Review

The use of antipsychotics in preschoolers: A veto or a sensible last option?

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Abstract

Recent reports have illustrated a dramatic rise in the use of antipsychotics in preschool children, medications originally designed and licensed for the treatment of adult psychotic disorders. Within this context, the current usage and the associated diagnoses are reviewed and compared with official guidelines and licensing for such use, highlighting a controversial challenge for clinicians. A review of the evidence base of the relative efficacy of such medications for a range of disorders is given. Associated safety and side effects are discussed, with compelling evidence for increased adverse events associated with use of antipsychotics in preschoolers, and neurodevelopmental hypotheses are used to guide predictions of long-term risk. An apparent gap in the literature and evidence base supporting such use and elucidating the risks and benefits leaves a challenge for clinicians and researchers and hinders the development of appropriate guidelines. Pragmatism in clinical practice, mindful of the limited evidence base that does exist and the propensity for harm, is necessary; far more research is required in this important area.

Keywords

Antipsychotics, children (preschool), practice guideline, license, long-term effects, safety, treatment efficacy, review

Introduction: rising prescribing rates and public concern

Great controversy surrounds the use of antipsychotics in children, especially in the preschooler group, for the purposes of this review defined as those yet to enter the education system or aged less than 6 years (in the UK, 'preschool' generally refers to up to and including aged 5; internationally, this can be up to age 6; due to the inclusion of international literature, we use this age bracket inclusive of those 6 years old). Use of antipsychotics in children has reportedly risen dramatically over the past decade (Egger, 2010; Olfson et al., 2010), instigating questions by the media, research bodies and practitioners about the reasons for this increase: is such use safe and effective, supported by clinical evidence and informed by appropriate guidelines? And where and how should future research in this age group be directed? The use of medications that were originally developed for adults suffering with schizophrenia raises concerns not only about the appropriateness of translating the evidences of effectiveness from adults to children, but also concerns about the effects on brain development and long-term effects in children.

Conversely, non-pharmacological treatment of mental health problems is not always successful and does not always show full response in children, and residual or untreated symptoms are associated with risks including child-care expulsion, impaired family and peer relationships, isolation, high-risk behaviours and future mental health problems (Byrne et al., 2003; Egger and Angold, 2006; Gilliam, 2005; Gleason et al., 2007; Lavigne et al., 1998). This can leave clinicians puzzled whether to treat such young children with drugs developed for adults, with the fear of uncharted effectiveness and safety, or to risk not treating some children who are still symptomatic despite attempting all other avenues.

Current usage, licensing and guidelines: the challenge for clinicians

Recent reviews of pharmaco-epidemiological studies have shown an international increase in antipsychotic prescribing trends in both child and adult populations (Comer et al., 2010; Olfson et al., 2006; Pathak et al., 2010; Verdoux et al., 2010; Zito et al., 2000). In the UK the use of antipsychotic medication in children (aged less than 18 years) is reported to have doubled between 1995 and 2005 (Rani et al., 2008), from a prevalence of 0.4 per 1000 patient-years to nearly 0.8 per 1000 patient-years, with children aged between 7 and 12 years showing the largest significant increase in prevalence of antipsychotic use (between 0.23 per 1000 patient-years in 1995 to 0.61 per 1000 patient-years in 2000).

In the United States the Food and Drug Administration reported a 22% increase in antipsychotic use in the paediatric population (0–17 years) between 2004 and 2008. Antipsychotics accounted for less than 1% of all prescriptions in preschool children, with the exception of risperidone, which represented 2% of prescriptions in the subcategory of 3–6-year-olds. The diagnoses associated with these prescriptions varied between age groups: in

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0–2-year-olds, most prescriptions were for the rather vague ICD-9 diagnostic category 'mental and behavioural problems not otherwise specified' (40%), and schizophrenic disorders (35%); while 3–6-year-olds received most prescriptions for episodic mood disorders including bipolar affective NOS (31%), conduct disturbance (15%), and hyperkinetic syndrome (15%). Other diagnoses included emotional disturbance and pervasive developmental disorders (PDD) including autism (Governale and Mehta, 2009).

More recently, a large cohort analysis (N = 400,196 in 1999; N = 755,793 in 2007) revealed an annualised rate increase from 0.78 to 1.59 per 1000 children using antipsychotic medication from 1999–2007 in a US population of privately insured 2–5-year-olds. PDD, attention deficit hyperactivity disorder (ADHD) and disruptive behaviour disorder (DBD) dominated the clinical diagnoses given to these children for such treatment (Olfson et al., 2010). Similarly, a recent population cohort study of young children who started antipsychotic medication before their sixth birthday highlighted how preschool children prescribed such medication tended to remain on such drugs for prolonged periods (Constantine et al., 2012). These children (identified from the Medicaid programme, n = 528) had a mean of approximately 2.3 years of treatment, and those with primary diagnoses of 'pervasive development disorder' and affective disorders were more likely to be prescribed such medications than those diagnosed with ADHD. In this paper, exposure (determined by duration of prescription) was also greater with existence of secondary diagnoses (including ADHD, DBD, PDD, psychotic disorder and affective disorders; odds ratios reported between 0.17–0.27, all $p < 0.01$) and use of other psychotropic drugs, which they assumed might indicate increased clinical severity.

Such rise in prescribing faces the considerable hurdles of conflicting national or professional guidelines (see Table 1 for UK and US guidelines for treatment) and a lack of drug licensing (see Table 2 for current UK and US licensing details). As an example, in the UK, the National Institute for Health and Clinical Excellence does not provide guidelines including any recommendation for the use of antipsychotics in preschool children for any disorder, although the national prescribing formulary, the BNF, licenses the use of some antipsychotics in certain instances in those aged less than 6 years (see Table 2). Other relevant guidelines for clinical practice may be found from the Preschool Psychopharmacology Working Group developed by the American Academy of Child and Adolescent Psychiatry (AACAP) (Gleason et al., 2007), the National Institute of Mental Health (NIMH), and from review papers of practice guidelines (Danielyan et al., 2007; Gleason et al., 2007; Spetie and Arnold, 2007). The AACAP guidelines for clinicians considering antipsychotic use in preschool children advised: '1) signed parental consent must be obtained once parents have been given a clear outline of lack of approval for use, the risks and benefits; 2) to titrate dose slowly, starting from the lowest dose possible; 3) to use monotherapy; 4) to monitor treatment effects and side effects closely; and if effective, to plan to discontinue after 6 to 9 months, using trial of tapered discontinuation, 5) to make sure medication is still necessary and effective; 6) furthermore, in all cases psychosocial, psychotherapy, behavioural or family interventions must be continued throughout treatment, 7) and it is advised to avoid use entirely in children less than 2 years of age, unless facing rare and extenuating circumstances' (Gleason et al., 2007).

In many instances, antipsychotic drugs are not licensed for use in preschool children (although they may be licensed for use in older children or for alternative uses), and so any prescribing practice of them for this age group is not explicitly supported by national licensing authorities, deeming it 'off-label use'. Because of these discrepancies, the lack of consensus and the paucity of national guidelines for use inevitably mean that clinicians take greater medico-legal responsibility for any adverse outcomes. In the UK the Royal College of Psychiatrists (RCP, 2007) suggests clinicians seek reasonable balanced justification and rationale for individualised prescribing from scientific evidence and in accordance with a respectable body of professional opinion, aiming to achieve the best prospect of benefit for a given child.

The evidence base: what does the scientific literature say?

Diagnostic dilemmas: apples and oranges?

As well as the concern about the prescribing of medications designed for adult populations, there are nosological debates about the usage of adult diagnostic criteria and scales in children and adolescents, particularly for bipolar affective disorders and schizophrenia. The existence of bipolar affective disorders in very young children has only recently been seriously re-evaluated, challenging the longstanding belief that first episodes of mania occurred very rarely before puberty: Kraepelin (1921) described 0.4% of 903 patients having an onset before age 10; similarly 0.5% prevalence was described by Loranger and Levine, (1978); and 0.3% found by Goodwin and Jamison (1990). Other authors have recently suggested that early-onset bipolar disorder (EOBD) might be more common (Luby and Belden, 2008; Luby et al., 2009; Wilens et al., 2003), especially in the USA (Soutullo et al., 2005), with reported rates of 16% of children referred to a psychiatrist with a diagnosis of bipolar affective disorder, 70% of these having an onset of manic symptoms before their fifth birthday (Wozniak et al., 1995). However, the expansion of EOBD diagnoses in preschoolers has been felt by many to be unsolicited, and is dependent upon non-validated interpretations of diagnostic criteria due to the lack of specific criteria within the DSM-IV for EOBD, with 'adult' criteria for bipolar disorder typically being used. Furthermore, the DSM-V has recently revealed a change in direction within this area: children who may previously have been diagnosed with EOBD may now have a diagnosis of 'severe mood dysregulation', a condition predictive of anxiety and unipolar depression not bipolar disorder later on in life, and more responsive to selective serotonin reuptake inhibitors or stimulants than to antipsychotics or mood stabilisers (Towbin et al., 2013). However, there has evidently been an increase in diagnoses of EOBD and treatment for it with antipsychotics in very young children, despite a lack of sufficient data revealing phenomenology, aetiology and comorbidity to inform accurate diagnosis and correct treatment strategy (Danielyan et al., 2007).

Biederman et al. (2005a) noted the need for development of assessment measures for this very young population, as the rating scales and assessment methods often used in such studies such as the Young Mania Rating Scale (YMRS) (Young et al., 1978) and NIMH Clinical Global Impression (CGI) of severity and improvement scales have only been previously validated in adult

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Table 1.

Disorder	UK (NICE)	US (AACAP)
ADHD/ADD	Parent training/education programme. If more help needed, refer to tertiary care. Drug treatment is not recommended for preschool children.	1st line: parent management training & other behavioural intervention (min 8 weeks); 2nd line methylphenidate; 3rd line amphetamine (dexamphetamine/ alpha-agonist).
Anxiety	No clear guidelines for management of anxiety in children.	Cognitive behavioural therapy/behavioural therapy (min 12 weeks); 2nd line fluoxetine; 3rd line fluvoxamine.
Severe aggression/ irritability caused by PDD	No apparent guidelines for treatment in preschool children; all guidelines for ASD in children simply outline protocol for recognition, referral and diagnosis, and services and support available once diagnosed.	Behavioural, developmental, psychoeducational intervention; 2nd line and if severe impairment use risperidone.
EOBD	Only guidelines for pre-pubescent children; none for preschool specifically: Psychotherapy. Only licensed drug <18yrs is lithium (>12), but unlicensed medication may be prescribed for children if no suitable alternative and justified by a responsible body of professional opinion.	Dyadic psychotherapy, target emotional dysregulation; 2nd line risperidone; 3rd line adjunctive mood stabiliser/ alternative antipsychotic (olanzapine).
Severe behavioural problems	No guidelines for management of behavioural problems in preschool children. NICE guidelines refer to the management of conduct disorder in those aged over 6 years: psychosocial interventions (parent training/child-focussed) recommended. Pharmacological interventions should not be offered 'for routine management'; risperidone considered for 'short-term management of …severe aggression/emotional dysregulation… when no response to psychosocial interventions'.	Psychotherapy, parent management training and parent-child interaction therapy. 2nd line: risperidone.
COS	No apparent guidelines for management and treatment of COS in preschool children. NICE guidelines for COS are currently under review and development.	No apparent guidelines for management and treatment of COS in preschool children.
Tourette Syndrome	No apparent guidelines for management and treatment in preschool children.	No apparent guidelines for management and treatment in preschool children.

UK and US guidelines for treatment of disorders in preschool children. NICE: National Institute for health and Care Excellence; AACAP: American Academy of Child and Adolescent Psychiatry; ADHD: attention deficit hyperactivity disorder; ADD: attention deficit disorder; ASD: autism spectrum disorder; PDD: pervasive developmental disorder; EOBD: early-onset bipolar disorder; CD: conduct disorder; COS: childhood-onset schizophrenia

populations. This need for development of uniform assessment methods for this patient group has been justified by Galanter et al.'s (2012) argument that there is variance in interpretation of DSM-IV criteria for a manic episode and bipolar disorder and recommendations for administration and scoring methods, due to the underlying problem that the DSM-IV was developed for adult bipolar disorder.

Similarly, the DSM-IV criteria for schizophrenia are not age specific; however, the criteria were primarily designed in reference to adolescents and adults, and hence must be applied with caution to young children. Childhood-onset schizophrenia (COS), defined in DSM-IV by schizophreniform symptoms presenting before age 13 (McKenna et al., 1994), has been shown to present in preschool children (Schaeffer and Ross, 2002), although is arguably extremely rare (just 0.01% 2–5-year-olds in 2007, reported by Olfson et al. (2010)). To our knowledge, there are no other studies illustrating formal incidence or prevalence of COS in preschool children; however, there have been a few studies that have documented the rare existence of the disorder in this age group (Beresford et al., 2005; Campbell et al., 1972; Russell, 1994; Schaeffer and Ross, 2002). Others have argued that despite the occurrence of social, cognitive and sensory symptoms of schizophrenia in preschoolers, fully diagnosable schizophrenia as defined by the DSM is not possible before the age of six (Watkins et al., 1988). There are reported similarities in children aged 6–12 to adolescent and adult-onset schizophrenia in symptom presentation (Russell, 1994; Watkins et al., 1988), performance on physiological tests (Strandburg et al., 1999), neuropsychological performance (Asarnow et al., 1994), neuroanatomical findings (Alaghband-Rad et al., 1997), neurofunctional findings (Thomas et al., 1998) and antipsychotic responsiveness (Spencer and Campbell, 1994), but there have been very few studies of preschoolers (Beresford et al., 2005). Furthermore, premorbid and prodromal symptoms and symptom similarity with other childhood disorders may lead to other diagnoses (for example, ADHD) being given before COS is recognised and treatment is given (Schaeffer and Ross, 2002).

The safety and efficacy of antipsychotic treatment in young children

We performed a systematic search for original studies testing the efficacy of antipsychotic drug treatments in preschool children. A search of articles published since 1999 via the PubMed interface

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Table 2.

Disorder	UK license (BNF)		US license (FDA)	
	Drug	Age / restrictions	Drug	Age / restrictions
ADD/ADHD			Chlorpromazine	1–12
Anxiety	Trifluoperazine	≥3; Severe		
ASD	Risperidone	≥5; Aggressive behaviour	Aripiprazole	≥6; Irritable, disruptive or aggressive behaviour
			Risperidone	≥5
EOBD	Haloperidol	≥12	Aripiprazole	≥10
	Risperidone	≥12	Chlorpromazine	
			Olanzapine	≥13; Manic or mixed episodes
			Quetiapine	≥10; Acute mania
			Risperidone	≥10; Manic or mixed episodes
Behavioural problems	Haloperidol	≥12; Agitation or violent behaviour	Chlorpromazine	≥ 12; Severe
	Trifluoperazine	≥12; Agitation or violent behaviour		
COS	Chlorpromazine	≥1; Also 'acute psychoses'	Aripiprazole	
	Haloperidol	≥12; Also 'other psychoses'	Chlorpromazine	
	Pericyazine	≥1; Also 'acute psychoses'	Loxapine	≥12
	Pimozide	≥12	Perphenazine	≥12
	Risperidone	≥12	Quetiapine	≥13
	Sulpiride	≥14	Olanzapine	
	Trifluoperazine	≥3	Prochlorperazine	≥2
			Risperidone	≥13
			Thioridazine	≥12
			Trifluoperazine	≥6
Tourette syndrome	Haloperidol	≥5	Pimozide	≥12

Current UK and US antipsychotic drug licensing. BNF: British National Formulary; FDA: Food and Drug Administration; ADHD: attention deficit hyperactivity disorder; ADD: attention deficit disorder; ASD: autism spectrum disorder; EOBD: early-onset bipolar disorder; COS: childhood-onset schizophrenia.

was conducted, using search terms 'children' or 'preschool' (or 'pre-school', 'pre-schoolers', 'preschoolers'), and 'antipsychotic' (including specific antipsychotic agents, e.g. 'aripiprazole', 'ziprasidone', 'risperidone', etc.). We also retrieved additional references from review articles. All search results were inspected, and the following selection criteria were used. All original studies of the efficacy of one or more antipsychotic treatment within a) preschool children specifically (aged 0–6 years) and b) a sample of young children incorporating preschool-aged children but also school-aged children (0–16 years). This was done for the purpose of completeness and review of as much relevant literature as possible, due to the small number of studies specific to preschool-aged children. Any repetitions of studies within separate publications were ignored. Our search found 42 relevant studies in total: 15 specific to preschool children, and 27 inclusive of preschool children and school-aged children. Of the studies of just preschool children, just one utilised double-blind, placebo-controlled measures, five were open-label trials, five were case reports, three were retrospective clinical chart reviews and one was a naturalistic follow-up study of treatment within a clinic. Of those not specific to preschool children, but inclusive of preschool children, there were eight randomised controlled trials (RCTs), 12 open-label trials, four retrospective clinical chart reviews, one was double-blind and placebo controlled, one was a randomised trial, and one was a follow-up study of treatment. A summary of these studies is presented in Table 3.

A recent review of the comparative effectiveness and safety of antipsychotics in young people (inclusive of aged <24 years) provides a relevant overview of the evidence base related to the use of antipsychotic drugs in the general paediatric population (Seida et al., 2012). Low or insufficient strength of evidence and a high risk of bias were concluded to be pervasive in the evidence base, which notably would be more pronounced in our more specific focus on the preschool population. Olanzapine was argued to have a moderate strength of evidence supporting its efficacy, although it is associated with more weight gain than quetiapine and risperidone. Risperidone was associated with fewer prolactin-related events than olanzapine. Generally, atypical antipsychotics were associated with improved CGIs in paediatric patients with schizophrenia, bipolar disorder, Tourette syndrome and DBD, compared with placebo (Seida et al., 2012). Our review will give a more focussed overview of the evidence base of the efficacy and safety of antipsychotic treatment for preschool children.

Early-onset bipolar affective disorders

The prevalence of children treated for bipolar disorder has been shown to have risen in the recent years (between 0.24% in 2005

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Table 3. Results of systematic review of studies testing the efficacy of antipsychotic drugs in preschool and school-aged children, ordered by disorder then age range (studies specific to preschool children listed first, followed by those also including school-aged children). Abbreviations of study design and bias terms: open-label (O-L); randomised controlled trial (RCT); retrospective chart review (RCR); non-randomised (NR); non-blind (NB); no placebo (NP).

Author	Disorder	Treatment	Age range (years)	Design	*N*	Bias	Results	Conclusions
(Biederman et al., 2005a)	EOBD	Olanzapine vs. risperidone	4–6	8 week O-L	31	NR, NB, NP	18.3±11.9 (t=-5.6, p<0.001, r=0.82) YMRS point reduction in risperidone-treated; 12.1±10.4 point (t=-4.4, p<0.001, r=0.76) reduction in olanzapine-treated; no difference between groups (t=1.4, p=0.2).	Preliminary evidence for efficacy of both
(Joshi et al., 2012b)	EOBD	Quetiapine	4–6 (n=30) 6–15 (n=19)	8 week O-L	49	NR, NB, NP	14.5±11.5 (t(29) = -6.92, p<0.001, r=0.79,) YMRS point reduction in preschool and 13±9.8 (t(18)=-5.85, p<0.001, r=0.82) reduction in school-aged. Treatment-limiting ADEs in 3/30 preschool and 1/19 school-aged.	Improvement in both preschool & school-age, more preschool than school-age reported AEs
(Findling et al., 2012)	EOBD	Aripiprazole + placebo	4–9	16 week O-L, then 72 week RCT	96		Patients randomised to aripiprazole treatment arm showed longer maintenance on study (mean 25.93 weeks, SE±5.53) compared with placebo (mean 3 weeks, SE±0.57, Breslow χ^2_1=8.81 p=0.003, r=0.3). Aripiprazole decreased the odds of discontinuation by ~60% (hazard ratio 0.32 and 0.41 for aripiprazole and placebo, respectively).	Superior to placebo in short and long term
(Frazier et al., 2001)	EOBD	Olanzapine	5–14	8 week O-L	23	NB, NP	19±9.2 (p<0.001) reduction in YMRS. 61% overall response rate (defined as ≥30% YMRS reduction and CGI-S score ≤3 at endpoint). EPSE not significantly different from baseline.	Efficacious and well tolerated
Beresford et al., (2005)	COS	Clozapine, olanzapine, molindone & ziprasidone	4 & 5	Case report	2	NB, small sample	Case-by-case description of partial symptom reduction in each child.	Improved symptoms, both children sensitive to side effects
(Kowalski et al., 2011)-	ASD	Paliperidonepalmitate (IM depot)	5	Case report	1	Small sample	CGI-S improvement from 6 ('severely ill') to 2 ('minimally ill) and CGI-I score of 1 ('very much improved) at 3 month follow-up. BMI increased from 16.4 to 19.2.	CGI-I 'very much improved', but increased BMI
(Posey et al., 1999)	ASD	Risperidone	1–2	Case report	2	Small sample	Significantly reduced aggression and improved social relatedness.	Significant improvement, one showed dose-related cardiac symptoms
(Luby et al., 2006)	ASD	Risperidone	2–6	6 month, double-blind, placebo-controlled			Significantly greater reduction of autism symptoms (CARS) from baseline to endpoint in risperidone vs. placebo group (λ=0.74, F(1,21)=6.92, p<0.05, d=0.95).	Minimal symptom improvement over placebo – larger study needed
Masi et al., (2001c)	ASD	Low-dose risperidone	3–6	16 week O-L	10	NP	Improvement in CARS (t=3.23, p=0.015, r=0.77); CPRS (t=7.87, p<0.001, r=0.94); CGAS (t=-6.77, p<0.001, r=0.93); CGI-I ranged from 'minimally' to 'very much improved'.	Improved clinical outcome, no severe side effects

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Table 3. (Continued)

Author	Disorder	Treatment	Age range (years)	Design	*N*	Bias	Results	Conclusions
(Masi et al., 2001b)	ASD	Risperidone	3–6	16 week O-L	24	NP	21% improvement in CPRS; 14% improvement in CARS; 25% C-GAS improvement; 8 participants deemed 'responders' (≥25% CPRS improvement and CGI-I score of 1 or 2).	Improved disruptive/ hyperactive behaviour, 54% free of side effects, all rest well tolerated
(Masi et al., 2003)	ASD	Risperidone	3–6	Naturalistic study	53	NP	Significant improvement on CPRS (p<0.001), and C-GAS (p<0.001); 47% deemed responders (≥25% CPRS improvement and CGI-I score of 1 or 2).	Improvement in short and long term, responders had higher doses but more side effects
(Masi et al., 2001a)	ASD	Risperidone	3–7	10 week follow-up of treatment effects	25	NP	Improvement as measured by CGI-I. No data given.	Improvement. No clinical hyperprolactinaemia, though 28% had 2× higher than upper limit
(Diler et al., 2002)	ASD	Risperidone	3–7	6 month O-L	20	NB	Mean CARS score decreased from 39.06±6.23 to 32.03±8.73 after 6 months (p<0.001). 81% showed ≥1 grade improvement on CGI-SI scales.	Improved clinical symptoms
(Mukaddes et al., 2004)-	ASD	Risperidone	4–8	6 week O-L	19	NB, NP	Significant improvement on Conner's Parent Index (t=5.76, p<0.001, r=0.8) and an ASD symptoms checklist (p<0.05).	Clinically significant improvement, but weight gain
(Nagaraj et al., 2006)	ASD	Risperidone	2–9	Double-blind, placebo-controlled	39		63% showed ≥20% improvement of CARS, none of placebo group showed improvement; 89% showed ≥20% improvement on C-GAS, only 2 in placebo group showed this improvement.	Improved social responsiveness, verbal communication, aggression
(Gagliano et al., 2004)	ASD	Risperidone	3–10	24 week O-L	20	NB, NP	CPRS scores significantly decreased from 63.7±10 to 52.9±14.3 at week 12 (p<0.01). 8 deemed 'responders' (≥25% decrease on CPRS and CGI-I score of 1 or 2); 10 showed minimal improvement (CGI-I). Serum prolactin levels increased in all children (p<0.001).	Significant improvement but weight gain and increased prolactin serum levels
(Lemmon et al., 2011)	ASD	Risperidone	3–15	RCR	<5 yrs n=13; total n=80	Retrospective, NB, NP	66% met criteria for success at 6 months, and 53% at 1 year (CGI-I and clinician's impression of symptom improvement). 67% of non-success group and 47% of success group reported side effects, weight gain most common.	69% <5 years showed successful treatment, weight gain common side effect
(Rezaei et al., 2010)	ASD	Risperidone/ topiramate + risperidone/ placebo	4–12	RCT	40		Combination of topiramate + risperidone is superior to both placebo and risperidone monotherapy as measured by the ABC (p<0.05).	Combination is superior to risperidone monotherapy.
(Aman et al., 2009b)	ASD/ PDD-NOS	Risperidone / risperidone + PT	4–13	24 week, randomised	124	No PT alone condition, NP	HSQ score decline in COMB group by 71% compared to 60% in risperidone alone group (p=0.006, effect size=0.34 at week 24); COMB group also showed significantly greater improvement on ABC scales (p<0.05).	Medication + PT is most effective in reduction of behavioural symptoms

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Table 3. (Continued)

Author	Disorder	Treatment	Age range (years)	Design	*N*	Bias	Results	Conclusions
(Scahill et al., 2012)	ASD/PDD	Risperidone + PT	4–13	24 week 'RCT'	124		Socialisation and communication improved more (measured by VABS) more in COMB (p=0.03, effect size=0.33) than risperidone alone (p=0.05, effect size=0.14).	Combination shows benefit over medication alone
(Shea et al., 2004)	ASD or other PDD	Risperidone vs. placebo	5–12	8 week RCT	79		87% showed CGI improvement compared with 40% placebo group. Risperidone group showed significantly more ABC (irritability scale) improvement than placebo group from week 1 (p<0.05) to week 8 (p<0.001) with 64% improvement over baseline compared with 31% in placebo group.	Well tolerated and efficacious
(Malone et al., 2002)	ASD	Risperidone	2–16	O-L, 1 month short phase, 6 month long phase	22	NB, NP	Significant clinical improvement assessed by CPRS (mean difference -0.82, SD=0.65, 95%CI(-1.11, -0.52), p<0.001) and CGI-I (55% very much improved; 36% much improved).	Improved clinical outcome, withdrawal effects noted
(Stigler et al., 2009)	PDD-NOS/ ASD	Aripiprazole	5–17	14 week O-L	25	NB, NP	88% responders (ABC-Irritability scale ≥25% improvement and CGI-I score of 1 or 2). Mean CGI-I and ABC-I improved over 14 weeks (p<0.001 for both measures).	Effective and well-tolerated
Valicenti-McDermott et al. (2006)	ASD/ mental retardation	Aripiprazole	5–19	RCR	32	NB, NP, retrospective	56% showed improvement in target symptoms. According to clinicians' global impression of changes, 54% showed improvement in aggression, and 48% improved in hyperactivity.	56% improved symptoms, 50% report adverse side effects
(Masi et al., 2009)	PDD	Aripiprazole	4–15	Retrospective study, 4–12 month follow-up	34	NB, NP, retrospective	CGI-I improved from 'markedly/severely ill' to 'much /very much improved' at endpoint (32.4%); 35.3% 'minimally improved'; 29.4% 'unchanged/worsened'. C-GAS and CARS scores significantly improved (p<0.001, effect sizes 0.59 and 0.62, respectively). 26.5% experienced moderate/severe agitation.	3rd showed significant improvement, adverse effects
Owen et al. (2009)	ASD	Aripiprazole	6–17	8 week, RCT	98		ABC-irritability score significantly greater improvement in aripiprazole group (-12.9) than placebo (-5), p<0.001; and greater improvement in CGI-I scores at week 1 (p<0.001) through to week 8 (2.2 vs. 3.6, 95%CI(-1.9, -1) p<0.001). More aripiprazole-treated deemed 'responders (≥25% ABC-I reduction and CGI-I score 1 or 2) than placebo at week 2 (30.4% vs. 4.1%, p<0.001) through to week 8 (52.5% vs. 14.3%, p<0.001).	Efficacious, safe and well tolerated

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Table 3. (Continued)

Author	Disorder	Treatment	Age range (years)	Design	*N*	Bias	Results	Conclusions
(Malone et al., 2001)	ASD	Olanzapine vs. haloperidol	5–10	6 week O-L, randomised	12	NP	Five of olanzapine group and 3 of haloperidol group deemed responders according to CGI-I. Significant improvement on CPRS autism factor ($F_{1,9}$=24.4, p=0.0008, r=0.85).	Olanzapine showed more clinical improvement
(Cesena et al., 2002)	Aggression	Risperidone	<6	RCR	8	NR, NB, NP retrospective	Average CGI-S improvement from 5.5 to 3.5 at last visit (p<0.001); mean CGI-I score of 1.9 (SD=0.6). Significant weight gain in 6 patients (mean 5.5±4.9kg, p<0.05).	Improvement in CGI-I but also weight gain
(Aman et al., 2009a)	Disruptive behaviour	Risperidone/ placebo	4–14	4 week RCT; 2 week crossover	16	Short term	Risperidone-treated superior to placebo on response time tasks (p=0.01, η_p^2=0.44), seat movement (p<0.05, η_p^2=0.29), on three subscales of Nisonger Child Behaviour Rating Form: 'overly sensitive' (p=0.01, η_p^2=0.44); 'conduct problem' (p=0.02, η_p^2=0.36); 'hyperactivity' p=0.03, η_p^2=0.32); and on ABC (p=0.01, η_p^2=0.41).	Cognitive-motor and behavioural improvements
(Ad-Dab'bagh et al., 2000)-	DBD	Risperidone + milieu therapy	Mean 9.9	RCR	15	Retrospective, NR, NB, NP	Mean C-GAS scores improved from 21.9 (SD =7) at admission to 50.3 (SD = 5.3), p<0.001 at discharge.	Clinically significant improvement after mean 46 days. Safe and effective
(LeBlanc et al., 2005)	DBD	Risperidone	5–12	2×RCTs	163 male		Risperidone-treated had significantly greater decrease in Aggression Score than placebo group (p<0.001); at endpoint, aggression decreased by 56.4% compared with 21.7% reduction in placebo group.	Reduced symptoms of aggression
(Findling et al., 2004)-	DBD	Risperidone	5–12	48 week O-L	107	NB, NP	71% had CGI-S scores of 'marked, severe or extremely severe behavioural problems' at baseline, 62% had 'no symptoms' or 'very mild symptoms' at endpoint.	Safe, well-tolerated and effective; somnolence and weight gain
(Croonenberghs et al., 2005)-	DBD	Risperidone	5–14	1 year O-L	504	NB, NP	Nisonger Child Behaviour Rating Form (conduct problem scale) scores significantly improved at week 1 and at each point throughout trial (p<0.001 at each timepoint). Significant improvements on ABC (mean change -28.3±1.4, p<0.001) and CGI-S (72% marked to extremely severe symptoms at baseline to 66% rated as not ill or minimal symptoms at endpoint).	Well tolerated and effective in long term
(Pandina et al., 2007)	DBD	Risperidone	5–14	2× 6 week RCTs + 3× 1 year O-L studies	RCTs n=288, O-L n=688		NCBRF conduct subscale improvement significantly greater for risperidone vs. placebo group (-15.8 vs. -6.4, p<0.001) in short term RCTs; and in long-term RCTs (-16.3, p<0.001).	Efficacious over placebo in short and long term, improved symptoms

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Table 3. (Continued)

Author	Disorder	Treatment	Age range (years)	Design	*N*	Bias	Results	Conclusions
Reyes et al., (2006)	Behaviour disorders	Risperidone	5–17	6 month RCT	527		Symptom recurrence in 25% of patients occurred after 119 days with risperidone and after 37 days with placebo; risperidone associated with lower rate of symptom recurrence than placebo (27.3% vs. 42.3%, c^2=10.4, p=0.002). Greater improvement also seen in NCBRF (conduct problems: $F_{1,293}$=13.17, p<0.001, r=0.21), the CGI-S ($F_{1,293}$=20.67, p<0.001, r=0.26) and C-GAS ($F_{1,293}$=23.09, p<0.001, r=0.27) in risperidone vs. placebo group.	Symptom recurrence faster in placebo, efficacious, but weight gain
Ercan et al., 2011)	CD	Risperidone	3–6	8 week O-L	12	NB, NP	78% reduction in CGI-S (mean 6.4, SD=0.5 at baseline; mean 1.4 SD=0.5 at endpoint, p<0.001), all patients classified as 'responders' (CGI-I 'very much' or 'much improved'). DSM-IV-S score reduction of 37.8 (SD=19.2, p=0.001) on parent and 40.8 on clinical (SD=15.3, p<0.001) forms.	Effective and well tolerated
(Ho et al., 2009)	Tourette Syndrome	Sulpiride	3–15	6 week O-L	189	NB, NP	Significantly improved motor tics (p<0.05), vocal tics (p<0.05) and total Yale Global Tic Severity score (p<0.05). Sedation experienced in 16.4% participants.	Tics significantly improved, side effect of sedation
(Oner and Oner, 2008)	OCD	Risperidone plus sertraline	4–5	Case report	3	Small sample	1st case: CY-BOCS reduction from 50 to 0 after 9 months risperidone + sertraline. 2nd case: CY-BOCS 37 to 0 after 6 months risperidone + sertraline, but relapsed after 1 month discontinuation of medication. 3rd case: CY-BOCS 40 'effectively decreased' after 4 weeks sertraline.	Symptoms resolved with treatment
(Meighen et al., 2007)	Acute stress disorder	Risperidone	'Preschool'	Case report	3	Small sample	"Risperidone provided rapid and sustained improvement across all clusters of ASD symptoms… improved emotional responsiveness and reduced dissociative symptoms, less frequent and less intense episodes of re-experiencing of the trauma, diminished avoidance of stimuli that arouse recollection of the event, and a decrease in hyperarousal."	Rapid and sustained improvement, no adverse effects
(Nahshoni et al., 2007)	–	Risperidone, clotiapine or propericiazine	4–6	RCR	12	Retrospective	Significant decrease in CGI-S scores (3.67±0.89 to 3.17±0.83, t=2.2, p=0.026, r=0.55).	Improved; cardiac health was normal and unaffected by treatment

ABC: Aberrant Behaviour Checklist; ADE: adverse drug effect; AE: adverse event; ASD: autism spectrum disorder; BMI: body mass index; C-GAS: Children's Global Assessment Scale; CARS: Childhood Autism Rating Scale; CGI; CGI-I; CGI-S: Clinical Global Impression; -Improvement scale; -Severity scale; COS: childhood-onset schizophrenia; CPRS: Children's Psychiatric Rating Scale; DBD: Disruptive Behaviour Disorder; EOBD: early-onset bipolar disorder; EPSE: extrapyramidal side-effects; HSQ: Home Situations Questionnaire; PDD-NOS: Pervasive Developmental Disorder; - Not Otherwise Specified; PT: parent behaviour management training; VABS: Vineland Adaptive Behaviour Scale; YMRS: Young Mania Rating Scale.

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and 0.26% in 2007), with 25% of those being treated aged less than 13 years; 15% using one drug and 40% prescribed with two or more drugs, particularly a combination of antipsychotics and mood stabilisers (Dusetzina et al., 2012).

Within the general paediatric population (aged ≤18 years), a meta-analysis of evidence ($N = 1474$ in total) suggests an overall significant efficacy, with both open-label and double-blinded studies showing superiority of atypical antipsychotics over placebo for the treatment of EOBD (Liu et al., 2011), with summary responses of the data indicating 53% and 66% response rates respectively, and the interesting finding that the double-blind data showed greater efficacy. Our literature review found just two studies have been published on the efficacy of antipsychotic treatment with a focus specifically on preschool children (see Table 1); both were open-label trials and illustrated improvement in symptoms following 8 weeks of treatment from olanzapine, risperidone or quetiapine, though the lack of blinding weakens the findings (Biederman et al., 2005a; Joshi et al., 2012a). Two other studies presented findings of treatment efficacy for EOBD where school-age as well as preschool children were included; one showed improvement (19±9.2 ($p < 0.001$) reduction in YMRS scores) in symptoms after 8 weeks of treatment with olanzapine (open-label: Frazier et al., 2001). The other (Findling et al., 2012) evaluated the longer-term efficacy of aripiprazole wherein a cohort with EOBD stabilised over 16 weeks on an open-label dose of the drug were randomised in a double-blind manner to either continue treatment ($N = 30$) or tapered discontinuation followed by placebo ($N = 30$) over 72 weeks. Both groups showed high rates of discontinuation (50% in the active group, 90% in the placebo group) that the authors hypothesise might be a 'nocebo' effect, but those assigned to the active treatment had a statistically significantly longer time until discontinuation (median 6.14 weeks, SE ± 11.88, $p = 0.05$) than the placebo group (median 4.00 weeks, SE ± 3.91, $p = 0.03$).

Both olanzapine and risperidone have shown to be equally effective in reducing manic symptoms (18.3 ± 11.9 ($t = -5.6$, $p < 0.001$, $r = 0.82$) YMRS point reduction in risperidone-treated; 12.1±10.4 point ($t = -4.4$, $p < 0.001$, $r = 0.76$) reduction in olanzapine-treated; no difference between groups ($t = 1.4$, $p = 0.2$)) in preschool children with EOBD and displaying manic, hypomanic or mixed symptoms; however, risperidone has been associated with a faster improvement in manic symptoms (statistically significant ($p < 0.05$) after 1 week, compared with 2 weeks with olanzapine) and significant improvements in symptoms of depression (36% CGI-I improvement), but with important increment of serum prolactin levels (although only statistical increases were reported, and no clinical problems associated were reported); on the other hand olanzapine has shown a greater drop-out rate (Biederman et al., 2005a). The evidence from this open-label non-randomised trial has been supported by the open-label trial including older children and from double-blind, placebo-controlled trials of school-age children; response rates (generally defined with use of the CGI-I and symptom reduction) of 61% (Frazier et al., 2001) and 49% (Tohen et al., 2007) for olanzapine, and 63% (Haas et al., 2009) and 70% (Biederman et al., 2005b) for risperidone. The evidence for aripiprazole efficacy for treating EOBD in young children is also limited to a small number of studies; an RCT in 4–9-year-olds illustrated both short-term (16 weeks) and long-term (72 weeks) efficacy and evidenced long-term tolerance of the medication in this young group; few and only minor side effects were reported (33% stomach aches, 30% increased appetite; 30% headaches) (Findling et al., 2012), with response rates of 64% also reported in school-aged children (Findling et al., 2009). There is also evidence, although limited, supporting the efficacy of quetiapine in improving symptoms of EOBD in both preschool (YMRS score reduction of 14.5 ± 11.5, $t(29) = -6.92$, $p < 0.001$, $r = 0.79$) and school-aged children (YMRS -13 ± 9.8, $t(18) = -5.85$, $p < 0.001$, $r = 0.82$), with a single open-label trial not controlled with a placebo. In this work more adverse drug events were reported in the preschool children (Joshi et al., 2012a).

Childhood-onset schizophrenia and other psychotic disorders

Just one study of the treatment of COS in preschool children was found: a case report of two preschool children described best improvement of symptoms when treated with clozapine, ziprasidone and molindone (the last of which is no longer licensed in the USA). Both cases described notable onset of psychotic symptoms between 2.5 and 3 years of age, and developing severe and disabling symptoms including hallucinations and delusions. The first case was treated initially with olanzapine (showing improved engagement and thought process, but discontinued due to weight gain and tantrums over food), then switched to quetiapine (hallucinations decreased but had side effects of frequent painful penile erections); then treated with molindone (well tolerated, and effectively treated the patient's psychosis); finally medication was switched to ziprasidone in the hope of achieving some weight loss, which did not occur, but good symptom relief continued. The second case described only partial symptom improvement from thioridazine, risperidone, olanzapine and molindone, and was finally treated long term with clozapine. Both were highly sensitive to side effects of each treatment and required close monitoring (Beresford et al., 2005).

Clozapine has shown effectiveness for treatment-resistant COS in older children (Gogtay and Rapoport, 2008; Remschmidt et al., 2000) and, fitting with data from adult populations, has been found superior to haloperidol (Kumra et al., 1996) and olanzapine (Shaw et al., 2006). As COS is deemed likely to be refractory, due to the severity, complexity and disabling nature associated with such an early onset of disorder (Schaeffer and Ross, 2002; Shaw et al., 2006), clozapine use appears appealing, and has shown to be effective in achieving clinical improvement in symptoms in treatment-resistant (to two antipsychotics) school-aged children (Shaw et al., 2006).

Autism spectrum disorders

In contrast with psychotic and mood disorders, neurodevelopmental autism spectrum disorders (ASD) are inherently very early onset, and often acquire diagnosis before school age. Antipsychotics are now commonly used – in 24% of paediatric ASD patients evaluated in a study by Esbensen et al. (2009) to manage collateral symptoms, for example aggressive and self-harming behaviour and irritability (McCracken et al., 2002; McDougle et al., 2002; Myers, 2007). Perhaps reflective of this, most studies of treatment of preschool children with antipsychotics fell in this group. Due to the change in category terms from

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the separate DSM-IV 'pervasive development disorders not otherwise specified (PDD-NOS)', 'autistic disorder' and 'Asperger's disorder', to the DSM-V Autism Spectrum Disorders category, we incorporated all studies of the above disorders under this category. Six studies were found reporting the efficacy of antipsychotic treatment for preschool children specifically: two case reports, two open-label trials, one double-blind placebo-controlled trial, and one naturalistic follow-up study; all supporting the efficacy of risperidone treatment. A further 17 studies emerged which included preschool and school-aged children, including three RCTs of risperidone treatment, and one RCT of aripiprazole treatment.

Low-dose risperidone has been shown in some instances to reduce symptoms associated with ASDs, for example irritability, aggression and emotional disturbance, and positively effect clinical outcome in the short and long term in preschoolers (Luby et al., 2006; Masi et al., 2001b, 2003, 2001c). Generally, evidence suggests that at a low dose risperidone is well tolerated in this age group, though dose-related cardiac symptoms (including persistent tachycardia and QTc interval prolongation) (Posey et al., 1999) and increased body mass index (BMI) (Kowalski et al., 2011) have been reported; difficulty in balancing dose-related side effects with response likelihood was illustrated by one naturalistic study showing that responders tended to be treated with higher doses, but also had more side effects (Masi et al., 2003).

The largest body of evidence for the pharmacological treatment of ASDs in preschool and school-age children is for the use of risperidone (see Table 1). Interestingly, risperidone shows clinical efficacy (as measured by significant behavioural symptom reduction on the Home Situations Questionnaire (HSQ) and the Aberrant Behaviour Checklist (ABC)) at even lower doses when medication is given to young children in combination with parent training in behaviour management (Aman et al., 2009b), hence reducing the risk of more severe side-effect profile seen with higher doses. However, the reporting of weight gain associated with risperidone treatment is not uncommon. Aripiprazole may be a favourable medication for the treatment of irritability and aggression in ASDs (Marcus et al., 2009; Masi et al., 2009; Owen et al., 2009; Stigler et al., 2009; Valicenti-McDermott and Demb, 2006), as it was demonstrated to show clinical efficacy (between 30–80% responders according to CGI-I scores of 'much improved' or 'very much improved' and ≥25% ABC-I improvement, see Table 3 for details), and, fitting with data from adult populations, its mechanism of action appears to lead to a better side-effect profile than risperidone (Farmer and Aman, 2011). However, conclusions were made from a brief review of studies and no direct comparison with risperidone in ASD patients was found. Furthermore, no studies of aripiprazole treatment within preschool children specifically were found, and its use in this younger age group requires further investigation. A recent systematic review of treatments for autism revealed greater benefit from risperidone and aripiprazole in treating challenging and repetitive behaviours (commonly measured by the ABC) compared with any other medical treatment for autism. The authors rated the strength of evidence as moderate for risperidone and high for aripiprazole; however, their use was recommended to be limited to patients with severe impairment, due to what was deemed to be high strength of evidence for adverse events for both medications (McPheeters et al., 2011).

Similarly, olanzapine has shown to be effective in reducing symptoms (quantified by the Children's Psychiatric Rating Scale (CPRS) autism factor; $F_{1,9} = 24.4$, $p = 0.0008$, r = 0.85) of ASD in preschool and school-age children and is more effective than haloperidol (5 out of 6 vs. 3 out of 6 deemed 'responders' as measured by the CGI improvement scale) (Malone et al., 2001). The weight gain associated with aripiprazole (Marcus et al., 2009;Owen et al., 2009), risperidone (Safer, 2004), haloperidol and olanzapine (Malone et al., 2001), may be avoided with use of ziprasidone, which has shown to be effective in reducing symptoms in ASD children adolescents and adults (Malone et al., 2007; McDougle et al., 2002). The efficacy and safety of ziprasidone needs to be further studied in preschool children, particularly given its known risk of altered QTc in adult cardiac contractility (Malone et al., 2007).

Behavioural disorders

Disruptive behaviour disorders, including conduct disorder and oppositional defiant disorder (ODD), can emerge at a very young age and can be stable diagnoses over time, with often unfavourable longer-term outcomes and comorbid diagnoses (Ercan et al., 2011; Masi et al., 2001c). A significant increase (odds ratio = 1.13, 95% CI (1.06, 1.2), $p < 0.05$) in antipsychotic use for very young children with diagnosed with DBDs was seen between 1999 and 2007 (Olfson et al., 2010). Just one study emerged which was specific to preschool children with behaviour disorders, advocating risperidone as an effective for the treatment of conduct disorder (78% reduction in CGI-I score; all patients were deemed 'responders' as they showed CGI-I scores of 'much' or 'very much improved') in preschool children by a preliminary small study (Ercan et al., 2011). This study was deemed preliminary due to its small sample size and lack of placebo control; however, seven other studies which included preschool children as well as school-aged children were identified, including the report of five RCTs within three publications. Results suggested that risperidone has the propensity to reduce clinical symptoms of DBDs, and improve cognitive-motor and behavioural functions in the short term and the long term, according to measurement with the CGI-I, the Nisonger Child Behaviour Rating Form (NCBRF) and the Children's Global Assessment Scale (C-GAS) along with other behavioural measures (see Table 3 for data). However, as seen in the studies of ASD, risperidone was commonly associated with weight gain, although generally it was seen to be otherwise well tolerated and safe. A recent review of RCTs of risperidone treatment for paediatric (children up to aged 18) DBDs (Duhig et al., 2013) illustrated clinical improvement (again measured by the NCBRF, the ABC and/or the CGI-I) in all seven studies found ($n = 657$), although adverse events were common, most significantly associated with weight gain. It was noted that the longest study was 10 weeks, so longer-term safety and efficacy is not certain.

Tourette syndrome

The rationale for using antipsychotics in Tourette syndrome is based on the pharmacodynamic action of antipsychotic drugs, via primarily blocking dopamine D_2 receptors and decreasing the excessive dopaminergic activity associated with Tourette

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syndrome, that is thought to give them an effective 'tic-suppressing' property (Bestha et al., 2010). However, just one study tested the efficacy of these classes of drugs for the treatment of Tourette syndrome in very young children. Six weeks of treatment with sulpiride led to a significant reduction in motor and vocal tics ($p < 0.05$, and a significant reduction on the Yale Global Tic Severity scale, $p < 0.05$), although 16% reported side effects of sedation (Ho et al., 2009). The likelihood of a diagnosis being given for Tourette syndrome for children under 6 years of age is fairly low, as symptoms of tics will more commonly be seen as a transient tic disorder at this age, perhaps explaining the infrequency of studies found of this age group. For children above this age, evidence has suggested that haloperidol has been found to be effective in treating Tourette syndrome, despite extrapyramidal side effects (Sallee et al., 1997), as has risperidone (Scahill et al., 2001), clonidine and ziprasidone (Gaffney et al., 2002; Sallee et al., 2000).

Safety: short-term side effects and longer-term neurodevelopment

Side effects

In adult populations there is no consistent evidence for differences in efficacy between older, 'typical' or first-generation antipsychotics (FGA) and newer, 'atypical' second-generation antipsychotics (SGA) except for the drug clozapine (Leucht et al., 2009), and current prescribing practices are largely based on expected side-effect profiles. This has tended to favour SGAs (Bleakley et al., 2007; Jauhar et al., 2012), although the influential CATIE (Lieberman et al., 2005) and CUtLASS (Jones et al., 2006) showed high rates of discontinuation amongst all the drugs. FGAs are typically associated with prominent movement and endocrine effects (such as altered libido, cessation of menstrual periods and inappropriate breast milk expression), while atypical compounds are more commonly linked to metabolic (such as weight gain and development of diabetes) and cardiovascular complications (Arana, 2000; De Hert et al., 2012; Reynolds and Kirk, 2010). The safety and side-effect profile of particular medications in adults illustrated by such research cannot be necessarily applied to children, as there are remarkable differences in adverse drug effects resulting from antipsychotics between ages (Safer, 2011), and some neuroendocrine effects – such as alteration to libido, menstruation, and breast milk expression – are biologically not possible. The incidence of adverse drug effect-related visits to outpatient and emergency departments are double in children under the age of 5 in comparison with 5–17 year olds (Bourgeois et al., 2010). This could be due to a number of age-related vulnerabilities (Safer, 2011): developmental disabilities in preschool years increase the risks of adverse drug effects (Dreifuss et al., 1987); brain maturation factors; pharmacokinetic factors; and body and hormonal developmental factors.

A recent review paper (Safer, 2011) illustrated increased adverse drug effects in young children prescribed with psychotropic drugs in general when compared with adults. Antipsychotics in particular showed increased weight gain in children – especially with olanzapine in preschoolers (mean age 5 years) (Biederman et al., 2005a) – as one of the most pervasive side effects, with polypharmacy increasing the risk for obesity (illustrated by a review of studies of children and adolescents: Maayan and Correll, 2011) and thus potentially leading to life-long health problems (Correll and Carlson, 2006; Spetie and Arnold, 2007). Furthermore, there is increased severity of associated extrapyramidal side effects, including Parkinsonian symptoms and dystonia, in children and adolescents compared with adults (Correll, 2008) when treated with both FGAs and SGAs (illustrated by a study of 8–19-year-olds: Sikich et al., 2004). Fitting with data from adult populations, the severity of extrapyramidal side effects and dystonia appear worst with haloperidol and risperidone, showing rates that varied from 8–26% in short-term RCTs of 5–12-year-olds (Correll, 2008), and lower rates in 7–16-year-olds when treated with clozapine (Shaw et al., 2006) and quetiapine (RCT of 12–18-year-olds: Delbello et al., 2002). There were increased rates of sedation, rash, convulsions, weight gain, sickness and agitation in children (birth to 9 years) using olanzapine compared with adults (20+ years) (Woods et al., 2002); clozapine shows higher rates of tachycardia and seizures in children (7–12-year-olds) than adults, occurring in up to 6%, although this did not appear correlated to clozapine dose (Sporn et al., 2003, 2007; Safer, 2011). Risperidone is associated with weight gain, with this effect decreasing with advancing age – being most pronounced in pre-adolescents – with pooled results showing children (less than 13 years of age) demonstrated over 50% more weight gain than adults at 10-month follow-up (Safer, 2004); increased risk of sialorrhoea in those less than 18 years of age (Aman et al., 2005); and significant blood level deviations of insulin, glucose and liver enzymes in children less than 13 years of age (Safer, 2011). Quetiapine has been associated with higher rates of weight gain (mean 6.1 kg, 95% CI (4.9, 7.2 kg) over a median of 10.8 weeks) in drug-naïve (4–19-year-old) youths (Correll et al., 2009) compared with adults (Young et al., 2010), and of hypothyroidism, acute dystonia, prolactin blood levels and changes in cardiovascular functioning in children (<13 years) (Safer, 2011). Aripiprazole also shows increased weight gain (mean 4.4 kg, 95% CI (3.7, 5.2 kg) over a median of 10.8 weeks) in children (<19 years) compared with adults (Correll et al., 2009).

Similarly, a recent review (31 RCTS, $n = 3595$) of the cardiometabolic and endocrine side effects in those treated with atypical antipsychotics aged <18 years of age (De Hert et al., 2011) illustrated that children and adolescents are likely to experience hyperprolactinaemia, weight gain and metabolic disturbances. Weight gain risk was shown to be lowest for ziprasidone (-0.04 kg, 95% CI (-0.38, 0.3)), then aripiprazole (0.79 kg 95% CI (0.54, 1.04)), followed by quetiapine (1.43 kg, 95% CI (1.17, 1.69)), with risperidone (1.76 kg, 95% CI (1.27, 2.25)) and olanzapine (3.45 kg, 95% CI (2.93, 3.97)) showing the most weight gain. Most significant weight gain was seen in the youngest of patients, mostly with ASD, who were less likely to have been exposed to antipsychotics previously.

In very young children the ongoing development of the liver, the kidneys, the lungs and other organs should be taken into consideration, as the pharmacokinetics of medication via these organs will inevitably be different in developing organs. Kearns et al. (2003) suggested that in children, compared with adults, psychotropic drugs typically have shorter half-lives, plasma drug levels have sharper peaks and hepatic biotransformation of drugs into active metabolites is faster (Safer, 2004); generally, children need higher relative doses for body weight to reach comparable

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plasma levels and hence have the required effect (Cote, 2005), but we also must consider the increased likelihood of adverse effects with higher doses.

Longer-term effects on neurodevelopment

The preschool years are a vital stage in neurodevelopment. The first three years of life in particular are marked by a significant increase in synaptic density, and development of monoaminergic pathways and receptor density including dopamine and norepinephrine (Shonkoff and Phillips, 2000; Young et al., 1984), followed by gradual glutamatergic synaptic pruning (Wiznitzer and Findling, 2003) and increase in neuronal myelination (Benes et al., 1994). The impact of early use of antipsychotic medication on these processes has not been well studied in young children; it has already been shown that there are insufficient clinical data on these drugs, and the ethical and practical implications of studying potential pathological brain changes are enormous. However, animal models have shown that permanent changes in the distribution of neurotransmitter receptors can result from early exposure to psychotropic medication (Maciag et al., 2005). The investigation of the neurodevelopmental effects of early exposure to antipsychotics is absolutely vital if we are to come to a valid conclusion as to whether such use is sensible and safe. Much work is required in this area; Andersen and Navalta (2004) present a heuristic framework for assessing and making predictions of the effect of childhood drug exposure to inform clinical assessments of developmental effects, efficacy, effectiveness and safety. Central principles are: 1) drug exposure during childhood alters the development of brain regions where the drug is active; 2) this effect has a delayed presentation, becoming apparent at adolescence or later (once the brain reaches maturation); and 3) the nature and the degree of the effect from exposure is influenced by the timing of the maturational phase of critical factors of change in neuroanatomy, connectivity, and reactivity of neurotransmitter systems (Andersen and Navalta, 2004). They apply this framework to assess the evidence of safety and long-term developmental effects of the use of stimulants for ADHD and antidepressants; more longitudinal research into the neurodevelopmental effects of early exposure to antipsychotic drugs is required to extrapolate similar conclusions.

Conclusion: pragmatic practice and the need for better research and guidelines

Despite an increase in use of antipsychotics in preschool children, there are currently very few RCTs exploring the applicability, efficacy, pharmacodynamics, pharmacokinetics, and physiology of side-effect profiles and long-term effects of antipsychotics in this preschool population. There is difficulty in carrying out psychopharmacological research in young children, for ethical, logistical, economical and epidemiological reasons, as discussed by the AACAP (Greenhill et al., 2003), which often prevent studies being carried out. Greenhill et al. (2003) highlighted the important need to establish proper guidelines and recommendations for research into effective diagnosis, assessment, ethical issues, study design and special considerations for this age group, informed by literature reviews, clinical experience and expert consensus including developmental specialists. As is clear from this review, more research is needed to more fully elucidate the risks and benefits of use of antipsychotics in such a young patient population; however, careful acknowledgement and handling of ethical issues associated with research in this young group is vital. If guidelines, such as those outlined by Gleason et al. (2007) are followed, we would encourage more careful research into the longer-term evaluation of both efficacy and safety of such use, specifically in this young age group. In parallel, basic neuroscience and neuroimaging work ought to be done to monitor for and further develop our understanding of positive or adverse changes evident in child brain development in response to antipsychotic use. More utilisation of animal studies and research in older children may be sensible to precede work in preschoolers. At a local level, where prescribing for such use is currently in practice, services ought to vigilantly audit clinical prescribing practices, carry out careful and frequent surveillance of adverse effects, and compare their practice with guidelines given, evaluating any reasons for any differences.

Spetie and Arnold (2007) argued that preschool children are a 'vulnerable population at risk of harm by unethical or suboptimal practice and research and are in need of special protection'. They highlighted ethical principles of respect for autonomy, beneficence, justice and equity, and saw that these issues are particularly profound when working with young children, leading to physicians' and parents' increased ethical responsibility for the child, due to their immature level of autonomy and cognition (Spetie and Arnold, 2007). It should also be noted that in certain cases, parents may benefit from the pharmacological treatment of a child, whereby the child still may bear long-term and potentially irreversible hazards; these two factors must be conscientiously balanced against one another. Algorithms and guidelines for guided assessment, diagnosis and treatment strategies may be used (developed from reviewing preschool psychopharmacology evidence), although inconsistencies between different protocols is confusing for clinicians and parents. A review of guidelines by Gleason et al. (2007) summarised that therapies – used in a broad sense to include a wide range of psychosocial interventions – should be the first treatment choice, and continued alongside medication; severity of impairment should determine the need for medication; informed consent should be gained; and medication discontinuation trials are encouraged to avoid prolonged unnecessary use. Similarly, Haw and Stubbs (2007) argue that in the use of off-label antipsychotics, alternative treatment options should be addressed first, the risk-benefit ratio should be weighed up for the use of an antipsychotic, and a '3T' approach may be used to try to achieve safety in use: only target symptoms requiring treatment, titrate the dose from a low level, and time-limit the prescription. A difficulty for the practising clinician is that this does not specify the degree or nature of necessary intervention, or the training of the delivering professional, and indeed one may face the real-world dilemma of a lack of availability or delayed access to such care when balancing decisions about medication usage.

In cases where the medication is being used, regular evaluation of its necessity and checks of side effects should be routinely carried out. Clinicians are ultimately acting in a way that best relieves patients' distress (Haw and Stubbs, 2007); however, while the evidence base remains sparse, a number of factors must be considered if deeming the use of an antipsychotic in

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a preschool child sensible. Due to the implicated long-term effects on health and development, and the unknown nature of the extent of this, careful consideration of risk-benefit of an antipsychotic should be assessed, with attention to the patient's history and family history (that may suggest vulnerability to adverse effects), individual disorder profile and symptom severity (through many careful observations), and prognosis. It must be concluded patients' cases must be addressed on individual bases; if clinical severity, distress, harm to self and/or others, and risk of long-term detrimental effects of lack of treatment before an older (potentially safer to treat) age are high enough to warrant use, short-term treatment with a low-dose antipsychotic could be explored (i.e. involving informed discussion with parents addressing the sparse evidence base, the risks and side-effect profiles) only when all other treatment options have failed (family intervention, behavioural treatments, individual interventions, etc.). Evidence is perhaps stronger for certain antipsychotics for the treatment of certain disorders (e.g. risperidone for ASDs), although we advise particular caution when deciding the appropriateness of the use of any antipsychotic for any preschool disorder. If medication is started in a preschool child, we recommend that the appropriateness of its use must be evaluated at least month by month, accompanied with strict monitoring of biometrics, blood samples and side effects. On the other hand, in less severe cases, it is more appropriate to 'veto' the use of an antipsychotic in the preschool years, with implementation of psychotherapy and other treatment strategies first, and regular reassessment of diagnosis, development of disorder and recognition of potential premorbid or prodromal symptoms, as the child develops.

Conflict of interest

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