelen 2015	Tics	1/17
Valdizán Usón 2004	Tics	1/155
Varley 2001	Tics	31/374
Wilens 2005	Twitching	40/229
Yildiz 2010	Tics	1/47
Yildiz 2011	Tics	2/11
Çetin 2015	Tics	1/16
	Isolation and lack of interest in others	
Blader 2010	Lack of interest	6/65
Efron 1997	Uninterested in others	39/123
El-Fiky 2014	Uninterested in others	2/31
Green 2011	Uninterested	4/14
Hazell 2003	Uninterested	6/10
Khajehpiri 2014	Isolation	6/71
Maia 2008	Uninterested others	6/31
Perera 2010	Social withdrawal	6/102
Sahin 2014	Being in own world	5/30
Yildiz 2010	Introversion (maybe isolation)	5/47
	'Zombie like' demeanour	
Davari-Ashtiani 2010	Zombie like	3/16
Jensen 1999 (MTA)	Zombie like	18/245
Wilens 2005	Apathy	4/407
	Somnolence	
Chou 2012b	Somnolence	1/230
Khajehpiri 2014	Somnolence	5/71
McCracken 2016	Somnolence	3/61
Na 2013	Somnolence	8/103
Shang 2015	Somnolence	1/66
Wang 2007	Somnolence	6/166
Weiss 2007	Somnolence	7/79
Wilens 2005	Somnolence	1/229
Yildiz 2011	Somnolence	1/11
	Obsession	
Cortese 2015	Obsessive behaviour	6/1426
Khajehpiri 2014	Obsession	1/71

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Study	Symptom	Adverse events/total number of participants
	Central nervous system	
Çetin 2015	Obsession	2/32
	Mood disorder	
Cortese 2015	Mood disorder	49/1426
Haertling 2015	Emotional disorder of childhood	1/239
	Confusional state	
Haertling 2015	Confusional state	1/262
Zelnik 2015	Sense of dopiness	13/128
	Sleep disorder	
Dittmann 2014	Sleep disorder	6/195
Döpfner 2011a, OBSEER	Sleep disorder	9/777
Su 2015	Sleep disorder	26/239
	Propensity to cry	
El-Fiky 2014	Prone to cry	4/31
Sahin 2014	Sudden crying	12/30
	Sedation	
McCracken 2016	Sedation	4/61
Mohammadi 2010	Sedation	4/19
	Daytime sleepiness	
Galland 2010	Daytime sleepiness	2/27
Tomás Vila 2010b	Datime sleepiness	2/114
	Dysphoria	
Atzori 2009	Dysphoria	2/134
	Logorrhoea	
Atzori 2009	Loggorrhoea	1/129
	Impaired concentration	
Berek 2011	Impaired concentration	14/822
	Difficulty waking up	
Galland 2010	Difficult to wake up	7/28
	Urinary incontinence	
Garg 2014	Urinary incontinence	1/32
	Paralysis	
Haertling 2015	Paralysis	1/239
	Affective disorder	
Haertling 2015	Affective disorder	1/239
	Jumbled thoughts	
Hammerness 2009	Jumbled thoughts	1/154
	Bulimia	
Khajehpiri 2014	Bulimia	5/71
	Sleep late	
Khajehpiri 2014	Sleeping late	22/71
	Tooth grinding	
Khajehpiri 2014	Tooth grinding	3/71
	Tremor	
Khajehpiri 2014	Tremor	2/71
	Stuttering	
Khajehpiri 2014	Stuttering	4/71
	Flushing	
Khajehpiri 2014	Flushing	9/71
	Apathy	
Kordon 2011	Apathy	6/541
	Abnormal behaviour	
Lee 2014	Abnormal behaviour	5/100
	Stereotypies	
Mohammadi 2004	Stereotypies	0/16

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Central nervous system		
Study	**Symptom**	**Adverse events/total number of participants**
	Quietness	
Sahin 2014	Quietness	6/30
	EEG changes	
Schmidt 2002	Pathologic	25/124
	Did not like themselves	
Thorell 2009	Does not like him- or herself	10/79
	Sleep walking	
Tomás Vila 2010b	Sleep walking	2/114
	Personality and behaviour disorders	
Valdizán Usón 2013	Personality and behavior disorders	14/633
	Vertigo	
Yildiz 2011	Vertigo	3/11

Analysis 7.3. Comparison 7 Non-comparative studies: proportion of participants with non-serious adverse events, Outcome 3 Cardiovascular and respiratory system.

Cardiovascular and respiratory system		
Study	**Symptom**	**Adverse events/total number of participants**
	Cough	
Arnold 2004	Cough increased	7/76
Arnold 2010	Cough	5/150
Findling 2009	Cough	38/157
Kratochvil 2002	Cough increased	2/25
Pierce 2010	Cough	2/71
Sangal 2006	Cough	7/79
Wang 2007	Cough	10/166
	Pharyngolaryngeal pain	
Arnold 2010	Pharyngolaryngeal pain	5/150
Findling 2009	Pharyngolaryngeal pain	19/326
Pierce 2010	Pharyngolaryngeal pain	3/71
	Upper respiratory tract infection	
Findling 2009	Upper respiratory tract infection	40/157
Pierce 2010	Upper respiratory tract infection	2/71
Wang 2007	Upper respiratory tract infection	11/166
Wigal 2015	Upper respiratory tract infection	13/200
Wiguna 2012	Upper respiratory tract infection	5/20
	Tachycardia	
Blader 2010	Heart races	2/65
Cortese 2015	Tachycardia	24/1426
Findling 2009	Tachycardia	3/326
Jafarinia 2012	Tachycardia	1/20
Kratochvil 2002	Tachycardia	2/25
Su 2015	Tachycardia	8/239
	Abnormal ECG	
Findling 2009	Abnormal ECG	1/326
Findling 2010	Abnormal ECG	30/162
	Nasal congestion	
Findling 2009	Nasal congestion	18/157
Maayan 2009	Nasal congestion	1/11
Sangal 2006	Nasal congestion	10/79
	Palpitation	
Mohammadi 2004	Palpation	3/11
Na 2013	Palpitations	8/103

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Study	Symptom	Adverse events/total number of participants
Cardiovascular and respiratory system		
Shang 2015	Palpation	1/66
Systolic blood pressure		
Cho 2012	No difference	Non-significant increase following methylphenidate
Döpfner 2011b	No difference	-
Findling 2009	Increased	The proportion of participants with a systolic blood pressure above the upper limit of normal (> 123 mmHg) ranged from 1% to 10%, whereas 1.5% had an above normal systolic blood pressure at baseline
Gadow 1995	Increased	-
Germinario 2013	No difference	100.6 mmHg (SD = 12.3)
Gerwe 2009	No difference	Mean change from baseline: 0.1 mmHg (SD = 10.8)
Hazell 2003	Decreased	Drop in systolic blood pressure in 8/10 participants
Kim 2010	Decreased	113.8 mmHg (SD = 10.2)
Kratochvil 2002	Increased	102.2 mmHg (SD = 9.89)
Lamberti 2015	Increased	105.4 mmHg (SD = 10.3)
Maayan 2009	No difference	96.2 mmHg (SD = 14.0)
McCracken 2016	Increased	-
Na 2013	Increased	-
Song 2012	Increased	105.3 mmHg (SD = 12.6)
Wilens 2005	Increased	104.7 mmHg (SD = 8.10)
Winsberg 1982	Increased	103.1 mmHg (SD = no information)
Yildiz 2011	Decreased	97 mmHg (SD = 10.8)
Zheng 2011	No difference	96.6 mmHg (SD = 10.6)
Zheng 2015	No difference	No changes
Diastolic blood pressure		
Cho 2012	No difference	Non-significant, marginal increase after methylphenidate
Döpfner 2011b	Increased	69 mmHg (SD = 1.00)
Findling 2009	Decreased	-
Germinario 2013	Decreased	63.2 mmHg (SD = 10.9)
Gerwe 2009	-	-
Hazell 2003	Decreased	Drop in diastolic blood pressure in 9/10 participants
Kim 2010	Decreased	75.2 mmHg (SD = 12.0)
Kratochvil 2002	Increased	63.5 mmHg (SD = 7.90)
Lamberti 2015	Increased	59.2 mmHg (SD = 7.10)
Maayan 2009	No difference	61.4 mmHg (SD = 13.7)
McCracken 2016	Increased	-
Na 2013	Increased	-
Song 2012	Increased	66.9 mmHg (SD = 10.1)
Yildiz 2011	Decreased	63.5 mmHg (SD = 12.0)
Zheng 2011	Increased	64.6 mmHg (SD = 7.51)
Zheng 2015	No change	-
Pulse rate		
Cho 2012	Increased	-
Döpfner 2011b	No difference	79 beats/min (SD = 1.00)
Germinario 2013	Decreased	79.9 beats/min (SD = 12.9)
Ilgenli 2007	No difference	88 beats/min (SD = 13.80)
Kim 2010	No difference	87.5 beats/min (SD = 6.10)
Kim 2015a	Increased	86.4 beats/min (SD = 11.2)
Kratochvil 2002	Increased	80.4 beats/min (SD = 9.70)
Lamberti 2015	Increased	80.5 beats/min (SD = 15.5)
Maayan 2009	Decreased	95.5 beats/min (SD = 16.0)
McCracken 2016	Increased	-
Na 2013	Increased	75.57 beats/min (SD = 7.33)
Yildiz 2011	Increased	80.8 beats/min (SD = 9.80)
Zheng 2011	No difference	82.5 beats/min (SD = 7.81)

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Study	Symptom	Adverse events/total number of participants
	Cardiovascular and respiratory system	
Zheng 2015	No difference	82.5 beats/min (SD = 7.81)
Özcan 2004	Decreased	148.2 beats/min (SD = 29.70)
	ECG-QT	
Cho 2012	Non-significant change in QT and QRS	-
Germinario 2013	-	After 24 months, out of 77 patients treated with methylphenidate: 8 (10.4%) with altered ECG (electrocardiogram) at 24 months 11 (29.0%) with sinus bradycardia 12 (31.6%) with sinus tachycardia 6 (15.8%) with lengthened QTc
Ilgenli 2007	Minimum QT of 317.00 (23.3) Maximum QT of 373.7 (21.8)	After 2 hours: Minimum QT of 322.3 (21.6) Maximum QT of 361.8 (29.0)
Lamberti 2015	QTc of 407.6 (12.4)	After 2 hours: QTc of 409.8 (12.0)
	Cold fingers	
Khajehpiri 2014	Cold fingers	13/71
	Sweating	
Khajehpiri 2014	Sweating	6/71
	Hypertension	
Cortese 2015	Hypertension	8/1426
	Hypotension	
Cortese 2015	Hypotension	3/1426
	Respiratory, thoracic and mediastinal disorders	
Haertling 2015	Respiratory, thoracic, and mediastinal disorders	1/239
	Proportion of patients with micro-nucleated (Mn) peripheral lymphocytes	
Walitza 2009	(MN-Cells/1000 Cells mean)	Baseline: 4.90 (SD = 4.00) 6 months: 4.50 (SD = 3.50)

Analysis 7.4. Comparison 7 Non-comparative studies: proportion of participants with non-serious adverse events, Outcome 4 Gastrointestinal system.

Study	Symptom	Adverse events/total number of participants
	Gastrointestinal system	
	Abdominal pain	
Abbasi 2011	Abdominal pain	8/20
Akhondzadeh 2003	Abdominal pain	3/10
Akhondzadeh 2004	Abdominal pain	4/20
Amiri 2008	Abdominal pain	7/27
Ardic 2014	Stomach ache	16/101
Arnold 2004	Abdominal pain	15/89
Arnold 2010	Abdominal pain	7/150
Atzori 2009	Stomach pain	3/129
Barrickman 1995	Stomach ache	1/15
Berek 2011	Abdominal pain	12/762
Blader 2010	Abdominal pain	6/65
Chou 2012b	Abdominal pain	12/230
Cortese 2015	Abdominal pain	22/1426
Davari-Ashtiani 2010	Abdominal pain	1/16
Dirksen 2002	Stomach ache	14/287
Dittmann 2014	Upper abdominal pain	4/195
Döpfner 2011a, OBSEER	Gastrointestinal pain	9/777
Döpfner 2011b	Gastrointestinal pain	6/113
Efron 1997	Stomach aches	40/123
El-Fiky 2014	Stomach aches	9/31
Findling 2009	Abdominal pain	27/157

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	Gastrointestinal system	
Study	**Symptom**	**Adverse events/total number of participants**
Garg 2014	Abdominal pain	3/27
Gau 2006	Stomach aches	8/32
Gerwe 2009	Abdominal pain	10/306
Golubchik 2011	Abdominal pain	1/9
Grcevich 2001	Stomach ache	2/75
Green 2011	Stomach aches	9/34
Greenhill 1983	Stomach aches	4/7
Gucuyener 2003	Stomach ache	14/119
Haertling 2015	Abdominal pain	4/239
Hammerness 2009	Stomach ache	2/57
Hazell 2003	Stomach pain	6/10
Işeri 2007	Abdominal pain	3/20
Jafarinia 2012	Abdominal pain	6/20
Kemner 2005 (FOCUS)	Abdominal pain	33/850
Khajehpiri 2014	Abdominal pain	9/71
Kim 2010	Abdominal pain	1/27
Kordon 2011	Abdominal pain	11/541
Kratochvil 2002	Abdominal pain	7/25
Lee 2007	Abdominal pain	6/110
Li 2011	Abdominal pain	12/34
Lyon 2010	Stomach discomfort	2/10
Maayan 2009	Gastrointestinal pain	2/8
Maia 2008	Stomach ache	2/31
McCracken 2016	Abdominal pain	28/61
Mohammadi 2004	Abdominal pain	0/11
Mohammadi 2010	Abdominal pain	8/19
Mohammadi 2012a	Stomach ache	5/23
Mohammadi 2012b	Abdominal pain	5/20
Na 2013	Stomach ache (abdominal pain)	19/103
Perera 2010	Abdominal pain	15/102
Peyre 2012a	Abdominal pain	7/121
Pierce 2010	Abdominal pain	3/71
Remschmidt 2005	Abdominal pain	3/89
Sahin 2014	Abdominal pain	7/30
Sangal 2006	Abdominal pain	4/79
Schulz 2010	Abdominal pain	9/145
Shang 2015	Abdominal pain	4/66
Silva 2004	Stomach ache	3/22
Song 2012	Abdominal pain	20/116
Steele 2006	Abdominal pain	10/72
Su 2015	Abdominal pain	10/205
Tasdelen 2015	Abdominal pain	4/17
Thorell 2009	Stomach aches	2/79
Valdizán Usón 2004	Abdominal pain	1/155
Wang 2007	Abdominal pain	15/166
Warshaw 2010	Abdominal pain	9/260
Weiss 2007	Abdominal pain	5/79
Wigal 2013	Abdominal pain	17/39
Wigal 2015	Abdominal pain	29/200
Wilens 2005	Abdominal pain	45/229
Wilens 2006	Abdominal pain	9/220
Wilens 2008	Abdominal pain	15/127
Yildiz 2010	Stomach ache	6/47
Yildiz 2011	Abdominal pain	3/11

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Study	Symptom	Adverse events/total number of participants
	Gastrointestinal system	
Zarinara 2010	Abdominal pain	3/18
Zelnik 2015	Abdominal pain	36/128
Zheng 2011	Stomach ache	140/1154
Çetin 2015	Stomach ache	3/61
	Constipation	
Ardic 2014	Constipation	10/101
Khajehpiri 2014	Constipation	4/71
Mohammadi 2004	Constipation	2/11
Shang 2015	Constipation	1/66
	Decreased appetite	
Abbas 2006	Loss of appetite	2/90
Abbasi 2011	Loss of appetite	12/20
Akhondzadeh 2003	Decreased appetite	5/10
Akhondzadeh 2004	Decreased appetite	8/20
Altin 2013	Decreased appetite	27/221
Amiri 2008	Decreased appetite	26/27
Ardic 2014	Decreased appetite	47/101
Arnold 2010	Loss of appetite	11/150
Atzori 2009	Decreased appetite	27/129
Blader 2010	Decreased appetite	13/65
Chazan 2011	Decreased appetite	118/205
Chou 2012b	Decreased appetite	95/230
Cortese 2015	Decreased appetite	213/1426
Coşkun 2010	Decreased appetite	3/7
Davari-Ashtiani 2010	Loss of appetite	11/16
Dirksen 2002	Decreased appetite	8/287
Dittmann 2014	Lack of appetite	5/195
Döpfner 2011a, OBSEER	Decreased appetite	8/777
Döpfner 2011b	Decreased appetite	3/113
Efron 1997	Poor appetite	69/123
El-Fiky 2014	Decreased appetite	12/31
Famularo 1987	Decreased appetite	1/10
Findling 2009	Loss of appetite	81/157
Garg 2014	Decreased appetite	14/27
Gau 2006	Decreased appetite	19/32
Gau 2008	Loss of appetite	128/607
Germinario 2013	Decreased appetite	5/9
Gerwe 2009	Loss of appetite	83/263
Ghanizadeh 2013	Decreased appetite	1/26
Golubchik 2011	Decrease in appetite	4/9
Grcevich 2001	Appetite suppression	5/75
Green 2011	Poor appetite	13/14
Gucuyener 2003	Loss of appetite	23/119
Hammerness 2009	Decreased appetite	19/57
Hazell 2003	Appetite suppression	7/10
Hulvershorn 2012	Decreased appetite	6/25
Işeri 2007	Loss of appetite	3/20
Jafarinia 2012	Decreased appetite	11/20
Johnson 2013	Reduced appetite	26/45
Jung 2007	Appetite loss	16/83
Kemner 2005 (FOCUS)	Decreased appetite	49/850
Kim 2010	Decreased appetite	9/27
Kim 2011	Poor appetite	22/97
Kratochvil 2002	Anorexia	6/25

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Study	Symptom	Adverse events/total number of participants
	Gastrointestinal system	
Lakic 2012	Loss of appetite	68/68
Lee 2007	Decreased appetite	31/110
Li 2011	Decreased appetite	13/34
Maayan 2009	Decreased appetite	7/11
Maia 2008	Barkley decreased appetite	19/31
Mayes 1994	Decreased appetite	14/63
McCracken 2016	Decreased appetite	31/61
Miller-Horn 2008	Decreased appetite	2/23
Mohammadi 2004	Loss of appetite	4/11
Mohammadi 2010	Decreased appetite	17/19
Mohammadi 2012a	Loss of appetite	11/23
Mohammadi 2012b	Decreased appetite	9/20
Na 2013	Decreased appetite	66/103
Perera 2010	Loss of appetite	51/102
Peyre 2012a	Reduced appetite	9/121
Pierce 2010	Decreased appetite	7/71
Poulton 2003	Decreased appetite	12/13
Sahin 2014	Loss of appetite	21/30
Sangal 2006	Decreased appetite	19/79
Shang 2015	Decreased appetite	36/66
Silva 2004	Decreased appetite	7/22
Steele 2006	Decreased appetite	17/60
Su 2015	Decreased appetite	72/205
Tasdelen 2015	Loss of appetite	9/17
Thorell 2009	Loss of appetite	21/79
Valdizán Usón 2004	Loss of appetite	9/155
Valdizán Usón 2013	Appetite and nutrition disorders	68/689
Wang 2007	Decreased appetite	32/166
Warshaw 2010	Decreased appetite	77/260
Wigal 2013	Decreased appetite	21/39
Wigal 2015	Decreased appetite	38/200
Wilens 2005	Appetite suppression	55/229
Wilens 2008	Decreased appetite	35/127
Yalcin 2014	Decreased appetite	28/40
Yatsuga 2014	Decreased appetite	3/50
Yildiz 2010	Loss of appetite	27/47
Zarinara 2010	Decreased appetite	7/18
Zeni 2007	Decreased appetite	53/106
Zheng 2011	Loss of appetite	552/1154
Zheng 2015	Loss of appetite	16/123
	Decreased weight	
Abbas 2006	Weight loss	2/90
Abbasi 2011	Weight loss	6/20
Amiri 2008	Weight loss	7/27
Ardic 2014	Weight loss	25/101
Arnold 2004	Weight loss	3/76
Arnold 2010	Decreased weight	5/171
Berek 2011	Weight decrease	10/762
Cortese 2015	Weight loss	37/1426
Davari-Ashtiani 2010	Weight loss	4/16
Dittmann 2014	Weight decrease	3/195
Döpfner 2011b	Weight loss	0/113
Findling 2009	Decreased weight	33/157
Grcevich 2001	Weight loss	3/75

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Study	Symptom	Adverse events/total number of participants
	Gastrointestinal system	
Haertling 2015	Weight decreased	3/239
Işeri 2007	Weight loss	2/20
Johnson 2013	Weight loss	9/45
Kordon 2011	Weight decrease	8/541
Kratochvil 2002	Weight loss	2/25
Lakic 2012	Moderate loss of body weight	68/68
Mohammadi 2012a	Weight loss	9/23
Remschmidt 2005	Weight decrease	1/105
Sahin 2014	Weight loss	20/30
Song 2012	Weight loss	4/116
Warshaw 2010	Decreased weight	9/260
Wilens 2005	Weight loss	8/407
Yildiz 2010	Weight loss	12/47
Yildiz 2011	Weight loss	5/11
Çetin 2015	Weight loss	1/16
	Diarrhoea	
Abbasi 2011	Diarrhoea	5/20
Blader 2010	Diarrhoea	2/65
Hammerness 2009	Diarrhoea	3/57
Khajehpiri 2014	Diarrhoea	3/71
Kordon 2011	Diarrhoea	7/541
Kratochvil 2002	Diarrhoea	1/25
Mohammadi 2004	Diarrhoea	0/11
Mohammadi 2010	Diarrhoea	1/19
	Dry mouth	
Abbasi 2011	Dry mouth	8/20
Amiri 2008	Dry mouth	10/27
Blader 2010	Dry mouth	2/65
Davari-Ashtiani 2010	Dry mouth	0/16
Işeri 2007	Dry mouth	1/20
Mohammadi 2004	Dry mouth	3/11
Mohammadi 2010	Dry mouth	6/19
Mohammadi 2012a	Dry mouth	3/23
Mohammadi 2012b	Dry mouth	3/20
	Gastrointestinal adverse events	
Dittmann 2014	Gastrointestinal disorders	6/247
Gau 2008	Gastrointestinal upset	36/607
Valdizán Usón 2013	Gastrointestinal symptomatology	9/633
	Nausea	
Abbasi 2011	Nausea	5/20
Akhondzadeh 2003	Nausea	2/14
Akhondzadeh 2004	Nausea	3/20
Amiri 2008	Nausea	4/27
Ardic 2014	Nausea	14/101
Arnold 2004	Nausea	7/76
Barrickman 1995	Nausea	1/18
Chou 2012b	Nausea	15/230
Dittmann 2014	Nausea	2/195
Döpfner 2011a, OBSEER	Nausea	9/777
Döpfner 2011b	Nausea	1/113
Findling 2009	Nausea	20/157
Garg 2014	Nausea	1/27
Ghanizadeh 2013	Nausea + vomiting	1/26
Gucuyener 2003	Nausea	11/119

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Study	Symptom	Adverse events/total number of participants
	Gastrointestinal system	
Guerreiro 1996	Nausea	1/22
Haertling 2015	Nausea	4/239
Hammerness 2009	Nausea	4/57
Işeri 2007	Nausea	1/20
Kemner 2005 (FOCUS)	Nausea	9/850
Khajehpiri 2014	Nausea	4/71
Kim 2010	Nausea	1/27
Kordon 2011	Nausea	10/541
Kratochvil 2002	Vomiting + nausea + dyspepsia	4/25
Lee 2007	Nausea	5/110
Lee 2014	Nausea	5/100
Li 2011	Nausea	16/34
Mohammadi 2004	Nausea	0/11
Mohammadi 2010	Nausea	4/19
Na 2013	Nausea	32/103
Pierce 2010	Nausea	3/71
Schulz 2010	Nausea	8/145
Song 2012	Nausea	9/116
Su 2015	Nausea	11/205
Tasdelen 2015	Nausea	1/17
Wang 2007	Nausea	17/166
Warshaw 2010	Nausea	13/260
Wilens 2005	Nausea	7/407
Yildiz 2010	Nausea	9/47
Yildiz 2011	Nausea	5/11
Zarinara 2010	Nausea	5/18
	Upset stomach	
Arnold 2004	Dyspepsia	6/89
Hulvershorn 2012	Upset stomach	4/25
Na 2013	Dyspepsia	13/103
	Vomiting	
Arnold 2004	Vomiting	3/76
Dittmann 2014	Vomiting	1/195
Findling 2009	Vomiting	23/157
Jafarinia 2012	Vomiting	3/20
Kemner 2005 (FOCUS)	Vomiting	11/850
Lee 2007	Vomiting	8/110
Lee 2014	Vomiting	5/100
Maayan 2009	Vomiting	1/8
Mohammadi 2010	Vomiting	2/19
Mohammadi 2012a	Vomiting	3/23
Mohammadi 2012b	Vomiting	2/20
Na 2013	Vomiting	7/103
Shang 2015	Vomiting	5/66
Silva 2004	Vomiting	6/22
Su 2015	Vomiting	9/205
Valdizán Usón 2004	Vomiting	2/155
Wang 2007	Vomiting	6/166
Wilens 2005	Vomiting	6/407
Yildiz 2011	Vomiting	1/11
Zarinara 2010	Vomiting	4/18
	Dyspepsia	
Arnold 2004	Dyspepsia	6/76
Cortese 2015	Dyspepsia	9/1426

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Gastrointestinal system		
Study	**Symptom**	**Adverse events/total number of participants**
	Gastroenteritis	
Arnold 2004	Gastroenteritis	0/76
Wigal 2015	Gastroenteritis	4/200
	Increased appetite	
Blader 2010	Increased appetite	1/65
	Xerostomia	
Khajehpiri 2014	Xerostomia	12/71

Analysis 7.5. Comparison 7 Non-comparative studies: proportion of participants with non-serious adverse events, Outcome 5 Musculoskeletal system.

Musculoskeletal system		
Study	**Symptom**	**Adverse events/total number of participants**
	Chest pain	
Arnold 2004	Chest pain	0/76
Hammerness 2009	Chest pain	2/57
Shang 2015	Chest pain	1/66
	Height	
Jensen 1999 (MTA)	No difference	-
Kim 2010	Increased from baseline	128.7 cm (SD = 9.10)
Mohammadi 2012a	Increased from baseline	133.8 cm (SD = 14.81)
Vincent 1990	No difference	158.7 cm (SD = 10.2)
Wiguna 2012	Increased from baseline	0.55 cm (SD = no information)
Yalcin 2014	Increased from baseline	134.6 cm (SD = 12.32)
	Weight	
Davari-Ashtiani 2010	Increased from baseline	Weight gain in 1/16 participants
Germinario 2013	Increased from baseline	38.4 kg (SD = 11.3)
Kim 2010	No difference	28.5 kg (SD = 6.40)
Kratochvil 2002	No difference	40.7 kg (SD = 17.2)
Mohammadi 2012a	Increased from baseline	32.7 kg (SD = 14.7)
Vincent 1990	No difference	Observed weight: 47.9 kg (SD = 10.3) Expected weight: 48.1 kg (SD = 10.6)
Wiguna 2012	Decreased from baseline	36.2 kg (SD = 11.9)
Yalcin 2014	Increased from baseline	Weight gain in 15/33 participants
	BMI	
Gerwe 2009	No difference	Mean change from baseline: −0.3 kg/m^2 (SD = 0.70)
Mohammadi 2012a	No difference	18.2 kg/m^2 (SD = 4.74)
Yalcin 2014	No difference	Methylphenidate group: 18.1 kg/m^2 (SD = 2.76) Untreated group: 17.8k kg/m^2 (SD = 2.71)
	Height z score	
Bereket 2005	Decreased from baseline	-
Germinario 2013	Decreased from baseline	Z score = 0.36 (SD = 1.21)
Moungnoi 2011	Decreased from baseline	Z score = 0.09 (SD = no information)
Poulton 2003	Decreased from baseline	Z score = 0.26 (SD = 0.82)
Poulton 2012	Decreased from baseline	Z score = 0.34 (SD = 0.81)
Schertz 1996	Decreased from baseline	Z score = -0.1(SD = no information)
Spencer 1992	Decreased from baseline	Z score = -0.23 (SD = 0.42)
	Weight z score	
Bereket 2005	Decreased from baseline	0.2 (SD = 1.04)
Gerwe 2009	Decreased from baseline	0.26 kg (SD = 1.40)
Moungnoi 2011	Decreased from baseline	Z score = 0.01 (SD = no information)
Poulton 2003	Decreased from baseline	Z score = 0.44 (SD = 0.97)
Schertz 1996	Decreased from baseline	-

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Musculoskeletal system		
Study	**Symptom**	**Adverse events/total number of participants**
BMI z score		
Bereket 2005	No difference	After 14 months: Age-adjusted SD = 0.71 Sex-adjusted SD = 0.65
Dubnov-Raz 2011	No difference	-
Poulton 2012	No difference	-
Increased mobility		
Ardic 2014	Increased mobility	22/122
Bone mineral density		
Lahat 2000	**Quote:** "There was no significant difference between serum calcium, phosphorus or bone-specific alkaline phosphatase, urinary deoxypyridinoline, or bone mineral density in the two groups of children. No child deviated from his height percentile during the treatment period."	NA

Analysis 7.6. Comparison 7 Non-comparative studies: proportion of participants with non-serious adverse events, Outcome 6 Immune system.

Immune system		
Study	**Symptom**	**Adverse events/total number of participants**
Nasopharyngitis		
Arnold 2004	Rhinitis	5/76
Arnold 2010	Rhinitis	6/150
Döpfner 2011b	Rhinitis	2/113
Findling 2009	Rhinitis	24/157
Kratochvil 2002	Rhinitis	8/25
Pyrexia		
Arnold 2004	Fever	7/89
Findling 2009	Fever	33/157
Wang 2007	Pyrexia	17/166
Allergies		
Hammerness 2009	Allergies	3/154
Pierce 2010	Pruritis	2/71
Cold symptoms		
Hammerness 2009	Cold symptoms	2/57
Kratochvil 2002	Fever + flu syndrome	8/25
Steele 2006	Flu-like symptoms	7/72
Pharyngitis		
Arnold 2004	Pharyngitis	10/76
Döpfner 2011b	Pharyngitis	2/113
Kordon 2011	Pharyngitis	6/541
Kratochvil 2002	Pharyngitis	3/25
Sangal 2006	Pharyngitis	7/79
Viral infection		
Arnold 2004	Viral infection	18/76
Kordon 2011	Viral infection	8/598
Rash		
Arnold 2004	Rash	6/76
Garg 2014	Rash	1/27
Lee 2007	Rash	4/110
Rhinitis		
Arnold 2004	Rhinitis	5/76
Kordon 2011	Rhinitis	8/541
Ear disorders		

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Study	Symptom	Adverse events/total number of participants
	Immune system	
Hammerness 2009	Ear pain	3/57
	Fever	
Kordon 2011	Fever	9/541
	Infections	
Valdizán Usón 2013	Nonspecific pathogen	13/689

Analysis 7.7. Comparison 7 Non-comparative studies: proportion of participants with non-serious adverse events, Outcome 7 Urogenital system: enuresis.

Study	Symptom	Adverse events/total number of participants
	Urogenital system: enuresis	
Blader 2010	Enuresis	2/65
Galland 2010	Enuresis	3/27
Tomás Vila 2010b	Enuresis	16/114

Analysis 7.8. Comparison 7 Non-comparative studies: proportion of participants with non-serious adverse events, Outcome 8 Other body systems.

Study	Description	Adverse events/total number of participants
	Other body systems	
	Hair loss	
Abbas 2006	Hair loss	1/90
Khajehpiri 2014	Hair loss	3/71
	Skin problems	
Haertling 2015	Skin disorder	1/239
Khajehpiri 2014	Acne	2/71
Pierce 2010	Application site erythema	2/71
Shang 2015	Skin eruption	1/66
	Accidental injury	
Arnold 2004	Accidental injury	10/76
	Voice frequency	
Congologlu 2009	In conclusion, this clinical trial is the only study that has examined the effects of stimulant medication on vocal acoustic parameters in children with ADHD (attention deficit hyperactivity disorder), and evaluated a small sample on and off their clinical doses of methylphenidate. We suggest that methylphenidate decreases fundamental frequency in children with ADHD, but our findings should be replicated under blind drug administration and by supporting other vocal analyses	NA
	Hypersalivation	
Garg 2014	Hypersalivation	1/27
	Nasal bleeding	
Ghanizadeh 2013	Nasal bleeding	1/26
	Chromosomal aberration	
Witt 2008	% of cells with chromosomal abberations	Before: 0.48% (0.09). After: 0.46% (0.09) Study population: 25

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Comparison 8. Non-comparative studies: proportion of participants withdrawn from methylphenidate treatment due to non-serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants withdrawn from methylphenidate treatment due to non-serious adverse events			Other data	No numeric data
2 Proportion of participants withdrawn from methylphenidate for unknown reasons			Other data	No numeric data

Analysis 8.1. Comparison 8 Non-comparative studies: proportion of participants withdrawn from methylphenidate treatment due to non-serious adverse events, Outcome 1 Proportion of participants withdrawn from methylphenidate treatment due to non-serious adverse events.

Proportion of participants withdrawn from methylphenidate treatment due to non-serious adverse events	
Study	
Arabgol 2015	2/18
Arnold 2010	1/171
Berek 2011	60/822
Chou 2012a	26/521
Dirksen 2002	10/310
Döpfner 2011b	4/113
Efron 1997	1/125
Faraone 2007a	45/268
Findling 2010	13/162
Garg 2014	7/33
Gerwe 2009	43/306
Greenberg 1987	1/50
Guerreiro 1996	1/24
Hammerness 2009	19/152
Hong 2012	3/112
Karabekiroglu 2008	8/90
Khodadust 2012	1/15
Kim 2014b	3/57
Lee 2007	2/119
Maayan 2009	3/11
Na 2013	7/121
Shang 2015	3/80
Sobanski 2013	5/381
Song 2012	8/143
Su 2015	16/239
Tasdelen 2015	3/22
Wang 2007	6/166
Wang 2011	3/50
Warshaw 2010	21/305
Weber 2003	4/57
Weiss 2007	4/90
Wigal 2013	2/45
Wilens 2005	38/407
Winsberg 1982	5/25
Yildiz 2011	1/12
Zheng 2011	34/1447

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Proportion of participants withdrawn from methylphenidate treatment due to non-serious adverse events	
Study	
Çetin 2015	5/73

Analysis 8.2. Comparison 8 Non-comparative studies: proportion of participants withdrawn from methylphenidate treatment due to non-serious adverse events, Outcome 2 Proportion of participants withdrawn from methylphenidate for unknown reasons.

Proportion of participants withdrawn from methylphenidate for unknown reasons	
Study	
Akhondzadeh 2003	4/14
Akhondzadeh 2004	2/22
Altin 2013	30/204
Amiri 2008	3/30
Ardic 2014	21/122
Balázs 2011	3/37
Barbaresi 2006	84/379
Bereket 2005	58/72
Chou 2012b	34/296
Dirksen 2002	13/310
Dittmann 2014	52/247
El-Zein 2005	6/18
Findling 2009	109/326
Findling 2010	54/162
Gadow 1995	7/34
Galland 2010	2/30
Gau 2008	13/137
Germinario 2013	161/351
Guerreiro 1996	2/24
Haertling 2015	16/262
Hammerness 2009	97/152
Hong 2012	5/112
Jensen 1999 (MTA)	29/144
Kim 2011	5/102
Kim 2014b	12/75
Kim 2015a	49/86
Klein 2004	9/129
Lee 2009	6/144
Lee 2012	22/93
Li 2011	2/36
McCracken 2016	6/69
Mohammadi 2004	5/16
Mohammadi 2012a	8/32
Mohammadi 2012b	3/23
Peyre 2012a	37/173
Poulton 2003	6/19
Remschmidt 2005	26/89
Shang 2015	11/80
Sobanski 2013	29/381
Steele 2006	4/73
Tasdelen 2015	2/22
Walitza 2009	15/26
Wang 2007	7/166
Wang 2011	17/50
Warshaw 2010	28/305

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Proportion of participants withdrawn from methylphenidate for unknown reasons	
Study	
Weber 2003	8/57
Weiss 2007	3/90
Wigal 2013	3/45
Wilens 2005	140/407
Wilens 2006	36/171
Witt 2008	9/34
Yalcin 2014	2/40
Yang 2012	12/130
Zarinara 2010	1/19
Zheng 2011	202/1447
Zheng 2015	25/153
Çetin 2015	7/73

Comparison 9. Patient reports/series: number of participants with serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Central nervous system			Other data	No numeric data
1.1 Psychotic conditions			Other data	No numeric data
1.2 Seizures			Other data	No numeric data
1.3 Cerebral arteritis			Other data	No numeric data
1.4 Self-harm and suicidal behaviour			Other data	No numeric data
1.5 Death			Other data	No numeric data
1.6 Dyskinesia			Other data	No numeric data
2 Cardiovascular and respiratory system			Other data	No numeric data
2.1 Cardiovascular events			Other data	No numeric data
2.2 Hypertension			Other data	No numeric data
3 Gastrointestinal system: hepatoxicity			Other data	No numeric data
4 Urogenital system: priapism			Other data	No numeric data

Analysis 9.1. Comparison 9 Patient reports/series: number of participants with serious adverse events, Outcome 1 Central nervous system.

Central nervous system	
Study	
Psychotic conditions	
Abali 2007	A 14-year-old girl with diagnoses of ADHD (attention deficit hyperactivity disorder), major depression and conduct disorder. During her treatment with methylphenidate of 20 mg/day and fluoxetine of 20 mg/day, she developed visual and auditory hallucinations. It may be concluded that it is possible that

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Central nervous system	
Study	
	methylphenidate may cause hallucinations in patients treated simultaneously with fluoxetine
Aguilera-Albesa 2010	2 case reports of the appearance of hallucinations a few hours after methylphenidate ingestion in an 8-year-old boy (extended-release methylphenidate of 18 mg/day, given once daily for 2 days) and a 6-year-old girl (extended-release methylphenidate of 10 mg/day for 3 days and 20 mg/day for 1 day, given once a day). Both diagnosed with ADHD according to criteria in the DSM-IV (*Diagnostic and Statistical Manual, Fourth Edition*) and with IQs (intelligence quotients) > 85. These case reports suggest an individual susceptibility to psychotic symptoms after taking methylphenidate. This adverse event is considered idiosyncratic, extraordinary and unpredictable
Coşkun 2008	A paediatric patient who developed tactile and visual hallucinations with the combination of osmotic release oral system (OROS) methylphenidate and fluoxetine. Comments from the study authors: In conclusion, we think that the causative agent was the combination of both medications rather than either medication alone. However, in either situation, it is important to note that this distressing side effect may occur even in the absence of underlying psychotic or substance-related disorders, and clinicians' awareness is important in this issue, particularly in cases where polypharmacy is considered
Goetz 2011	A case report of nocturnal visual hallucinations during methylphenidate treatment. A girl with ADHD and ODD (oppositional defiant disorder) experienced a 3-hour episode of nocturnal complex bizarre visual hallucinations when treated with 18 mg of OROS methylphenidate. Nocturnal polysomnography performed 2 weeks later revealed REM (rapid eye movement) sleep reduction (17%) and fragmentation. 2 episodes of confusional arousals were recorded. This finding is typical of parasomnia associated with NREM sleep – disorder of arousal. It is hypothesized that this pre-existing sleep impairment represents a factor of vulnerability to methylphenidate sleep side effects
Gross-Tsur 2004	3 children with ADHD, who were treated with low doses of methylphenidate and who developed complex visual and haptic hallucinations Comments from the study authors: The causal role of methylphenidate in the development of hallucinations was based on their appearance after ingestion of the drug, resolving after its withdrawal, and the absence of psychiatric comorbidity that could explain such phenomena. In 1 patient, the hallucinations reappeared after an inadvertent re-challenge. Because methylphenidate is a widely used, well-studied, and safe pharmacologic agent, physicians who prescribe methylphenidate should be aware of even rare adverse manifestations occurring at therapeutic doses
Halevy 2009	Several days after initiation of treatment: visual hallucinations of rats, accompanied by some tactile hallucinations. Only present during the time the patient was under the influence of methylphenidate and disappeared thereafter; immediate complete resolution upon discontinuation of the drug. Reintroduction of metyhlphenidate treatment after 2 days resulted in same complex visual hallucinations, with immediate complete resolution upon discontinuation of the drug Key conclusions of the study authors: In our case, the occurrence of hallucinations after a very low dose of methylphenidate on 2 occasions may suggest an idiosyncratic reaction. The phenomenon might also be explained by a drug-induced dysfunction of the monoamine transmitters. Given the wide use of methylphenidate, clinicians should be aware of this possible side effect
Irmak 2014	A case report of phobias and visual hallucinations during methylphenidate treatment in a 9-year-old boy. OROS methylphenidate gradually titrated up to 1 mg/kg. Methylphenidate prescribed at initial ADHD diagnosis and then withdrawn following the onset of phobias and visual hallucinations, as well as lack of improvement in attention problems
Mino 1999	A case report on methylphenidate-induced psychosis in an adolescent with hyperkinetic disorder; use of methylphenidate for 1 month. Three weeks after starting methylphenidate (10 mg/day), the mother reported by telephone that the patient seemed depressed. Dose of methylphenidate was reduced to 5 mg/day. A week later the patient visited the clinic. The therapist diagnosed her condition as a depressive state and discontinued methylphenidate. Six weeks after discontinuation of methylphenidate she was diagnosed with a schizophrenic-like psychotic state, due to symptoms of delusions of reference and persecution, delusional mood, silly smile and thought block. There was no evident hallucination. The patient took antipsychotic medication for 2 months and her psychotic symptoms disappeared
Porfirio 2011	3 years after start of methylphenidate treatment: An episode of complex visual hallucinations (dramatic scenes appearing before going to sleep, sometimes during the day after ingestion of methylphenidate
Rashid 2007	A case report of intensified somatic hallucinations during dose increase of methylphenidate treatment in a 10-year-old boy with a chronic pattern of somatization, which evolved into overt somatic hallucinations with an increase in methylphenidate dosage. This pattern of somatization was retrospectively recognized as partial somatic hallucinations
Shibib 2009	A report of four cases of psychosis during methylphenidate treatment

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Central nervous system	
Study	
	Key conclusion of the study authors: Psychosis is an important, unpredictable side effect of stimulant medication. Symptoms resolve with discontinuation of treatment. Reemergence of ADHD symptoms are rapid and re-challenge is often indicated. It would be advisable for all professionals involved in the care and treatment of patients with ADHD to receive mental health training to aid the early recognition and appropriate management of such side effects
Tomás Vila 2010a	After two weeks of 50% immediate-release and 50% extended-release methylphenidate: visual hallucinations (insects on hands, feet, abdomen and thorax), with associated itching, initiated two hours after ingestion and ceased five hours after. Discontinuation of methylphenidate and initiation of risperidone resulted in no visual hallucinations. No re-administration of methylphenidate due to ethical reasons Key conclusions of the study authors: This is the first case report of visual hallucinations caused by 50% immediate-release and 50% extended-release methylphenidate, which is not surprising considering the relative recent appearance of this preparation on the market
Seizures	
Feeney 1997	First-reported seizure in a patient being treated with methylphenidate and sertraline combined
Hemmer 2001	Reported seizures in a boy aged six, and two girls aged six and seven, receiving 0.3 to 1 mg/kg/day of methylphenidate for six weeks, 10 and three months, respectively
Cerebral arteritis	
Trugman 1988	Key conclusions of the study authors: Cerebral arteritis and infarction were caused by chronic use of oral methylphenidate. The Cerebrospinal fluid (CSF) profile and angiogram support the diagnosis of inflammatory arteritis, yet laboratory evaluation revealed no identifiable cause. In the six years since the stroke, while not on methylphenidate, there has been no evidence of active central nervous system or systemic vasculitis
Self-harm and suicidal behaviour	
Arun 2014	2 case reports with 2 children having suicidal ideation
Gökce 2015	Reported a 12-year-old boy who made a suicide attempt after switching from 27 mg to 36 mg of OROS methylphenidate: The patient reported irritable mood when he took the first dose of 36 mg of long-acting methylphenidate. This might be the cause of the suicide attempt. He had a full recovery after withdrawal from methylphenidate
Strandell 2007	Reported concerns about suicidal behaviour, including suicide, based on information retrieved from the WHO Collaborating Centre for International Drug Monitoring (Uppsala, Sweden). A total of 116 reports of methylphenidate related to "suicide attempts", although this term was not explicitly defined. The data included reports of methylphenidate and atomoxetine
Death	
Tølløfsrud 2006	A case report of death caused by heart failure (acute dilated cardiomyopathy) during methylphenidate treatment
Dyskinesia	
Yilmaz 2013	Involuntary movements started about 5 hours after taking MPH. Lip-licking, lip-smacking and tongue-rolling movements. Dyskinetic tongue movements inside and outside the mouth and involuntary bilateral arm swinging while sitting and standing. Opening and closing his fingers without complete extension. Occasional repetitive movements of the feet, such as beating them against each other while sitting. About 15 hours after MPH intake both hand-mouth movements and excessive mobility had significantly resolved. Dyskinetic symptoms had completely disappeared on the second day of hospitalization, and the patient was discharged Key conclusions of the study authors: This case is reported to emphasize the potential side effects of methylphenidate, individual differences in drug sensitivities, and drug-receptor interactions via different mechanisms

Analysis 9.2. Comparison 9 Patient reports/series: number of participants with serious adverse events, Outcome 2 Cardiovascular and respiratory system.

Cardiovascular and respiratory system	
Study	
Cardiovascular events	
Munk 2015	The present case demonstrates that myocardial infarction can occur due to methylphenidate exposure in a healthy 11-year-old boy, without other known cardiovascular risk factors. 54 mg methylphenidate/day. Treatment duration was 2

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Cardiovascular and respiratory system	
Study	
	years. Cardiac arrest followed exercise without prior complaints of chest pain/discomfort or shortness of breath. A week before the event, he had a short episode of tachycardia. Clinical examination showed that the myocardial infarct was not acute but had occurred weeks prior to the cardiac arrest. It was thought to be due to thinning of the myocardium and an adversely remodelled left ventricle. A pacemaker was inserted and methylphenidate treatment was discontinued. The only apparent cause, after extensive assessment, appeared to be the high-dose methylphenidate treatment (maximum recommended) over an extended period
Nymark 2008	A case report of serious cardiomyopathy during MPH treatment. Serious cardiovascular adverse effects (hypoxia and dyspnoea requiring hospitalisation) after 11 months of MPH treatment. Clinical examination showed signs of liver failure, renal failure and heart failure Comments of the study authors (Nymark et al): With a BMI of 40 our patient had extreme obesity. The hyperdynamic circulation, with increased cardiac output, was thought to be a compensatory adaptation to increased adipose tissue. This may have led to non-ischaemic dilated cardiomyopathy at the expense of left ventricular hypertrophy and remodeling as may occur in severely obese subjects (McGavock et al 2006). This is, however, unlikely as the only cause in our young patient. Human obesity is also characterized by sympathetic nervous system activation (Eikelis and Esler 2005). A possible obesity-linked susceptibility to the toxic effect of methylphenidate could therefore play a role in the development of DCM in our patient, especially with regards to the short treatment time of one year
Hypertension	
Saieh 2004	A case report of hospitalisation due to hypertension during MPH treatment Serious adverse events 72-hour hospitalisation, emergency unit Abdominal pain for four days prior to hospitalisation, intermittent accentuation (hours), no other symptoms Secondary hypertension: Persistent hypertension (158/88-170/105, pulse: 78-98 bpm). Normal physical examination. Normal eye fundus and normal cardiological examination Discontinuation of MPH: Hypertensive treatment only necessary for 24 hours Normal blood pressure after one week

Analysis 9.3. Comparison 9 Patient reports/series: number of participants with serious adverse events, Outcome 3 Gastrointestinal system: hepatoxicity.

Gastrointestinal system: hepatoxicity	
Study	
Bernhard 2009	A hepatotoxic reaction Liver enzymes were elevated prior to therapy. Vomiting starting 5 weeks after onset of methylphenidate therapy and increased within the next 3 days. Abdominal pain increased in intensity. Liver transaminases elevated over 30 times of the normal level, CK level also increased

Analysis 9.4. Comparison 9 Patient reports/series: number of participants with serious adverse events, Outcome 4 Urogenital system: priapism.

Urogenital system: priapism	
Study	
Cakin-Memik 2010	A case report of a 14-year-old male with attention deficit hyperactivity disorder (ADHD) who presented with priapism after administration of immediate-release methylphenidate. When the usage of immediate-release methylphenidate was terminated, priapism spontaneously disappeared
Schwartz 2004	A case report of a 15-year-old white male with ADHD (inattention subtype) who experienced painful erections two weeks after beginning sustained release (OROS) MPH and repeated painful erections that increased with increased doses (during withdrawal). MPH use for more than 2 months. It is likely that withdrawal from OROS methylphenidate was the cause of this adolescent boy's priapism. He was embarrassed to disclose the problem to an adult until it became quite severe. It is possible that this adverse event is under-reported due to sensitivity and embarrassment of young people

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Comparison 10. Patient reports/series: number of participants with non-serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Central nervous system: movement-related outcomes			Other data	No numeric data
1.1 Tics			Other data	No numeric data
1.2 Involuntary movements or dyskinesia			Other data	No numeric data
2 Central nervous system: mood disorders			Other data	No numeric data
2.1 Depression and disturbed mood			Other data	No numeric data
2.2 Irritability			Other data	No numeric data
2.3 Aggression			Other data	No numeric data
2.4 Mania/euphoria			Other data	No numeric data
3 Central nervous system: sleep problems			Other data	No numeric data
3.1 Disturbed sleep			Other data	No numeric data
3.2 Other sleep problems			Other data	No numeric data
4 Central nervous system: voice and speech disorders			Other data	No numeric data
4.1 Voice problems			Other data	No numeric data
4.2 Stuttering			Other data	No numeric data
5 Central nervous system: other specific adverse events			Other data	No numeric data
5.1 Anorexia			Other data	No numeric data
5.2 Obsessive compulsive disorder (OCD) symptoms			Other data	No numeric data
5.3 Headache			Other data	No numeric data
5.4 EEG changes			Other data	No numeric data
6 Cardiovascular and respiratory system			Other data	No numeric data
6.1 Vasculopathy			Other data	No numeric data
6.2 Cardiovascular problems			Other data	No numeric data
6.3 Bleeding			Other data	No numeric data

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.4 Tachycardia			Other data	No numeric data
7 Gastrointestinal system			Other data	No numeric data
7.1 Loss of appetite			Other data	No numeric data
7.2 Nausea and vomiting			Other data	No numeric data
8 Musculoskeletal system: growth			Other data	No numeric data
9 Immune system: allergic reactions			Other data	No numeric data
10 Urogenital system			Other data	No numeric data
10.1 Testicular failure			Other data	No numeric data
10.2 Sexual adverse events			Other data	No numeric data
10.3 Incontinence			Other data	No numeric data
10.4 Enuresis			Other data	No numeric data
11 Other body systems			Other data	No numeric data
11.1 Skin reactions			Other data	No numeric data
11.2 Problems with sedation			Other data	No numeric data
11.3 Eye problems			Other data	No numeric data

Analysis 10.1. Comparison 10 Patient reports/series: number of participants with non-serious adverse events, Outcome 1 Central nervous system: movement-related outcomes.

Central nervous system: movement-related outcomes

Study	Tics
Adrian 2001	A case report of a boy aged 10 years referred to a tertiary neurodevelopmental assessment clinic for a second opinion on the management of his ADHD. He started with 20 mg/day of methylphenidate at 7 years of age and gradually increased to 40 mg/day, for 2 to 3 years. Both motor and vocal tics started at 40 mg/day of methylphenidate and subsided spontaneously after a year of treatment Authors' conclusion: The clinically explosive outbursts of tics were coincident with a period of treatment with methylphenidate for the treatment of ADHD (attention deficit hyperactivity disorder) and should not be mistaken for a symptom of the disorder
Chandler 1989	Reported non-serious adverse events. After a month, the child's mother reported motor and phonic tics again. He was treated first with methylphenidate and then with nortriptyline. With both drugs he manifested severe facial grimacing and phonic tics; apparently, the tics had only occurred in the past when the child was treated with methylphenidate. It is, however, very difficult to attribute the tics to methylphenidate with any certainty because of the common co-occurrence of tics in children and young people with ADHD Key conclusions of the study authors: Side effects, such as hypomania, hyperreflexia and diaphoresis, have been reported in patients being treated with a combination of a monoamine oxidase inhibitor and tryptophan. By itself, L-tryptophan may be mildly sedating. In light of such a favourable side-effect profile, combined with no evidence for adverse interaction with stimulants, and at least some rationale

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Central nervous system: movement-related outcomes	
Study	
	from preclinical research, it should be investigated further as a means of alleviating some of the harsh consequences of psychostimulant treatment in ADHD
Involuntary movements or dyskinesia	
Hollis 2007	A case report of acute and transient dyskinesia occurring within hours of taking modified-release methylphenidate (Concerta XL) in a stimulant-naïve 7-year-old boy who had recently stopped taking risperidone Key conclusions of the study authors: This report is the first of a dyskinesia occurring after a single first dose of methylphenidate in a previously stimulant-naïve patient after neuroleptic withdrawal. It is also the first to link this effect with modified-release methylphenidate. The dyskinesia described here consisted of both brief tic-like movements
Machado 2010	Choreoathetoid movements of orofacial muscles, arms and legs, with transient dystonic postures of the right arm induced by a single dose of extended-release methylphenidate. Author believes that the immediate response ensuing chlorpromazine prescription argues in favour of a specific role for dopamine receptor antagonists in methylphenidate-induced chorea
McLaren 2010	The patient experienced spasmodic muscular contractions of his jaw. The staff noticed a forceful jaw closure, contraction and tension, and the patient had difficulties opening his mouth. 50 mg of diphenhydramine was administered intramuscularly and the patient could open his mouth within 30 minutes and with no further dystonia

Analysis 10.2. Comparison 10 Patient reports/series: number of participants with non-serious adverse events, Outcome 2 Central nervous system: mood disorders.

Central nervous system: mood disorders	
Study	
Depression and disturbed mood	
Hechtman 2011	A case report about a 5-year-old boy. MPH use for around a year. Reported non-serious adverse events. In late afternoon and early evening, he became very emotional, with frequent crying, marked irritability and many tantrums. The emotional side effects subsided after he discontinued methylphenidate treatment
Mino 1999	3 weeks after starting on 10 mg/day of methylphenidate, the mother reported by telephone that the patient seemed depressed. The dose of methylphenidate was reduced to 5 mg/day. A week later the patient visited the clinic. The therapist diagnosed her condition as a depressive state and discontinued methylphenidate. 6 weeks after discontinuation of methylphenidate, she was diagnosed with a schizophrenic-like psychotic state, due to symptoms of delusions of reference and persecution, delusional mood, silly smile and thought block. There was no evident hallucination. The patient took antipsychotic medication for 2 months and her psychotic symptoms disappeared
Niederhofer 2009	An 11-year-old boy received 20 mg/day of methylphenidate for 2 months, which led to depressed mood and appetite loss
Irritability	
Hechtman 2011	A case report about a boy, who became very emotional, with frequent crying episodes, marked irritability and many tantrums when treated with methylphenidate; methylphenidate was used for around a year
Sabuncuoglu 2007	3 case reports of hyperactivity and irritability during switch from risperidone to methylphenidate Case 1: Methylphenidate introduced 2 days after abrupt discontinuation of 1 mg/day of risperidone (8 months), and produced agitation, irritability, vigilance, and violent behavior. No dyskinetic movements. Methylphenidate was discontinued and the adverse events disappeared. After a 6-week long, drug-free period, methylphenidate was reintroduced at 15 mg/day. No adverse events were observed Case 2: Methylphenidate introduced after discontinuation of 1 mg/day of risperidone (2 years), and produced a near manic state, irritability, agitation, racing thoughts, and distractibility. No dyskinetic movements. Methylphenidate was discontinued and the adverse events disappeared. After a couple of months, methylphenidate was reintroduced at 15 mg/day and was well-tolerated Case 3: Methylphenidate introduced after a 1-week medication-free interval after treatment with 1 mg of risperidone, and produced irritability, agitation and discomfort. Methylphenidate was discontinued and the adverse events disappeared. The patient did not retry the medication Key conclusions of the study authors: This report of 3 patients draws attention to a unique condition that arises in switching from an atypical antipsychotic to stimulant medication. A drug-free interval is recommended in switching from risperidone to methylphenidate

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Central nervous system: mood disorders

Study	
Aggression	
Coignoux 2009	A case report of a 14-year-old boy receiving methylphenidate for 2 years who developed gestural stereotypies and verbal aggressiveness towards his parents whilst on methylphenidate treatment
Niederhofer 2011	A case series describing adverse effects (xerostomia, aggression and emotional instability) among children taking methylphenidate
Mania/euphoria	
Corrigall 1996	A case report of methylphenidate euphoria in an 11-year-old boy diagnosed with hyperkinetic disorder Key conclusions of the study authors: Methylphenidate euphoria can occur in young prepubertal children and this may lead to abuse of medication
Ghanizadeh 2009	Mother and nursery teacher complained about increased hyper-talkativity starting about 45 minutes after taking medication. The increased hyper-talkativity continued for about 3–4 hours. They scored the hyper-talking as 7–9 on a 1–10 visual analogue scale. Re-challenge was conducted many times (more than 20 times) and hyper-talking reoccurred after every time he took the medication

Analysis 10.3. Comparison 10 Patient reports/series: number of participants with non-serious adverse events, Outcome 3 Central nervous system: sleep problems.

Central nervous system: sleep problems

Study	
Disturbed sleep	
Langevin 2012	A controlled before-and-after study. Methylphenidate used to treat ADHD (attention deficit hyperactivity disorder), from December (time 1) to June (time 2) Key conclusions of the study authors: The principal results support the study's hypothesis and show a significant baseline difference (P = 0.008) between the nocturnal movements of children with ADHD and those of children in the control group
Other sleep problems	
Arun 2014	A case report of a child whose sleep was impaired for 1 night after receiving methylphenidate
Coşkun 2010	A case series of 7 children who experience side effects during methylphenidate treatment: Sleep problems: n = 4 Worsening of pre-existing sleep problems: n = 2 No worsening of pre-existing sleep problems: n = 1

Analysis 10.4. Comparison 10 Patient reports/series: number of participants with non-serious adverse events, Outcome 4 Central nervous system: voice and speech disorders.

Central nervous system: voice and speech disorders

Study	
Voice problems	
Yalcin 2012	Teacher and family observed disturbance of voice quality, hoarseness, bifurcation-strain and over vibration of voice. The symptoms began on the first day of treatment with methylphenidate. Hoarseness and reduction in the voice amplitude was evident during the first visit to a psychiatric out-hospital clinic. No symptoms were observed by parents or during the psychiatric control on drug-free days. Experienced hoarseness when methylphenidate administered in the clinic. Voice quality returned to normal three hours after ingestion. Laryngitis or other organic conditions causing hoarseness were not observed in physical and endoscopic examination. There were no important side effects with discontinuation of methylphenidate and administration of atomoxetine
Stuttering	
Alpaslan 2015	A case report of a 7-year-old boy who developed stuttering associated with the use of methylphenidate; received 10 mg/daily of short-acting methylphenidate. 10 days after beginning treatment with short-acting methylphenidate, the client began to stutter. Treatment was stopped. 1 week later, the patient's speech was back to normal. 4 weeks later atomoxetine treatment was started with no recurrence of stuttering

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Analysis 10.5. Comparison 10 Patient reports/series: number of participants with non-serious adverse events, Outcome 5 Central nervous system: other specific adverse events.

Central nervous system: other specific adverse events	
Study	
Anorexia	
Findling 1996	A case report about an 11-year-old girl who experienced transient side effects after receiving methylphenidate: mild and transient anorexia, transient weight loss of 2 kg observed in the initiation of methylphenidate therapy
Obsessive compulsive disorder (OCD) symptoms	
Coşkun 2011	A case report of OCD symptoms during methylphenidate treatment. Decreased appetite and initial headache with 18 mg/day of osmotic-controlled release oral delivery system (OROS) methylphenidate, and obsessive-compulsive symptoms, decreased appetite, facial grimace, and nail picking/biting with 27 mg/day of OROS methylphenidate. Gradual disappearance of symptoms, although still subsyndromal obsessive-compulsive symptoms, with discontinuation of medication. Mild facial grimace and similar obsessive-compulsive symptoms with re-administration of 27 mg/day of OROS methylphenidate. After three weeks, total score of 21 on Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS)
Woolley 2003	Obsessions and compulsions with anxiety. DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edtion*) diagnosis of OCD. Washing hands excessively, which was accompanied by checking rituals, reassurance seeking, and emetophobia. When methylphenidate was withdrawn, OCD symptoms decreased rapidly but increased when methylphenidate was reintroduced
Headache	
Mize 2004	A case report of headache and mild depression during methylphenidate treatment
EEG changes	
Dupuy 2008	A controlled before-and-after study investigating the effects of stimulants on EEG (electroencephaalography) coherence in 9 girls with ADHD (attention deficit hyperactivity disorder); intrahemispheric and interhemispheric coherences in girls with ADHD who were treated with stimulant medication. Girls had elevated frontal coherence in all frequency bands

Analysis 10.6. Comparison 10 Patient reports/series: number of participants with non-serious adverse events, Outcome 6 Cardiovascular and respiratory system.

Cardiovascular and respiratory system	
Study	
Vasculopathy	
Yu 2010	These case reports raise the concern that adverse effects in the peripheral vascular system of children and adolescents may be associated with psychostimulant treatment Patient 1: Tachycardia at age 11 while taking Concerta, 54 mg/d. Vasculopathy at age 16. His hands and feet were a continuous blue colour on his hands and fingers, which increased in frequency in cold weather. He was diagnosed with "decreased circulation but not Raynaud's syndrome". Occured when the Concerta dose was increased from 54 mg/d to 90 mg/d in 3 months with the same Focalin (dexmethylphenidate) dose (10mg/d) Patient 2: Vasculopathy. First diagnosed with Raynaud's syndrome with finger pain and colour changes during a neurology consultation at age 10 years. At age 12 years had diffuse erythema of both earlobes, the fingers of both hands, and the toes of his left foot. Tics at age 10 years but not clear if these were present prior to treatment for ADHD Patient 4: Vasculopathy. After taking Focalin for a year, he developed persistent curling of the toes of both feet. In addition, he had reddish and purple colour changes in his hands and feet with cold exposure that lasted for 20 minutes. No associated pain and only rare paraesthesia. At age 10 years, toes 2, 3 and 4 of both feet were held in a flexed position ("curled toes"), and there was skin discolouration and excoriation
Cardiovascular problems	
Karaman 2010	A case report of a 15-year old boy with ADHD who developed pulmonary arterial hypertension (PAH) during OROS MPH treatment Fourth day of treatment: The patient began to experience occasional episodes of slightly shortness of breath. Continued over several months. Not associated with either exercise or anxiety

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Cardiovascular and respiratory system	
Study	
	At 18th month of treatment: Fainting. Normal weight. No sign of allergy, hypersensitivity, or sleep apnoea. Mean pulmonary arterial pressure of 40 mmHg at rest, otherwise no pathological findings from extensive testing (Examination: clear lungs, no murmurs, rubs, or gallops, and otherwise unremarkable. Laboratory tests, including C-reactive protein, thyroid and liver function tests, electrolytes. Blood gases, antinuclear antibodies, D-dimers, chest X-ray, ventilation–perfusion scintigraphy, electrocardiography, respiratory function tests. Echography. Transthoracic echocardiogram: normal except for the mean pulmonary arterial pressure). No use of any other drug. No history of alcohol and substance use and no symptoms or signs of MPH misuse (intravenous injection). The personal and familial histories were also negative for pulmonary or cardiovascular diseases Discontinuation of OROS-MPH, one month: free of symptoms After the fourth week of discontinuation: Mean pulmonary arterial pressure of 28 mmHg
Bleeding	
Grossman 1985	A case report of a 7-year-old girl on methylphenidate treatment who developed idiopathic trombocytopenic purpura (ITP). Physical examination at the paediatric outpatient department found countless petechiae over the entire dermal surface. Numerous areas of purpura were noted, especially over her buttocks and extremities. Multiple areas of buccal mucosal and gingival bleeding with a large hematoma presented on the left lateral surface of her tongue. Clotted blood was seen in her nostrils and ear canals bilaterally. Bone marrow aspiration showed normal to increased megakaryocytes with normal red and white cell precursors. MPH was stopped and the patient was admitted. After one week of treatment for the condition, her petechia had begun to fade. She did not start on MPH again. There has been no recurrence of petechiae or bruising one year later. MPH use for seven months prior to presentation of ITP
Tachycardia	
Gracious 1999	A case report of atrioventricular (AV) nodal re-entrant tachycardia during stimulant treatment Key conclusions of the study authors: Stimulant medication may evoke onset of AV nodal tachyarrhythmias in patients who have the potential to develop them, possibly in combination with a selective serotonergic reuptake inhibitor Comments from the study authors: The cardiologist consulted believed this patient had a structural vulnerability of genetic etiology for the arrhythmia which was then precipitated by the stimulant

Analysis 10.7. Comparison 10 Patient reports/series: number of participants with non-serious adverse events, Outcome 7 Gastrointestinal system.

Gastrointestinal system	
Study	
Loss of appetite	
Agarwal 2008	A case report of the combination of atomoxetine and methylphenidate treatment of ADHD. Non-serious adverse events: decreased appetite and delayed onset in sleep
Coşkun 2009a	IR MPH, 10–20 mg/day, co-medication: valproate 400 mg/day. Decreased appetite, no weight decrease
Ghanizadeh 2008a	A case report of decrease in appetite during treatment with MPH
Rappaport 2004	A case report of side effects during MPH treatment in a 14-year-old boy with ADHD and a number of other co-morbid conditions (whilst taking immediate-release MPH)
Yalcin 2012	Significant appetite loss, drowsiness, disturbance of voice and hoarseness Disturbance of voice and hoarseness occurred on everyday since the first day of the medication. The symptoms started short after the single morning dose and decreased gradually to dinner time and disappeared before bedtime. Drug-free days: no symptoms. Otolaryngology consultation: no organic pathology was detected with respect to clinical and endoscopic observation. Discontinuation of MPH and prescription of atomoxetine: no symptom of hoarseness and disturbance of voice quality
Nausea and vomiting	
Rappaport 2004	A case report of side effects during MPH treatment in a 14-year-old boy with ADHD and a number of other co-morbid conditions (whilst taking extended-release MPH: Concerta)

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Analysis 10.8. Comparison 10 Patient reports/series: number of participants with non-serious adverse events, Outcome 8 Musculoskeletal system: growth.

Musculoskeletal system: growth

Study	
Holtkamp 2002	A case report of growth impairment during MPH treatment Key conclusions of the study authors: One may conclude that some children are at risk of serious growth decrement when treated with MPH. The growth of children should thus be monitored carefully, even if there are no alarming gastrointestinal side effects from MPH. We found that the determination of growth velocity was a sensitive marker for the evaluation of growth impairment in our patient

Analysis 10.9. Comparison 10 Patient reports/series: number of participants with non-serious adverse events, Outcome 9 Immune system: allergic reactions.

Immune system: allergic reactions

Study	
Confino-Cohen 2005	A case report of pruritic maculopapular skin rash developing during MPH treatment. The rash improved with antihistamines and re-challenge at a lower dose caused the reappearance, though less severe, of the rash. Desensitisation through graded exposure of MPH in incremental doses prevented further rash development
Vashi 2011	After 8 months of using an MPH patch the patient presented with pruritic dermatitis. She had itchy, burning, red lesions. Symptoms began on her hip at the area of patch placement, then progressively spread to her arms, legs, abdomen, and back. MPH discontinued: Symptoms lasted for 2 months. First and second patch test. Re-tested with MPH patch: Nine days after the first test the patient presented with recall reaction, characterized by a return of the original pruritic dermatitis to her entire back, similar to the eruption that had occurred months previously after therapeutical use of MPH patch. Avoidance of MPH patches: symptom-free

Analysis 10.10. Comparison 10 Patient reports/series: number of participants with non-serious adverse events, Outcome 10 Urogenitial system.

Urogenitial system

Study	
Testicular failure	
Ramasamy 2014	A case report of testicular failure possibly associated with chronic use of Methylphendiate. The patient was 20 years old with treatment duration of approximately 17 years with voluntary cessation a few years ago. Dosage varied with age. The patient's complaint was initially delayed puberty. He complained of high-pitched voice, lack of libido, low energy level, chronic fatigue and poor erectile function. The patient was advised to begin testosterone supplementation. The patient described in the case study seemed to exhibit characteristics related to the effects of chronic use of methylphenidate on development of human reproductive function. The unknown effects of methylphenidate are currently being studied, but as can be seen, one should exercise caution and patients should be followed closely when prescribing methylphenidate. However, because the developmental changes that occurred in the human participant occurred over a number of years of treatment with methylphenidate, there is very little information about the patient's condition and how it developed during that period of time
Sexual adverse events	
Coşkun 2009b	Case 1: Treated with 10-30 mg/day of immediate-release methylphenidate and experienced initial headache and nausea. Treated with 18 mg/day osmotic-controlled release oral delivery system (OROS) methylphenidate and experienced emotional side effects (sense of nervousness in the chest, occasional emotional numbing), multiple daily erections (unrelated to sexual stimuli, painless and without ejaculations), occurring a few hours after ingesting methylphenidate and lasting 5-10 minutes. No erections unrelated to sexual stimuli during a 1-week medication-free period. With re-administration of 35 mg/day OROS methylphenidate for 3 weeks, experienced re-emergence of erections of a longer duration compared with 18 mg/day of OROS methylphenidate, headache, nausea, and the same emotional side effects. No erections on drug-free days, and no erections with discontinuation of medication. Case 2: Treated with 18 mg/day of OROS methylphenidate and experienced loss of appetite, headache, abdominal pain, sleep problems, and conjunctival injection. Headache and abdominal pain almost disappeared after 1 week. Also experienced

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Urogenitial system	
Study	
	hypersexual behaviours, with morning erections lasting 1 hour before ingestion of methylphenidate, and a weight loss of 1.5 kg within 2 months. On drug-free days had almost no hypersexual behaviour during the day and no erection the following morning. When treated with 10-20 mg/day of immediate-release methylphenidate, morning erections and hypersexual behaviours decreased dramatically, sleep and appetite problems improved mildly, and there was no conjunctival injection (after three weeks). There were, however, possible withdrawal symptoms (increased irritability and hyperactivity, getting tearful easily), several hours after each dosage. Had no morning erections or hypersexual behaviours with discontinuation of OROS methylphenidate
Incontinence	
Tang 2010	Side effects reported by the mother: IR-MPH, 10 mg, no side effects. OROS-MPH, 18 mg/d, no side effects. OROS-MPH, 36 mg/d, double incontinence; stool incontinence (every day, frequent during daytime) and urinary incontinence (almost every day). The double incontinence completely resolved rapidly after the discontinuation of OROS methylphenidate 36 mg
Enuresis	
Ghanizadeh 2008b	A case report of nocturnal enuresis during MPH treatment Non-serious adverse events MPH, titrated to 20 mg/day: Nocturnal enuresis Discontinuation of MPH: enuresis stopped immediately MPH, when titrated to 20 mg/day: Immediate re-occurence of nocturnal enuresis Discontinuation of MPH: enuresis stopped immediately MPH, when titrated to 20 mg/day: Immediate re-occurence of nocturnal enuresis Discontinuation of MPH: enuresis stopped immediately
Williamson 2011	Two case reports showing resolution of enuresis when treated with MPH

Analysis 10.11. Comparison 10 Patient reports/series: number of participants with non-serious adverse events, Outcome 11 Other body systems.

Other body systems	
Study	
Skin reactions	
Cohen 1992	Case 1: 5 days of MPH treatment: hospitalisation due to two days of severe swelling and redness of the scrotum The skin eruption resolved spontaneously four days after MPH was discontinued. Two weeks later, 18 hour after MPH retrial, the same skin eruption of the scrotum was documented. Discontinued once again, and followed by a complete resolution of the rash in four days Case 2: 7 days of MPH treatment: Six hours of severe swelling and redness of the scrotum. Discontinuation of MPH was followed by a complete resolution of rash in three days.Rechallenge with MPH two months later was followed by the same skin eruption of the scrotum within two days. Complete resolution was seen after drug withdrawal
Coşkun 2009a	OROS-MPH 18 mg/day, co-medication: valproate 400 mg/day. Maculopapular pruritic skin eruptions on the patient's neck, arms, and legs, one week after starting OROS MPH treatment Re-administering of OROS-MPH 18 mg/day, comedication: gabapentine 300 mg/day. Same skin eruptions with same severity, nine days after starting OROS-MPH treatment again Discontinuation of medication: skin lesions abated within the next several weeks Restart of IR-MPH, 10–20 mg/day, co-medication gabapentine 300 mg/day, four months: no skin eruptions
Problems with sedation	
Ririe 1997	A case report (6-year-old boy) on unexpected interaction of methylphenidate (Ritalin) with anaesthetic agents: There could be a potential risk of unwanted interactions between methylphenidate and anaesthetic agents. Based on the observations from the case report, a more detailed and systematic investigation of methylphenidate in patients undergoing anaesthesia or sedation is warranted
Eye problems	
Ghanizadeh 2008c	Photophobia, occurring a few days after initiation of MPH treatment Discontinuation of MPH at least three times: no symptoms of photophobia Re-administration of MPH: immediate reoccurrence of photophobia
Lewis 2012	This report concluded stimulant medication (MPH) should not be withheld in patients with glaucoma as long as intraocular pressure (IOP) remains well controlled

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ADDITIONAL TABLES

Table 1. Study design

Study design	Description
Cohort study	An observational study in which a defined group with ≥ 1 samples of people (the cohort) is followed over time. The outcomes of people in subsets of this cohort might be compared, to examine people who were exposed or not exposed (or exposed at different levels) to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective (or historical) cohort study identifies participants from past records and follows them from the time of those records to the present. Because participants are not allocated by the investigator to different interventions or other exposures, adjusted analysis is usually required to minimise the influence of other factors (confounders).
Patient-control study	A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls), and which seeks to find associations between the outcome and prior exposure to particular risk factors. This design is particularly useful when the outcome is rare and when past exposure can be reliably measured. Patient-control studies are usually but not always retrospective.
Cross-sectional study	Studies in which the presence or absence of disease or other health-related variables are determined for each member of the study population or in a representative sample at one particular time. This contrasts with cohort studies, which are followed over a period of time.

Taken from the Cochrane Glossary.

Table 2. Data on adverse events from published systematic review on methylphenidate versus placebo or no intervention (Storebø 2015), National Summary of Product Characteristics, and from the present review

Adverse event	Randomised clinical trials: methylphenidate group (from Storebø 2015)	Randomised clinical trials: placebo or no intervention group (from Storebø 2015)	**National Summary of Product Characteristics (UK, USA, DK)**	**Non-comparative cohort studies and cohort studies from randomised trials (present review)**	**Non-comparative cohort studies (present review)**	**Non-comparative cohort studies from randomised trials (present review)**
Serious adverse events	1.90% (95% CI 1.10% to 3.20%; 9 studies, 919 participants)	2.80% (95% CI 1.70% to 4.80%; 9 studies, 613 participants)	No information	1.20% (95% CI 0.70% to 2.00%; 51 studies, 162,434 participants)	1.10% (95% CI 0.60% to 2.00%; 32 studies, 159,761 participants)	1.60% (95% CI 1.00% to 2.30%; 18 studies, 2661 participants)
Non-serious adverse events	51.4% (95% CI 41.9% to 60.9%; 21 studies, 1861 participants)	38.3% (95% CI 30.3% to 47.0%; 21 studies, 1271 participants)	No information	51.2% (95% CI 41.2% to 61.1%; 49 studies, 13,978 participants)	47.1% (95% CI 35.6% to 58.9%; 36 studies, 13,035 participants)	62.1% (95% CI 44.4% to 77.1%; 13 studies, 943 participants)
Headache	11.6% (95% CI 8.80% to 13.3%; 17 studies, 1642 participants)	9.40% (95% CI 7.10% to 12.4%; 17 studies, 1082 participants)	1% to 10%	14.4% (95% CI 11.3% to 18.3%; 90 studies, 13,469 participants)[a]	9.90% (95% CI 7.00% to 13.9%; 57 stud-	24.3% (95% CI 18.0% to 32.1%; 33 studies, 2540 participants)

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Table 2. Data on adverse events from published systematic review on methylphenidate versus placebo or no intervention (Storebø 2015), National Summary of Product Characteristics, and from the present review *(Continued)*

				ies, 10,929 participants		
Anxiety	6.50% (95% CI 1.20% to 29.2%; 3 studies, 356 participants)	12.4% (95% CI 8.30% to 18.0%; 3 studies, 240 participants)	1% to 10% (UK and DK); no information (USA)	18.4% (95% CI 11.3% to 28.7%; 22 studies, 1287 participants)[a]	10.2% (95% CI 5.30% to 18.9%; 8 studies, 938 participants	27.9% (95% CI 17.8% to 40.8%; 14 studies, 349 participants
Sleep difficulty	8.00% (95% CI 5.80% to 11.1%; 13 studies, 1417 participants)	8.30% (95% CI 6.40% to 10.7%; 13 studies, 999 participants)	1% to 10%	17.9% (95% CI 14.7% to 21.6%; 82 studies, 11,507 participants)[a]	14.3% (95% CI 11.2% to 18.2%; 51 studies, 9073 participants	25.4% (95% CI 18.2% to 34.4%, 31 studies, 2434 participants)
Irritability	6.40% (95% CI 3.70% to 10.8%; 11 studies, 1038 participants)	3.50% (95% CI 1.40% to 8.60%; 11 studies, 778 participants)	1% to 10%	17.2% (95% CI 11.5% to 25%; 35 studies, 4792 participants)[a]	15.5% (95% CI 10.2% to 22.7%; 21 studies, 3298 participants	20.6% (95% CI 7.90% to 44.1%; 14 studies, 1494 participants)
Tics	2.30% (95% CI 1.00% to 5.20%; 7 studies, 684 participants)	5.50% (95% CI 3.70% to 8.10%; 7 studies, 476 participants)	No information	6.40% (95% CI 4.50% to 8.90%; 39 studies, 1980 participants)[a]	5.60% (95% CI 3.80% to 8.10%; 29 studies, 1601 participants)	10.6% (95% CI 5.30% to 19.9%; 10 studies, 379 participants)
Drowsiness	7.30% (95% CI 2.40% to 20.2%; 4 studies, 510 participants)	6.70% (95% CI 2.60% to 16.2%; 4 studies, 310 participants)	1% to 10%	9.50% (95% CI 5.20% to 16.6%; 17 studies, 1146 participants)[a]	7.50% (95% CI 3.10% to 17.2%; 7 studies, 644 participants)	11.3% (95% CI 5.00% to 23.3%; 10 studies, 502 participants)
Sadness	5.70% (95% CI 1.30% to 21.9%; 4 studies, 382 participants)	4.20% (95% CI 0.90% to 16.9%; 4 studies, 318 participants)	No information	16.8% (95% CI 9.40% to 28.3%; 21 studies, 1802 participants)[a]	13.1% (95% CI 6.60% to 24.1%; 9 studies, 626 participants)	20.6% (95% CI 8.10% to 43.1%; 12 studies, 1176 participants)
Fatigue	4.80% (95% CI 2.30% to 9.90%; 6 studies, 471 participants)	6.50% (95% CI 4.30% to 9.60%; 6 studies, 387 participants)	1% to 10%	5.70% (95% CI 3.00% to 10.4%; 17 studies, 2182 participants)	5.60% (95% CI 2.80% to 10.9%; 5 studies, 673 participants)	7.80% (95% CI 5.80% to 10.5%; 12 studies, 1509 participants)
Abdominal pain	11.5% (95% CI 7.70% to 16.8%; 13 studies, 1406 participants)	7.60% (95% CI 5.00% to 11.5%; 13 studies, 935 participants)	0% to 10%	10.7% (95% CI 8.60% to 13.3%; 79 studies, 11,750 participants)[a]	7.60% (95% CI 5.70% to 10.0%; 46 studies, 9229 participants)	16.3% (95% CI 11.6% to 22.4%; 33 studies, 2521 participants)
Decreased appetite	17.3 (95% CI 12.3% to 24.2%; 16 studies, 1751 participants)	4.30% (95% CI 2.40% to 7.40%; 16 studies, 1211 participants)	1% to 10%	31.1% (95% CI 26.5% to 36.2%; 84 studies, 11,594 participants)[a]	28.8% (95% CI 23.0% to 33.5%; 57 studies, 9662 participants)	39.7% (95% CI 27.0% to 54.0%; 27 studies, 1967 participants)
Vomiting	5.70% (95% CI 4.00% to 8.00%; 11 studies, 1140 participants)	5.10% (95% CI 3.5% to 7.4%; 11 studies, 776 participants)	1% to 10%	7.30% (95% CI 3.70% to 13.4%; 20 studies, 2731 participants)[a]	7.10% (95% CI 2.80% to 17.0%; 11 studies, 1528 participants)	7.20% (95% CI 3.30% to 15.1%; 9 studies, 1203 participants)
Nausea	7.50% (95% CI 6.10% to 9.30%; 11 studies, 1174 participants)	5.20% (95% CI 3.80% to 7.10%; 11 studies, 821 participants)	> 10%	7.60% (95% CI 5.30% to 10.6%; 41 studies, 5612 participants)[a]	8.00% (95% CI 7.00% to 9.10%; 22 studies, 3921 participants)	10.4% (95% CI 5.80% to 17.9%; 19 studies, 1691 participants)

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Table 2. Data on adverse events from published systematic review on methylphenidate versus placebo or no intervention (Storebø 2015), National Summary of Product Characteristics, and from the present review *(Continued)*

Decreased weight	6.30% (95% CI 3.80% to 10.3%; 6 studies, 472 participants)	2.40% (95% CI 1.00% to 5.70%; 6 studies, 387 participants)	1% to 10%	8.70% (95% CI 4.80% to 15.3%; 26 studies, 5182 participants)[a]	6.60% (95% CI 3.10% to 13.3%; 17 studies, 4855 participants)	16.6% (95% CI 8.70% to 30.6%; 9 studies, 327 participants)

CI: confidence interval; **DK**: Denmark; **RCT**: randomised clinical trials.
[a]We found substantially larger proportions of several adverse events in the present review compared to both the proportions of adverse events in the placebo group in the RCTs included in our 2015 review (Storebø 2015), and the National Summary of Product Characteristics from the UK, USA, and Denmark.

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (Central) in the Cochrane Library

#1 MeSH descriptor: [Methylphenidate] explode all trees
#2 Methylphenidate
#3 Attenta
#4 Biphentin
#5 Calocain
#6 Centedrin*
#7 Concerta
#8 Daytrana
#9 Dexmethylphenidat*
#10 Equasym
#11 Focalin
#12 Medikinet
#13 Meridil
#14 Metadate
#15 Methyl phenidat*
#16 Methyl phenidylacetat*
#17 Methylfenid*
#18 Methylin
#19 Methylofenidan
#20 Methylphenid*
#21 Methyl phenidyl acetat*
#22 Methypatch
#23 Metilfenidato
#24 Motiron
#25 MPH
#26 Penid
#27 Phenidyl hydrochlorid*
#28 Phenidylat*
#29 Plimasin*
#30 PMS-Methylphenid*
#31 Richter Works
#32 Riphenidat*
#33 Ritalin*
#34 Rubifen
#35 Stimdat*
#36 Tsentedrin*
#37 MeSH descriptor: [Child] explode all trees
#38 MeSH descriptor: [Adolescent] explode all trees
#39 MeSH descriptor: [Infant] explode all trees
#40 (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*)

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#41 elmifiten or medikid or Omozin or Quazym or Tifinidat or Tranquilyn
#42 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #41
#43 #37 or #38 or #39 or #40
#44 #42 and #43
#45 MeSH descriptor: [Attention Deficit and Disruptive Behavior Disorders] explode all trees
#46 ADHD:ti,ab,kw
#47 ADDH:ti,ab,kw
#48 (ADHS):ti,ab,kw
#49 ("AD/HD"):ti,ab,kw
#50 ((attention* or behav*) near/3 (defic* or dysfunc* or disorder*)):ti,ab,kw
#51 (impulsiv* or inattentiv* or inattention*):ti,ab,kw
#52 ((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*)):ti,ab,kw
#53 MeSH descriptor: [Hyperkinesis] explode all trees
#54 (hyperkine*):ti,ab,kw
#55 (minimal near/3 brain near/3 (disorder* or dysfunct* or damage*)):ti,ab,kw
#56 (hyperactiv*):ti,ab,kw
#57 #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56
#58 #44 and #57

MEDLINE Ovid

Efficacy search

Block A: ADHD

1. exp "Attention Deficit and Disruptive Behavior Disorders"/
2. adhd.ti,ab.
3. addh.ti,ab.
4. adhs.ti,ab.
5. (ad adj hd).ti,ab.
6. ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).ti,ab.
7. ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).ti,ab.
8. (impulsiv$ or inattentiv$ or inattention$).ti,ab.
9. hyperactiv$.ti,ab.
10. hyperkinesis$.ti,ab.
11. exp Hyperkinesis/
12. (minimal adj brain adj3 disorder$).ti,ab.
13. (minimal adj brain adj3 dysfunction$).ti,ab.
14. (minimal adj brain adj3 damage$).ti,ab.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

Block B: Study design

16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. randomized controlled trials.mp.
19. random allocation.mp.
20. double blind method.mp.
21. single blind method.mp.
22. clinical trial.pt.
23. (clin$ adj25 trial$).ti,ab.
24. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$ or dummy$)).mp.
25. exp clinical trial/
26. placebos.mp.
27. placebo$.ti,ab.
28. random$.ti,ab.
29. comparative study.mp.
30. evaluation studies as topic/
31. exp clinical trials as topic/
32. follow up studies.mp.
33. prospective studies.mp.
34. (control$ or prospectiv$ or volunteer$).ti,ab.
35. longitudinal.tw.

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36. retrospective.tw.
37. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
38. exp Clinical Trials as Topic/
39. exp Cohort Studies/
40. exp Case-Control Studies/
41. "case report*".pt.
42. case control.tw.
43. (cohort adj (study or studies)).tw.
44. "cohort analy*".tw.
45. (observational adj (study or studies)).tw.
46. cross sectional.tw.
47. (follow up adj (study or studies)).tw.
48. (case* adj report*).tw.
49. (case* adj stud*).tw.
50. case reports.pt.
51. Cross-Sectional Studies/
52. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53. 37 or 52
54. 15 and 53 [Block A AND Block B]

Block C: Methylphenidate

55. Methylphenidate.mp. or Methylphenidate/
56. Attenta.mp.
57. Biphentin.mp.
58. Calocain.mp.
59. Centedrin*.mp.
60. Concerta.mp.
61. Daytrana.mp.
62. Dexmethylphenidat*.mp.
63. Equasym.mp.
64. Elmifiten.mp.
65. Focalin.mp.
66. Medikid.mp.
67. Medikinet.mp.
68. Meridil.mp.
69. Metadate.mp.
70. Methyl phenidat*.mp.
71. Methyl phenidylacetat*.mp.
72. Methylfenid*.mp.
73. Methylin.mp.
74. Methylofenidan.mp.
75. Methylphenid*.mp.
76. Methyl phenidyl acetat*.mp.
77. Methypatch.mp.
78. Metilfenidato.mp.
79. Motiron.mp.
80. MPH.mp.
81. Omozin.mp.
82. Penid.mp.
83. Phenidyl hydrochlorid*.mp.
84. Phenidylat*.mp.
85. Plimasin*.mp.
86. PMS-Methylphenid*.mp.
87. Quazym.mp.
88. Richter Works.mp.
89. Riphenidat*.mp.
90. Ritalin*.mp.
91. Rubifen.mp.
92. Stimdat*.mp.
93. Tifinidat.mp.
94. Tranquilyn.mp.
95. Tsentedrin*.mp.

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96. 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85
or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95
97. 54 and 96 [Block A AND Block B AND Block C]

Block D Children

98. exp child/
99. exp adolescent/
100. exp infant/
101. (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp.
102. 98 or 99 or 100 or 101
103. 97 and 102
104. 103 and 97 and 102 [Block A AND Block B AND Block C AND Block D]

Adverse events search

Block 1: Methylphenidate

105. Methylphenidate.mp. or Methylphenidate/
106. Attenta.mp.
107. Biphentin.mp.
108. Calocain.mp.
109. Centedrin*.mp.
110. Concerta.mp.
111. Daytrana.mp.
112. Dexmethylphenidat*.mp.
113. Elmifiten.mp.
114. Equasym.mp.
115. Focalin.mp.
116. Medikid.mp.
117. Medikinet.mp.
118. Meridil.mp.
119. Metadate.mp.
120. Methyl phenidat*.mp.
121. Methyl phenidylacetat*.mp.
122. Methylfenid*.mp.
123. Methylin.mp.
124. Methylofenidan.mp.
125. Methylphenid*.mp.
126. Methyl phenidyl acetat*.mp.
127. Methypatch.mp.
128. Metilfenidato.mp.
129. Motiron.mp.
130. MPH.mp.
131. Omozin.mp.
132. Penid.mp.
133. Phenidyl hydrochlorid*.mp.
134. Phenidylat*.mp.
135. Plimasin*.mp.
136. PMS-Methylphenid*.mp.
137. Richter Works.mp.
138. Quazym.mp.
139. Riphenidat*.mp.
140. Ritalin*.mp.
141. Rubifen.mp.
142. Stimdat*.mp.
143. Tifinidat.mp.
144. Tranquilyn.mp.
145. Tsentedrin*.mp.
146. 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145

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Block 2: Adverse events

147. (ae or co or de).fs.
148. (safe or safety or (side adj1 effect*) or (undesirable adj1 effect*) or (treatment adj1 emergent) or tolerability or tolerance or tolerate or toxicity or toxic or adrs or adr or harm or harms or harmful or complication* or risk or risks or (unintended adj1 event*) or (unintended adj1 effect*)).ti,ab.
149. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.
150. 147 or 148 or 149

Block 3: Children

151. exp child/
152. exp adolescent/
153. exp infant/
154. (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp.
155. 151 or 152 or 153 or 154
156. exp mood disorders/
157. (depression or depressive).ti,ab.
158. exp psychotic disorders/
159. (psychosis or (psychotic adj4 symptom*)).ti,ab.
160. exp Body Weight/ or anorexia/
161. ((loss or lose or losing or reduc*) adj3 (weight or appetite)).ti,ab.
162. ((reduc* or retard* or inhibit* or deficit*) adj4 growth).ti,ab.
163. exp Hypertension/
164. Heart Rate/
165. exp tachycardia/
166. (increas* adj4 (heart rate or pulse or blood pressure)).ti,ab.
167. exp Death, Sudden/
168. death.ti,ab.
169. exp Infertility/
170. (((loss or reduc*) adj4 fertility) or infertility).ti,ab.
171. exp Carcinogens/
172. exp neoplasms/
173. ((risk adj2 cancer) or (cytogenetic adj2 effect*)).ti,ab.
174. 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173
175. 150 or 174 [Block 2 Adverse events]
176. 146 and 155 and 175
177. Methylphenidate/ae, po, to [Adverse Effects, Poisoning, Toxicity]
178. 155 and 177
179. 176 or 178 [Methylphenidate AND Children AND Adverse events]
180. 104 or 179 [Efficacy OR Adverse events]

Embase Ovid

Embase efficacy search

Block A : ADHD

1. exp "Attention Deficit and Disruptive Behavior Disorders"/
2. adhd.ti,ab.
3. addh.ti,ab.
4. adhs.ti,ab.
5. (ad adj hd).ti,ab.
6. ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).ti,ab.
7. ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).ti,ab.
8. (impulsiv$ or inattentiv$ or inattention$).ti,ab.
9. hyperactiv$.ti,ab.
10. hyperkinesis$.ti,ab.
11. exp Hyperkinesis/
12. (minimal adj brain adj3 disorder$).ti,ab.
13. (minimal adj brain adj3 dysfunction$).ti,ab.
14. (minimal adj brain adj3 damage$).ti,ab.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

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Block B: Study design

16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. randomized controlled trials.mp.
19. random allocation.mp.
20. double blind method.mp.
21. single blind method.mp.
22. clinical trial.pt.
23. (clin$ adj25 trial$).ti,ab.
24. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$ or dummy$)).mp.
25. exp clinical trial/
26. placebos.mp.
27. placebo$.ti,ab.
28. random$.ti,ab.
29. comparative study.mp.
30. evaluation studies as topic/
31. exp clinical trials as topic/
32. follow up studies.mp.
33. prospective studies.mp.
34. (control$ or prospectiv$ or volunteer$).ti,ab.
35. longitudinal.tw.
36. retrospective.tw.
37. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
38. exp Clinical Trials as Topic/
39. exp Cohort Studies/
40. exp Case-Control Studies/
41. "case report*".pt.
42. case control.tw.
43. (cohort adj (study or studies)).tw.
44. "cohort analy*".tw.
45. (observational adj (study or studies)).tw.
46. cross sectional.tw.
47. (follow up adj (study or studies)).tw.
48. (case* adj report*).tw.
49. (case* adj stud*).tw.
50. case reports.pt.
51. Cross-Sectional Studies/
52. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53. 37 or 52
54. 15 and 53 [Block A AND Block B]

Block C: Methylphenidate

55. Methylphenidate.mp. or Methylphenidate/
56. Attenta.mp.
57. Biphentin.mp.
58. Calocain.mp.
59. Centedrin*.mp.
60. Concerta.mp.
61. Daytrana.mp.
62. Dexmethylphenidat*.mp.
63. Equasym.mp.
64. Elmifiten.mp.
65. Focalin.mp.
66. Medikid.mp.
67. Medikinet.mp.
68. Meridil.mp.
69. Metadate.mp.
70. Methyl phenidat*.mp.
71. Methyl phenidylacetat*.mp.
72. Methylfenid*.mp.
73. Methylin.mp.

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74. Methylofenidan.mp.
75. Methylphenid*.mp.
76. Methyl phenidyl acetat*.mp.
77. Methypatch.mp.
78. Metilfenidato.mp.
79. Motiron.mp.
80. MPH.mp.
81. Omozin.mp.
82. Penid.mp.
83. Phenidyl hydrochlorid*.mp.
84. Phenidylat*.mp.
85. Plimasin*.mp.
86. PMS-Methylphenid*.mp.
87. Quazym.mp.
88. Richter Works.mp.
89. Riphenidat*.mp.
90. Ritalin*.mp.
91. Rubifen.mp.
92. Stimdat*.mp.
93. Tifinidat.mp.
94. Tranquilyn.mp.
95. Tsentedrin*.mp.
96. 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or
86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95
97. 54 and 96 [Block A AND Block B AND Block C]

Block D: children

98. exp child/
99. exp adolescent/
100. exp infant/
101. (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp.
102. 98 or 99 or 100 or 101
103. 97 and 102 [Block A AND Block B AND Block C AND Block D]
104. 103 and 97 and 102

Adverse events search

105. Methylphenidate.mp. or Methylphenidate/
106. Attenta.mp.
107. Biphentin.mp.
108. Calocain.mp.
109. Centedrin*.mp.
110. Concerta.mp.
111. Daytrana.mp.
112. Dexmethylphenidat*.mp.
113. Elmifiten.mp.
114. Equasym.mp.
115. Focalin.mp.
116. Medikid.mp.
117. Medikinet.mp.
118. Meridil.mp.
119. Metadate.mp.
120. Methyl phenidat*.mp.
121. Methyl phenidylacetat*.mp.
122. Methylfenid*.mp.
123. Methylin.mp.
124. Methylofenidan.mp.
125. Methylphenid*.mp.
126. Methyl phenidyl acetat*.mp.
127. Methypatch.mp.

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128. Metilfenidato.mp.
129. Motiron.mp.
130. MPH.mp.
131. Omozin.mp.
132. Penid.mp.
133. Phenidyl hydrochlorid*.mp.
134. Phenidylat*.mp.
135. Plimasin*.mp.
136. PMS-Methylphenid*.mp.
137. Richter Works.mp.
138. Quazym.mp.
139. Riphenidat*.mp.
140. Ritalin*.mp.
141. Rubifen.mp.
142. Stimdat*.mp.
143. Tifinidat.mp.
144. Tranquilyn.mp.
145. Tsentedrin*.mp.
146. 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145
147. (ae or co or de).fs.
148. (safe or safety or (side adj1 effect*) or (undesirable adj1 effect*) or (treatment adj1 emergent) or tolerability or tolerance or tolerate or toxicity or toxic or adrs or adr or harm or harms or harmful or complication* or risk or risks or (unintended adj1 event*) or (unintended adj1 effect*)).ti,ab.
149. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.
150. 147 or 148 or 149
151. exp child/
152. exp adolescent/
153. exp infant/
154. (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp.
155. 151 or 152 or 153 or 154
156. exp mood disorders/
157. (depression or depressive).ti,ab.
158. exp psychotic disorders/
159. (psychosis or (psychotic adj4 symptom*)).ti,ab.
160. exp Body Weight/ or anorexia/
161. ((loss or lose or losing or reduc*) adj3 (weight or appetite)).ti,ab.
162. ((reduc* or retard* or inhibit* or deficit*) adj4 growth).ti,ab.
163. exp Hypertension/
164. Heart Rate/
165. exp tachycardia/
166. (increas* adj4 (heart rate or pulse or blood pressure)).ti,ab.
167. exp Death, Sudden/
168. death.ti,ab.
169. exp Infertility/
170. (((loss or reduc*) adj4 fertility) or infertility).ti,ab.
171. exp Carcinogens/
172. exp neoplasms/
173. ((risk adj2 cancer) or (cytogenetic adj2 effect*)).ti,ab.
174. 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173
175. 150 or 174
176. 146 and 155 and 175
177. Methylphenidate/ae, po, to [Adverse Effects, Poisoning, Toxicity]
178. 155 and 177
179. 176 or 178
180. 104 or 179

PsycINFO Ovid

Efficacy search

1. exp attention deficit disorder/

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2. adhd.ti,ab.
3. addh.ti,ab.
4. ADHS.ti,ab.
5. (AD adj HD).ti,ab.
6. ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).ti,ab.
7. ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).ti,ab.
8. (impulsiv$ or inattentiv$ or inattention$).ti,ab.
9. hyperactiv$.ti,ab.
10. hyperkinesis$.ti,ab.
11. exp Hyperkinesis/
12. (minimal adj brain adj3 disorder$).ti,ab.
13. (minimal adj brain adj3 dysfunction$).ti,ab.
14. (minimal adj brain adj3 damage$).ti,ab.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 [Block A]
16. random$.mp.
17. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or dummy or mask$)).mp.
18. placebo$.mp.
19. crossover.mp.
20. assign$.mp.
21. allocat$.mp.
22. ((clin$ or control$ or compar$ or evaluat$ or prospectiv$) adj25 (trial$ or studi$ or study)).mp.
23. exp placebo/
24. exp treatment effectiveness evaluation/
25. exp mental health program evaluation/
26. exp experimental design/
27. versus.id.
28. vs.id.
29. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. ((case* adj5 control*) or (case adj3 comparison*) or (case-comparison or control group*)).ab,id,ti.
31. (cohort or longitudinal or prospective or retrospective).ab,id,ti.
32. (cross section* or "prevalence study").ab,id,ti.
33. clinical case study.md.
34. prospective study.md.
35. longitudinal study.md.
36. exp Followup Studies/
37. followup study.md.
38. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 29 or 38 [Block B]
40. 15 and 39 [Block A and Block B]
41. Methylphenidate.mp. or Methylphenidate/
42. Attenta.mp.
43. Biphentin.mp.
44. Calocain.mp.
45. Centedrin*.mp.
46. Concerta.mp.
47. Daytrana.mp.
48. Dexmethylphenidat*.mp.
49. Elmifiten.mp.
50. Equasym.mp.
51. Focalin.mp.
52. Medikid.mp.
53. Medikinet.mp.
54. Meridil.mp.
55. Metadate.mp.
56. Methyl phenidat*.mp.
57. Methyl phenidylacetat*.mp.
58. Methylfenid*.mp.
59. Methylin.mp.
60. Methylofenidan.mp.
61. Methylphenid*.mp.
62. Methyl phenidyl acetat*.mp.
63. Methypatch.mp.

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64. Metilfenidato.mp.
65. Motiron.mp.
66. MPH.mp.
67. Omozin.mp.
68. Penid.mp.
69. Phenidyl hydrochlorid*.mp.
70. Phenidylat*.mp.
71. Plimasin*.mp.
72. PMS-Methylphenid*.mp.
73. Quazym.mp.
74. Richter Works.mp.
75. Riphenidat*.mp.
76. Ritalin*.mp.
77. Rubifen.mp.
78. Stimdat*.mp.
79. Tifinidat.mp.
80. Tranquilyn.mp.
81. Tsentedrin*.mp.
82. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or
72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 [Block C]
83. 40 and 82 [Block A AND Block B AND Block C]
84. (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp.
85. 83 and 84 [Block A AND Block B AND Block C AND Block D]

Adverse events search

86. Methylphenidate.mp. or Methylphenidate/
87. Attenta.mp.
88. Biphentin.mp.
89. Calocain.mp.
90. Centedrin*.mp.
91. Concerta.mp.
92. Daytrana.mp.
93. Dexmethylphenidat*.mp.
94. Elmifiten.mp.
95. Equasym.mp.
96. Focalin.mp.
97. Medikid.mp.
98. Medikinet.mp.
99. Meridil.mp.
100. Metadate.mp.
101. Methyl phenidat*.mp.
102. Methyl phenidylacetat*.mp.
103. Methylfenid*.mp.
104. Methylin.mp.
105. Methylofenidan.mp.
106. Methylphenid*.mp.
107. Methyl phenidyl acetat*.mp.
108. Methypatch.mp.
109. Metilfenidato.mp.
110. Motiron.mp.
111. MPH.mp.
112. Omozin.mp.
113. Penid.mp.
114. Phenidyl hydrochlorid*.mp.
115. Phenidylat*.mp.
116. Plimasin*.mp.
117. PMS-Methylphenid*.mp.
118. Quazym.mp.
119. Richter Works.mp.

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120. Riphenidat*.mp.
121. Ritalin*.mp.
122. Rubifen.mp.
123. Stimdat*.mp.
124. Tifinidat.mp.
125. Tranquilyn.mp.
126. Tsentedrin*.mp.
127. 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 [Block 1]
128. "Side effects (Drug)"/
129. (safe or safety or (side adj1 effect*) or (undesirable adj1 effect*) or (treatment adj1 emergent) or tolerability or tolerance or tolerate or toxicity or toxic or adrs or adr or harm or harms or harmful or complication* or risk or risks or (unintended adj1 event*) or (unintended adj1 effect*)).ti,ab.
130. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.
131. 128 or 129 or 130
132. exp major depression/ or affective disorders/
133. (depression or depressive).ti,ab.
134. exp psychosis/
135. (psychosis or (psychotic adj4 symptom*)).ti,ab.
136. exp body weight/
137. exp appetite depressing drugs/
138. Appetite/
139. ((loss or lose or losing or decreas* or reduc*) adj3 (weight or appetite)).ti,ab.
140. ((reduc* or retard* or inhibit* or deficit*) adj4 growth).ti,ab.
141. exp appetite depressing drugs/
142. Appetite/
143. exp cardiovascular disorders/
144. exp heart rate affecting drugs/
145. Heart rate/
146. (increas* adj4 (heart rate or pulse or blood pressure)).ti,ab.
147. "death and dying"/
148. death.ti,ab.
149. exp infertility/
150. (((loss or reduc*) adj4 fertility) or infertility).ti,ab.
151. exp neoplasms/
152. Carcinogens/
153. ((risk adj2 cancer) or (cytogenetic adj2 effect*)).ti,ab.
154. 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153
155. 131 or 154 [Block 2]
156. 127 and 155 [Block 1 AND Block 2]
157. (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*).mp.[Block 3]
158. 156 and 157 [Block 1 AND Block 2 AND Block 3]
159. 85 or 158 [Efficacy OR Adverse events]

CINAHL EBSCOhost (Cumulative Index to Nursing and Allied Health Literature)

#1 MeSH descriptor: [Methylphenidate] explode all trees
#2 Methylphenidate
#3 Attenta
#4 Biphentin
#5 Calocain
#6 Centedrin*
#7 Concerta
#8 Daytrana
#9 Dexmethylphenidat*
#10 Equasym
#11 Focalin
#12 Medikinet
#13 Meridil
#14 Metadate

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#15 Methyl phenidat*
#16 Methyl phenidylacetat*
#17 Methylfenid*
#18 Methylin
#19 Methylofenidan
#20 Methylphenid*
#21 Methyl phenidyl acetat*
#22 Methypatch
#23 Metilfenidato
#24 Motiron
#25 MPH
#26 Penid
#27 Phenidyl hydrochlorid*
#28 Phenidylat*
#29 Plimasin*
#30 PMS-Methylphenid*
#31 Richter Works
#32 Riphenidat*
#33 Ritalin*
#34 Rubifen
#35 Stimdat*
#36 Tsentedrin*
#37 MeSH descriptor: [Child] explode all trees
#38 MeSH descriptor: [Adolescent] explode all trees
#39 MeSH descriptor: [Infant] explode all trees
#40 (child* or boy* or girl* or adolescen* or teen* or preschool or pre school or infant* or baby or babies or toddler* or school child* or youth*)
#41 elmifiten or medikid or Omozin or Quazym or Tifinidat or Tranquilyn
#42 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #41
#43 #37 or #38 or #39 or #40
#44 #42 and #43
#45 MeSH descriptor: [Attention Deficit and Disruptive Behavior Disorders] explode all trees
#46 ADHD:ti,ab,kw
#47 ADDH:ti,ab,kw
#48 (ADHS):ti,ab,kw
#49 ("AD/HD"):ti,ab,kw
#50 ((attention* or behav*) near/3 (defic* or dysfunc* or disorder*)):ti,ab,kw
#51 (impulsiv* or inattentiv* or inattention*):ti,ab,kw
#52 ((disrupt* near/3 disorder*) or (disrupt* near/3 behav*) or (defian* near/3 disorder*) or (defian* near/3 behav*)):ti,ab,kw
#53 MeSH descriptor: [Hyperkinesis] explode all trees
#54 (hyperkine*):ti,ab,kw
#55 (minimal near/3 brain near/3 (disorder* or dysfunct* or damage*)):ti,ab,kw
#56 (hyperactiv*):ti,ab,kw
#57 #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56
#58 #44 and #57

Conference Proceedings Citation Index - Science (CPCI-S); Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SSH) Web of Science

#3 #2 AND #1
Databases=CPCI-S, CPCI-SSH

#2 TS=(child* or boy* or girl* or adolescen* or teen* orpreschool* or "pre school*" or infant* or baby or babies or toddler*or "school child*" or schoolchild* or youth*)
Databases=CPCI-S, CPCI-SSH

#1 TS=(Methylphenidate or Attenta or Biphentin or Calocain orCentedrin* or Concerta or Daytrana or Dexmethylphenidat* orElmifiten or Equasym or Focalin or Medikid or Medikinet or Meridilor Metadate or "Methyl phenidat*" or "Methyl phenidylacetat" or Methylfenid or Methylin or Methylofenidan or Methylphenid* or "Methyl phenidyl acetat*" or Methypatch or Metilfenidato or Motironor MPH or Penid or Omozin or Quazym or "Phenidyl hydrochlorid*" orPhenidylat* or Plimasin* or "PMS-Methylphenid* " or "Richter Works"or Riphenidat* or Ritalin* or Rubifen or Stimdat* or Tifinidat orTranquilyn or Tsentedrin*)
Databases=CPCI-S, CPCI-SSH

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NDLTD Theses Resources (ndltd.org/resources)

methylphenidate AND child* AND (attention deficit or hyperactiv*)

TROVE - National Library of Australia (trove.nla.gov.au)

methylphenidate AND child* AND (attention OR hyperactiv*)

British Library E-Theses Online Service (EThOS; ethos.bl.uk)

methylphenidate AND children AND attention deficit / methylphenidate AND child AND hyperactivity

Deutsche Nationalbibliothek Dissertations (www.dnb.de/EN/Home/home_node.html)

methylphenidate

Open Access Theses and Dissertations (OATD; oatd.org)

methylphenidate AND child* AND (attention deficit OR hyperactiv*)

Theses Collection Wales - The National Library of Wales (www.llgc.org.uk/en/discover/nlw-resources/theses-collection-wales)

methylphenidate AND child* AND (attention deficit OR hyperactiv*)

DART-Europe E-Theses Portal (www.dart-europe.eu/basic-search.php)

methylphenidate AND child*

Bielefeld Academic Search Engine (BASE; www.base-search.net/about/en)

methylphenidate AND adhd/attention deficit/hyperactive*

Theses France (www.theses.fr/en)

methylphenidate

ProQuest Open Access Dissertations (PQDT Open; pqdtopen.proquest.com/search.html)

methylphenidate AND children AND adhd

ClinicalTrials.gov (clinicaltrials.gov)

attention deficit or adhd or hyperactivity [Conditions] | methylphenidate [Interventions] | Child

World Health Organization International Clinical Trials Registry (WHO ICTRP; who.int/ictrp/en)

Methylphenidate AND adhd OR attention OR hyperactiv*

WHAT'S NEW

Date	Event	Description
25 June 2018	Amended	Correcting formatting issue in Summary of findings for the main comparison

CONTRIBUTIONS OF AUTHORS

All of the authors contributed to writing the protocol for this review (Storebø 2016).
KBR developed the search strategy.
OJS, NP, ER, HBK, CRMM, FLM, MH, TG, MS, SR, KBR, SJH, LA, and TB selected the studies.
All authors contributed to data extraction and evaluation of bias.
OJS, NP, ER, HBK, CRMM, and FLM entered data into RevMan 5 (Review Manager 2014).
OJS, NP, ER, HBK, RK, SJH, and LA performed the statistical analysis.
All authors contributed to writing the discussion and the final review.

OJS is the guarantor for the review

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DECLARATIONS OF INTEREST

Ole Jakob Storebø is an Associate Editor with Cochrane Developmental, Psychosocial and Learning Problems.
Nadia Pedersen - none known.
Erica Ramstad - none known.
Maja Lærke Kielsholm - none known.
Signe Sofie Nielsen - none known.
Helle B Krogh - none known.
Carlos R Moreira-Maia (CRMM) receives financial research support from the government agencies: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). CRMM received fees in February 2016 for the development of educational materials on excessive daytime sleepiness for Libbs. Libbs also make products for the treatment of ADHD. CRMM received travel awards from the Health Technology Assessment Institute (IATS), Universidade Federal do Rio Grande do Sul (UFRGS); and travel, accommodation, and registration support to the fourth and fifth World Congresses on ADHD from the World Federation of ADHD. Carlos is an author on Maia 2008 and declares that he was not involved in assessing the eligibility of this study, extracting data, assessing risk of bias or grading the quality of the evidence.
Frederik L Magnusson - none known.
Mathilde Holmskov - none known.
Trine Gerner - none known.
Maria Skoog - none known.
Susanne Rosendal - none known.
Camilla Groth's (CGr) institution received funds from the Lundbeck Foundation to finance part of her PhD in the paediatric field on Tourette syndrome. CGr confirms that none of these funds were used to work on this review.
Donna Gillies is an Editor with Cochrane Developmental, Psychosocial, and Learning Problems.
Kirsten Buch Rasmussen - none known.
Dorothy Gauci - none known.
Morris Zwi sits on the UK Paediatric Medicines Expert Advisory Group at the Medicines and Healthcare Regulatory Agency, which considers applications regarding the licensing of paediatric medicines. Payment for MZ's attendance at this meeting goes to his NHS organisation. As a clinician working with patients who have ADHD, he prescribes methylphenidate regularly.
Richard Kirubakaran is currently employed by Cochrane South Asia, funded by the Indian Council for Medical Research, India, and Effective Healthcare Research Consortium for the Department for International Development, UK.
Sasja J Håkonsen - none known.
Lise Aagaard (LA) received travelling grants from the pharmaceutical companies Pfizer, Swedish Orphan BioVitrum and Shire. None of the travelling grants are related to this review. LA confirms that she has nothing to declare in relation to ADHD research. The Pfizer travel grants were received in 2015 and 2016 for attending the European Association of Hospital Pharmacist Annual Conferences. No activities in relation to treatment of ADHD were observed. A travel grant was received in 2015 from Swedish Orphan Biovitrum for attending the C1 Inhibitor Conference in Budapest. C1 inhibitor drugs are involved in the treatment of the rare disease hereditary angioedema. Travel grants were received in 2015 and 2016 from Shire for attending the Bradykinin Scientific Meeting in Copenhagen and Stockholm. Bradykinin mediator drugs are involved in the treatment of the rare disease hereditary angioedema.
Erik Simonsen - none known.
Christian Gluud is Co-ordinating Editor of Cochrane Hepato-Biliary.

SOURCES OF SUPPORT

Internal sources

- Psychiatric Research Unit, Region Zealand Psychiatry, Roskilde, Denmark.

  Ole Jakob Storebø, Nadia Pedersen, Erica Ramstad, Helle B Krogh, Frederik Løgstrup Magnusson, Mathilde Holmskov, Trine Gerner, and Erik Simonsen worked on this review during office hours
- Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Denmark.

  Maria Skoog and Christian Gluud worked on this review during office hours

External sources

- Region Zealand Research Foundation, Denmark.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Types of studies
   a. We decided to also include the methylphenidate-treated group from RCTs assessing this stimulant versus other interventions as well as cross-sectional studies. Definitions are shown in Table 1.

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2. Types of participants
   a. In our protocol, Storebø 2016b, we stated that study participants had to be 18 years or younger with an intellectual quotient (IQ) greater than 70. However, we would have had to exclude many studies if we had followed these criteria. Consequently, we decided during the review process that studies eligible for inclusion were those in which at least 75% of participants were aged 18 years or younger, and the mean age of the trial population was 18 years or younger. We also required that at least 75% of participants had a normal IQ (> 70). These arbitrary decisions were taken without looking at the data of the individual studies.
3. Types of interventions
   a. We included studies where methylphenidate administered at any dosage or formulation was a part of any medical treatment regimen. Compared to what we wrote in our protocol (Storebø 2016), we decided to accept concurrent medication with "over-the-counter types of drugs", but not comedication with other types of ADHD medication.
4. Types of outcome measures
   a. We recategorised some outcomes that are usually considered as "not serious adverse events", like "hypertension" and "sleep disorder", as serious adverse events, in light of the data collected by some study authors.
   b. We decided to add withdrawal of methylphenidate due to serious adverse events and due to adverse events of unknown severity as primary outcomes, and withdrawal of methylphenidate due to non-serious adverse events and for unknown reasons as secondary outcomes, as these represent important data. There were several reasons for this decision. First, the description of adverse events generally lacked detail. Second, 'withdrawal' means that it is likely that the balance between beneficial and harmful effects will have been disrupted, with the latter prevailing, otherwise sane physicians would not stop a medication they had prescribed themselves. We have tried to be as fair as possible, listing withdrawal due to adverse events of unknown severity as a primary outcome and withdrawal for unknown reasons as a secondary outcome. However, we know that the primary outcome, withdrawal of methylphenidate due to adverse events of unknown severity, for example, may be due to non-serious adverse events, while the secondary outcome, withdrawal for unknown reasons, may be caused by serious adverse events and should have been a primary outcome. Nonetheless, we took these decisions without looking at the data of the individual studies, so they are not data driven. We decided to include withdrawal data also, as we believe that these are important.
5. We have divided our withdrawal data into the following categories.
   i. Withdrawal of methylphenidate due to serious adverse events (primary outcome).
   ii. Withdrawal of methylphenidate due to adverse events of unknown severity (primary outcome).
   iii. Withdrawal of methylphenidate due to non-serious adverse events (secondary outcome).
   iv. Withdrawal of methylphenidate for unknown reason (secondary outcome).
6. Electronic searches
   a. We widened the scope of our search to include the following databases.
      i. Trove - National Library of Australia (trove.nla.gov.au).
      ii. British Library E-theses Online Service (EThOS; ethos.bl.uk).
      iii. Deutsche Nationalbibliothek Dissertations (www.dnb.de/EN/Home/home_node.html).
      iv. Open Access Theses and Dissertations (OATD; oatd.org).
      v. Theses Collection Wales - The National Library of Wales (www.llgc.org.uk/en/discover/nlw-resources/theses-collection-wales).
      vi. DART-Europe E-theses portal (www.dart-europe.eu/basic-search.php).
      vii. Bielefeld Academic Search Engine (BASE; www.base-search.net/about/en).
      viii. Theses France (www.theses.fr/en).
      ix. ProQuest Open Access Dissertations (PQDT; pqdtopen.proquest.com/search.html).
7. Selection of studies and Data extraction and management
   a. More review authors than stated in the protocol screened titles and abstracts, entered data into RevMan 5 and conducted statistical analyses in RevMan 5 (Review Manager 2014).
8. Measures of treatment effect
   a. We chose only to summarise dichotomous data as risk ratios (RR) with 95% confidence intervals (CI) and to present pooled proportion data from non-comparative studies.
   b. We did not calculate the risk difference and the number needed to treat for an additional harmful outcome.
9. Assessment of reporting biases.
   a. We did not draw funnel plots (estimated differences in treatment effects against their standard error) due to there being too few studies.
   b. We also did not perform Egger's statistical test for small-study effects due to there being too few studies.
10. Data synthesis
   a. In the comparative cohort studies, we compared the intervention group to the control group and not to baseline values of the intervention group, as stated erroneously in the protocol (Storebø 2016).

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11. Subgroup analysis and investigation of heterogeneity
    a. We did not conduct subgroup analyses on sex and subtype of ADHD as stipulated in our protocol (Storebø 2016), due to lack of relevant data.
    b. We conducted the subgroup analyses (listed below) due to the very high heterogeneity of the data, to investigate whether these different aspects affected the proportion of adverse events. These analyses were not specifically planned in our protocol (Storebø 2016).
        i. Studies with concurrent medication compared to studies without any concurrent medication.
        ii. Studies with ADHD as the only disease compared to studies with ADHD and comorbidity.
        iii. Studies with a treatment duration shorter than six months compared to studies with a treatment duration of six months or longer.
        iv. Studies with participants with a mean age younger than 10 years compared to studies with participants with a mean age of 10 years or older.
        v. Studies with a low dosage of methylphenidate (below 20 mg/day) compared to studies with a high dosage of methylphenidate (20 mg/day and above).
        vi. Cohort studies on methylphenidate originating from RCTs assessing methylphenidate versus other ADHD interventions compared to studies with a classic cohort design.
        vii. Studies funded by industry compared to studies not funded by industry.
12. Sensitivity analysis
    a. We conducted only two sensitivity analyses:
        i. analytical technique used (for example, fixed-effect versus random-effects models); and
        ii. study design (patient-control studies compared to comparative cohort studies).
    b. We did not perform a sensitivity analysis to assess whether the findings were sensitive to decisions made during the review process.
    c. As all studies were assessed as having overall serious or critical risk of bias, we could not perform a sensitivity analysis on the impact of bias.
    d. We did not conduct a sensitivity analysis regarding the type of data collection (e.g. different ways to assess adverse events), due to lack of relevant data.
    e. We also did not conduct an analysis comparing available outcome data to those following the intention-to-treat (ITT) approach, due to lack of relevant data.
13. Excluded studies
    a. We excluded 112 studies (121 reports) because outcomes were outside the focus of this review (e.g. visual attention test, reaction time, memory skills, and functional abnormalities). These studies did not report any adverse events.
14. **Written language**
    a. In order to avoid demeaning patients to "cases", we chose to name "case-control studies" as "patient-control studies", and "case reports" as "patient reports/series".
    b. Instead of naming study participants as "subjects", we used the term "participants".

INDEX TERMS

Medical Subject Headings (MeSH)

Attention Deficit Disorder with Hyperactivity [*drug therapy]; Central Nervous System Stimulants [*adverse effects] [therapeutic use]; Methylphenidate [*adverse effects] [therapeutic use]; Non-Randomized Controlled Trials as Topic; Patient Dropouts [statistics & numerical data]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Young Adult

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