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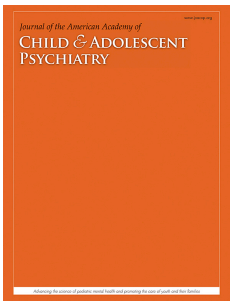

Meta-Analysis: Risk of Tics Associated With Psychostimulant Use in Randomized, Placebo-Controlled Trials

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Meta-Analysis: Risk of Tics Associated With Psychostimulant Use in Randomized, Placebo-Controlled Trials

RH = Tics with Psychostimulants

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This article is discussed in an editorial by Dr. John T. Walkup and Dr. Susan Friedland on page xx.

Clinical guidance is available at the end of this article.

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ABSTRACT

Objective: Clinical practice currently restricts the use of psychostimulant medications in children with tics or a family history of tics because of fear that tics will develop or worsen as a side effect of treatment. Our goal is to conduct a meta-analysis to examine the risk of new onset or worsening tics as an adverse event of psychostimulants in randomized, placebo-controlled trials.

Method: We conducted a PubMed search to identify all double-blind, randomized, placebo-controlled trials examining the efficacy of psychostimulant medications in the treatment of children with attention-deficit/hyperactivity disorder (ADHD). We used a fixed effects meta-analysis with risk ratio of new onset or worsening tics in children treated with psychostimulants compared to placebo. We used stratified subgroup analysis and meta-regression to examine the effects of stimulant type, dosage, duration of use, trial design, and mean age of participants on the measured risk of tics.

Results: We identified 22 studies involving 2,385 children with ADHD for inclusion in our meta-analysis. New onset tics or worsening of tic symptoms were commonly reported in the psychostimulant (event rate=5.7%, [95% CI: 3.7%, 8.6%]) and placebo groups (event rate=6.5%, [95% CI: 4.4%, 9.5%]). The risk of new onset or worsening of tics associated with psychostimulant treatment was similar to placebo (RR=0.99 [95% CI: 0.78, 1.27], z=-0.05, p=.962). Type of psychostimulant, dose, and duration of psychostimulant treatment did not affect risk of new onset or worsening of tics. Crossover studies were associated with a significantly greater measured risk of tics with psychostimulant use compared to parallel group trials.

Conclusion: Meta-analysis of controlled trials does not support an association between new onset or worsening of tics and psychostimulant use. Clinicians may want to consider re-challenging children who report new onset or worsening of tics with psychostimulant use, as these symptoms are much more likely to be coincidental rather than caused by psychostimulants.

Keywords: Tics, psychostimulants, methylphenidate, amphetamine, meta-analysis

INTRODUCTION

Psychostimulants are recommended as the first-line pharmacologic treatment for children with attention-deficit/hyperactivity disorder (ADHD).[1] Psychostimulants have demonstrated a larger effect size when compared to placebo, as compared to alternative pharmacological treatments for ADHD.[2] Randomized controlled trials have demonstrated that psychostimulants are more effective than behavioral treatments for ADHD for at least 14 months after the start of treatment.[3] When ADHD is present in children with tics, the symptoms of ADHD typically cause greater impairment in academic performance, social relationships, and neuropsychological performance, especially executive functioning, than the tics themselves.[4-8] Psychostimulants have been shown to be equally efficacious in treating ADHD symptoms in children with ADHD and comorbid tics as in children with ADHD alone.[2]

Clinical practice currently restricts the use of psychostimulant medications in children with ADHD and comorbid tics. The limited use of psychostimulants in patients with ADHD and comorbid tic symptoms is likely partially attributable to warnings placed on the medications by regulatory agencies. The Food and Drug Administration (FDA) currently requires that psychostimulants list tics and/or a family history of a tic disorder as a contraindication (methylphenidate) or significant adverse reaction (methylphenidate and amphetamines) to their use.[9,10] FDA labeling warns parents that psychostimulants "should not be taken by their child" (methylphenidate) and/or "may not be right for your child" (amphetamines) if they have tics.[11,12] Amphetamine/dextroamphetamine labeling also warns the public to "use with caution in patients with Tourette's syndrome; stimulants may unmask tics."[13] The FDA warnings resulted largely from a series of case reports and case series that were published in the 1970s and 1980s.[14-24] A particularly influential case series of 15 children who developed tics while on psychostimulants helped lead the FDA in 1983 to require listing contraindications and significant adverse reactions to psychostimulant medications.[25]

Since then, however, multiple randomized controlled trials (RCTs) have demonstrated no effect of psychostimulants on tics.[26-29] In fact, a National Institutes of Health (NIH)- and Tourette Syndrome Association-funded trial examining treatment of ADHD in children with tics concluded "that prior concerns that methylphenidate worsens tics and that the drug should be avoided in patients with tics may be unwarranted."[26] Recent meta-analyses examining pharmacological treatment of children with tics and ADHD demonstrated that methylphenidate did not significantly worsen tic symptoms and was beneficial in treating ADHD symptoms in children with both conditions.[2,30] In fact, psychostimulants appear to be equally efficacious in treating ADHD symptoms in children with ADHD and comorbid tics as in children with ADHD alone.[2]

There is, however, strong biological rationale to suggest that psychostimulants might exacerbate tics. Methylphenidate and dextroamphetamine induce stereotypies in rats in a dose-dependent manner.[31-33] Stimulant-induced stereotypies in rodents are hypothesized to be an animal model for tic disorders.[34] Furthermore, psychostimulants have been demonstrated to increase dopamine in the synaptic cleft,[35] whereas the most effective anti-tic medications available, antipsychotic medications, act as dopamine antagonists.[36-38]

On the other hand, the timing of onset of ADHD and Tourette syndrome represents a possible confounder. Roughly 20% of children with ADHD go on to develop a chronic tic disorder.[39] When ADHD and tics co-occur in an individual, the onset of ADHD typically precedes that of tic symptoms by 2 to 3 years.[37] Therefore, it is difficult to determine whether the tics are a result of a side effect of psychostimulants or if they were to occur anyway, as children with ADHD are at higher risk of developing tics regardless of medication use. Also, tics in Tourette syndrome typically wax and wane in severity, so it is unclear whether a patient's tics are going to naturally increase at a given time or if the increase is a result of psychostimulant side effects.

Clinicians are uncertain regarding use of psychostimulants in children with existing tics or a family history of tics because of conflict between strong FDA labelling advising against

psychostimulant use in this population and randomized, controlled trial and meta-analysis data suggesting efficacy without any apparent risk in the same population. The goal of this meta-analysis is to provide an evidence base for future guidelines, warnings, and clinical decisions for the use of psychostimulants in children who develop tics after psychostimulant use or are judged to be at increased risk of developing tics prior to psychostimulant use. We will examine all available data on side effects in previous randomized, placebo-controlled trials of psychostimulants in childhood ADHD to determine the risk of new onset or worsening of tics associated with psychostimulants compared to placebo. We will conduct secondary analyses to examine the effects of psychostimulant type (long versus short-acting formulations, methylphenidate vs. mixed amphetamine salt derivatives), rater of side effects, trial design (parallel vs. crossover trial) and length of psychostimulant treatment on the risk of tics with psychostimulant treatment.

METHOD

Search Strategy for Identification of Studies

Two reviewers searched the electronic database of PubMed on August 18, 2013 for relevant studies using the search: (Attention deficit disorder with hyperactivity OR ADHD OR ADDH OR hyperactiv* OR hyperkin* OR “attention deficit*” OR “brain dysfunction”) AND (methylphenidate OR Ritalin OR Metadate OR Equasym OR Daytrana OR Concerta OR Dextroamphetamine OR amphetamine OR Adderall OR Vyvanse OR Dexedrine OR Dextrostat). The search only utilized randomized controlled trials. The references of appropriate papers on the safety and efficacy of psychostimulant medications were searched for citations of further relevant published and unpublished research.

Selection of Studies

The titles and abstracts of studies obtained by this search strategy were examined by two reviewers to determine inclusion in this meta-analysis. Any discrepancies were resolved by a final

reviewer. Eligibility for the study was based upon analysis of the full articles for the following criteria (1) they are randomized, double-blind, placebo-controlled clinical trials of psychostimulant medications (methylphenidate or dextroamphetamine derivatives) compared with placebo and (2) participants included are children and adolescents less than 18 years of age diagnosed with ADHD or hyperkinetic disorder by explicit criteria, i.e. *DSM* or *International Classification of Diseases (ICD)* criteria. Exclusion criteria for the studies included if (1) the study was not published in English, (2) the study population included only patients with ADHD plus another primary comorbidity i.e. mental retardation, pervasive developmental disorder, oppositional defiant disorder, tics, or anxiety, (3) the medication of interest was given for less than 7 days in duration(4) there were fewer than 10 participants (crossover design) or fewer than 20 participants (parallel design), and (5) the primary goal of the trial was not treatment for ADHD (e.g. studies that were primarily concerned with neuroimaging or neuropsychological measures were excluded). We required medication/placebo each to be given for at least 7 days in trial because the authors a priori decided that this was the minimum required time needed in order to be confident regarding a change in tic symptoms. A 7-day assessment period is similar to that utilized for common clinical rating scales of tic symptoms such as the Yale Global Tic Severity Scale.[40] We additionally restricted trials to treatment trials, as studies utilizing non-treatment-related outcome measures such as magnetic resonance imaging (MRI), electroencephalogram (EEG) or neuropsychological testing were less likely to systematically assess side effects of medications.

Meta-Analytic Procedures

Data were extracted by independent reviewers (Z.D.S., S.C.C., J.M.M., and C.G.C.) on specially designed Microsoft Excel spreadsheets. Our primary outcome measure was the proportion of children reporting tics as a side effect of medication. When possible, clinician-rated side effect measures were utilized as the main outcome measure. When this information was unavailable, participant-rated, parent-rated, or teacher-rated side effect measures were used. Reviewers

additionally gathered data on trial medication, trial design, maximum daily medication dose, number of participants, mean age of participants, duration of active treatment in trials, who recorded side-effect ratings (clinician vs. parent/teacher) and other relevant attributes and results of the studies. Any disagreement among reviewers was mitigated through discussion and the procurement of more information from the study investigators when possible. When agreement could not be attained between the initial reviewers, the senior investigator (M.H.B.) resolved all disputes. When information about proportion of tics was not available in the original manuscripts, the corresponding author was contacted for further information. If contacting the corresponding author was ineffective, we additionally searched pharmaceutical company databases for the data.

All statistical analyses were completed in Comprehensive Meta-Analysis Version 2. For our outcome measures of interest, proportion of participants experiencing tics was analyzed using pooled risk ratio (RR). Absolute risk difference (ARD) and number needed to harm (NNH) were also reported for the primary outcome as both the absolute and relative risks are clinically relevant when considering the use of medications. For all outcome measures, 95% CIs were conveyed. A fixed-effects model for meta-analysis was used, as well as a random-effects model in sensitivity analysis. Publication bias was assessed by plotting the effect size against standard error for each included trial (i.e., funnel plot). In addition, publication bias was statistically tested by the Egger's test and by determining the association between sample size and effect size in meta-regression. We additionally reported the risk of new onset or worsening of tics in both the psychostimulant and placebo groups in order to assist clinicians in decision-making. We report results of a random effects model for these data as it is clear there was significant heterogeneity in how tics were assessed and the frequency that tics were reported within the placebo and psychostimulant groups based on trial methodology.

For secondary analyses, several subgroup analyses and meta-regressions were accomplished. Stratified subgroup analyses were conducted based on (1) type of psychostimulant (methylphenidate vs. mixed-amphetamine derivatives), (2) duration of action of medications (long-

acting vs. short-acting psychostimulants), (3) recorder of side effect data, and (4) trial design (crossover vs. parallel group trials). We utilized the test for subgroup differences (between group heterogeneity chi-square) in the mixed-effects model of comprehensive meta-analysis to test for subgroup differences. Meta-regression analysis was used to examine the effect of (1) maximum daily dose of psychostimulants utilized in trials, (2) length of active psychostimulant treatment, and (3) age of participants on the risk of developing new onset or worsening of tics with psychostimulants compared to placebo. All daily doses of psychostimulants were converted into methylphenidate equivalents using previously described methodology.[41] Our threshold for statistical significance was $p<.05$ for the primary analysis, as well as for all stratified subgroup analyses and meta-regression.

RESULTS

Included Trials

Figure 1 depicts the selection of trials for this meta-analysis. A total of 815 references were identified in PubMED. A total of 92 trials were eligible for inclusion. Of these 92 trials, 16 trials published data on tics as a side effect of psychostimulant medication. Authors of 6 additional trials responded to email requests with unpublished data regarding the risks of tics in psychostimulant trials. Therefore, a total of 22 trials, involving 2,385 participants, was included in our meta-analysis.[42-63] The characteristics of included trials are depicted in Table 1.

INSERT FIGURE 1 HERE

INSERT TABLE 1 HERE

Risk of New Onset or Worsening of Tics With Psychostimulants

Meta-analysis of 22 studies involving 2,385 participants demonstrated no significant increase in the risk of new onset or worsening of tics when comparing psychostimulant to placebo (Figure 2, RR=0.99 (95% CI: 0.78, 1.27), z=-0.05, p=.96. There was no significant heterogeneity between trials (I^2 =12.7%, p=0.28) or evidence of publication bias (Egger's test: p=0.88). A random effects model

produced similar estimates of risk when examined in a sensitivity analysis (RR=0.97 [95%CI: 0.72, 1.32], z=-0.18, p=.86).

INSERT FIGURE 2 HERE

There was also no evidence of increased risk of new onset or worsening of tics when examining absolute risk difference of tics with psychostimulants compared to placebo (Figure 3, ARD=0.001 [95% CI: -0.009, 0.011], z=0.18, p=.86). There was no significant heterogeneity among trials (I^2 =9.6%, p=.32) or evidence of publication bias (Egger's test: p=.88). A random effects model produced similar estimates of risk when examined in a sensitivity analysis (ARD=0.001 [95% CI: -0.011, 0.013], z=0.16, p=.88).

INSERT FIGURE 3 HERE

In random effects meta-analysis, 5.7% of children in the psychostimulant arms of trials reported new onset or worsening of tics (event rate=5.7% [95% CI: 3.7%, 8.6%], I^2 =72%, p<.001). However, the event rate for new onset or worsening of tics was higher in the placebo arms of included trials (event rate=6.5% [95% CI: 4.4%, 9.5%], I^2 =64%, p<.001).

Methylphenidate vs. Amphetamine Derivatives

Stratified subgroup analysis demonstrated no significant difference in risk of new onset or worsening of tics (test for subgroup differences X^2=0.26, p=.61) between methylphenidate derivatives (RR=1.02 [95% CI: 0.78, 1.33], k=20, z=0.14, p=.89) and amphetamine derivatives (RR=0.84 [95% CI: 0.42, 1.68], k=4, z=-0.49, p=.63).

Long- vs. Short-Acting Psychostimulants

Stratified subgroup analysis demonstrated no significant difference in risk of new onset or worsening of tics (test for subgroup differences X^2=0.22, p=.64) between short-acting (RR=1.04 [95% CI: 0.76, 1.43], z=0.25, p=.80) and long-acting psychostimulants (RR=0.92 [95% CI: 0.62, 1.38], z=-0.40, p=.69).

Psychostimulant Dose

Meta-regression demonstrated no significant association between dosage of psychostimulants and the risk of new onset or worsening of tics (β=-0.0023 [95% CI: -0.0142, 0.0097], z=-0.37, p=.71). There was no significant association between dosage of psychostimulants and risk of new onset or worsening of tics when analysis was restricted to methylphenidate (β=-0.0005 [95% CI: -0.0159, 0.0150], z=-0.06, p=.95) or amphetamine derivatives (β=-0.0028 [95% CI: -0.0280, 0.0224], z=-0.22, p=.83).

Duration of Active Treatment

Meta-regression demonstrated no significant association between duration of active treatment and the risk of new onset or worsening of tics associated with psychostimulant medication (β=-0.010 [95% CI: -0.022, 0.002], z=-1.69, p=.09).

Recorder of Side Effect Data

Stratified subgroup analysis demonstrated no significant difference in risk of new onset or worsening of tics based on whether clinicians or non-clinical informants (parents and/or teachers) were rating tic outcomes (test for subgroup differences X^2=1.49, p=.22). The relative risk of tics was non-significantly lower when utilizing clinician recorders of tics (RR=0.72 [95% CI: 0.41, 1.29], z=-1.10, p=.28) rather than nonclinical report (RR=1.08 [95% CI: 0.82, 1.42], z=0.53, p=.59).

Trial Design

Crossover studies reported a significantly greater association of new onset or worsening of tics with psychostimulants compared to parallel-group studies (test for subgroup differences X^2=5.3, p=.02). However, neither crossover trials (RR=1.23 [95% CI: 0.90, 1.68], z=1.3, p=.19) nor parallel-group studies (RR=0.67 [95% CI: 0.44, 1.02], z=-1.88, p=.06) reported a significant association of tics with psychostimulant use.

Age of Participants

Meta-regression demonstrated no significant association between participants' age and measured risk of new onset or worsening of tics with psychostimulant medications (β=-0.39 [95% CI: -0.83, 0.05], z=-1.75, p=.08).

DISCUSSION

Meta-analysis demonstrated no statistically significant relationship between psychostimulant use and new onset or worsening of tics in children with ADHD. Specifically, the relative risk of new onset or worsening of tics was 0.99 (95% CI: 0.78, 1.27), indicating no evidence of an association between psychostimulants and tics. Furthermore, we found no association between risk of new onset or worsening of tics and dosage, type or duration of use, psychostimulant agent, or recorder of side effect data. Taken together, data from this meta-analysis is most consistent with an absence of a risk of new onset or worsening of tics with psychostimulant medications. However, the power of this meta-analysis is not sufficient to rule out the possibility of a small increased risk of tics with psychostimulant use. However, based on the available data, it remains equally likely that psychostimulants reduce the risk of tics as they do raising the risk of tics.

Current evidence from this meta-analysis and previous work examining the effects of psychostimulants in children with tics and ADHD does not support the clinical practice of restricting the use of psychostimulants in children with tics or at high risk of developing tics.[11,12] Previous meta-analysis examining the effects of methylphenidate in children with ADHD and comorbid tics demonstrated that psychostimulants appear to have a similar effect size in reducing ADHD symptoms in children with comorbid tics as in children without comorbid tic disorders.[2] Furthermore, there was no evidence that psychostimulants worsened tic symptoms in children with both ADHD and tics.[2] Randomized controlled trials in children with ADHD and tics have further demonstrated that combination treatment with methylphenidate and clonidine is more effective than either medication alone.[26] Our meta-analysis extends upon these previous results by demonstrating that there is no

increased risk of new onset or worsening tics with psychostimulant use compared to placebo in meta-analysis of randomized, placebo-controlled trials in children with ADHD alone.

The results of this meta-analysis also provide strong support for re-challenging children (or even continuing children on psychostimulants) who develop tics that are temporally related to the initiation of psychostimulants. Assuming the absolute risk difference of 0.001 observed in the meta-analysis, the number needed to harm for new onset or worsening tics with psychostimulants is 1,000 (95%CI: 77-∞). If additionally assuming the baseline risk of experiencing new onset tics over short-term trials of medications is equivalent to the 6.5% observed in the placebo arms of randomized, controlled trials of psychostimulants than in a child who develops tics shortly after initiating psychostimulants, the tics are 65-fold more likely to be the result of coincidence than caused by the medication. Even assuming the highest risk of tics (0.011 -- at the upper bound of the 95% confidence interval of absolute risk difference), when new onset or worsening of tics appear after the initiation of psychostimulants, the tics are 6-fold more likely to be a result of coincidence than be caused by the medications. Given the absence of data suggesting psychostimulants make existing tics worse,[2,26] re-challenging appears reasonable, whether or not the tics persist after discontinuation of the psychostimulant. Re-challenging appears particularly advisable in children whose ADHD does not respond sufficiently to other medications such as alpha-2 agonists and atomoxetine, which are used to help ADHD and may additionally help improve tics symptoms.[38,64,65]

There are several limitations to this meta-analysis that may have affected its findings. Foremost among these limitations is the fact that a limited number of randomized, placebo-controlled trials of psychostimulants for children with ADHD actually reported on the frequency of tics as side effects. The selective reporting of tics in side effect data, if it existed, could lead to publication bias that would likely exaggerate the association between tics and psychostimulants. Many trials only report side effects that were above a certain percent threshold in the active treatment group or were

statistically different between groups. This practice would also lead to an inflated estimate of the association between psychostimulants and tics, as trials with increased associations would be selectively published and included in our meta-analysis. In order to minimize this potential bias, we emailed authors of potentially eligible trials that did not include data on tics in order to obtain additional data to include in the meta-analysis. However, many authors were unresponsive or did not have available data from the trial, so this potential bias should not be discounted. Another potential limitation is the inclusion of crossover trials in addition to parallel group trials in this meta-analysis. We made the decision to include crossover trials to maximize power in our meta-analysis. Crossover trials of psychostimulants were designed using washout periods of sufficient time to eliminate any beneficial effects of psychostimulants before the start of the next phase of the trial. It remains quite possible that if tics occurred as an adverse event in crossover trials, they might still carryover to the next trial phase and thus dampen our ability to detect tics as an adverse effect of treatment. However, stratified analysis demonstrated an increased measured risk of tics with psychostimulants in crossover studies compared to parallel-group studies, arguing against this phenomenon occurring. An additional potential limitation is the heterogeneity in how tics were assessed as a side effect between trials—some trials relied on parent report, whereas others included direct observation of participants. We conducted stratified subgroup analysis based on whether or not a clinician was rating side effects. We did not observe any significant effect based on who was rating side effect symptoms. Additionally, some trials require significant impairment for side effects to be reported while others do not. Because of the manner in which tics are reported as a side effect in trials, we are unable to determine whether individual reported adverse events in trials were due to (1) a new onset of tics or (2) worsening of preexisting tics. We therefore are only able to comment on the aggregate risk of either of these two events occurring but not of each event individually. It should also be emphasized that our data only applies to use of psychostimulants within the recommended therapeutic dose range. Both data in animal models and children with tics has suggested that

supratherapeutic doses of psychostimulant medications may worsen tics.[27,31-33] Another limitation to this meta-analysis is the fact that the studies included in our meta-analysis do not have available data on whether tics resolve or persist after medication or placebo discontinuation.

In conclusion, this meta-analysis suggests that new onset or worsening of tics appears to occur at a fairly high rate (5-7%) in the period immediately after starting psychostimulants. However, tics were no more likely to be associated with psychostimulant treatment than with placebo. When tics occur in temporal relationship to psychostimulant use, this relationship is much more often coincidental than causative. There are several potential confounding factors that may explain the high rate of tics reported in children after starting psychostimulants. The high rate of tics observed in children with ADHD and the waxing and waning nature of tic symptoms may explain some of this phenomenon.[66] Additionally, tics have been demonstrated to worsen during periods of stress, excitement, and fatigue.[66] The initiation of psychostimulants often coincides with the start of the academic year or in the face of increasing academic/social difficulties—natural periods of high stress, excitement, and fatigue for children. Therefore, the temporal relationship between psychostimulant use and new onset tics could be largely or completely attributable to confounding. Future research investigating side effects associated with medications could be greatly enhanced by requiring pivotal trials to make side-effect data publically available. Additionally, this research would benefit from a standardized method of reporting and measuring tics and other side effects in clinical trials of psychostimulants.

Clinical Guidance:

- New onset or worsening tics are commonly experienced by children with ADHD in both the active and placebo groups of psychostimulant trials.
- There is no evidence of an association between psychostimulant use and risk of new onset or worsening tics in placebo-controlled trials.

- When new onset or worsening of tics occurs after the initiation of a psychostimulant medication, it is much more likely to be a result of coincidence than caused by the medication.
- Using psychostimulant medications in children with ADHD and comorbid tics (or with a family history of tics) should be considered, especially when agents that target both ADHD and tic symptoms (e.g. alpha-2 agonists) have failed.
- Re-challenging children who experience new onset or worsening tics on psychostimulants appears to be a reasonable treatment strategy if ADHD symptoms remain impairing.

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Table 1. Characteristics of Included Trials in the Meta-Analysis of the Risk of Tics With Psychostimulants

Authors	Year	Medication	Stimulant Class	Duration of Action	Maximum Dose	Design	Duration of Active Treatment	n	Mean Age (years)
Werry et al. [42]	1974	MPH IR	MPH	Short	0.5 - 1 mg/kg/day	Crossover	4 week	37	8.9
Gittelman-Klein et al. [43]	1976	MPH IR	MPH	Short	60 mg/day	Parallel	4 weeks	80	8.6
Werry et al. [44]	1980	MPH IR	MPH	Short	0.4 mg/kg/day	Crossover	3-4 weeks	30	8.4
Rapport et al. [45]	1985	MPH IR	MPH	Short	15 mg/day	Crossover	1 week	12	6-10
Barkley et al. [46]	1990	MPH IR	MPH	Short	0.5 mg/kg BID	Crossover	7-10 days	82	8.2
Buitelaar et al. [47]	1996	MPH IR	MPH	Short	10 mg BID	Parallel	4 weeks	21	9.2
Stein et al. [48]	1996	MPH IR	MPH	Short	20 mg TID	Crossover	1 week	25	8.0
Gillberg et al. [49]	1997	MAS IR	AMP	Short	45 mg/day	Parallel	3 months	56	9
Firestone et al. [50]	1998	MPH IR	MPH	Short	0.5 mg/kg BID	Crossover	7-10 days	32	4.8
Pliszka et al. [51]	2000	MPH IR	MPH	Short	50 mg/day	Parallel	3 weeks	58	8.1
		MAS IR	AMP	Short	30 mg/day				
Pelham et al. [52]	2001	OROS® MPH	MPH	Long	54 mg/day	Crossover	1 week	68	9.1
		MPH IR	MPH	Short	15 mg TID				
Wolraich et al. [53]	2001	OROS® MPH	MPH	Long	54 mg/day	Parallel	4 weeks	282	9.0
		MPH IR	MPH	Short	15 mg TID				
Greenhill et al. [54]	2002	MPH MR	MPH	Long	60 mg/day	Parallel	3 weeks	316	9
McCracken et al. [55]	2003	MAS XR	AMP	Long	30 mg/day	Crossover	1 week	49	9.5
		MAS IR	AMP	Short	10 mg/day				
Stein et al. [56]	2003	OROS® MPH	MPH	Long	54 mg/day	Crossover	1 week	47	9
Findling et al. [57]	2006	EqXL	MPH	Long	60 mg/day	Parallel	3 weeks	318	9.5
		MPH IR	MPH	Short	30 mg BID				
Gorman et al. [58]	2006	MPH IR	MPH	Short	1 mg/kg divided daily	Crossover	3 weeks	41	9.1
Findling et al. [59]	2008	MPH Patch	MPH	Short	30 mg 9hr/day	Parallel	2 weeks	274	8.7
		OROS® MPH	MPH	Long	54 mg/day				
Newcorn et al. [60]	2008	OROS® MPH	MPH	Long	54 mg/day	Parallel	6 weeks	293	10.2
Silva et al. [61]	2008	dMPH ER	MPH	Long	30 mg/day	Crossover	1 week	82	9.4
		MPH MR	MPH	Long	54 mg/day				
Solanto et al. [62]	2009	MPH IR	MPH	Short	50 mg/day	Crossover	1 week	25	8.8
Lee et al. [63]	2011	MPH IR	MPH	Short	0.5 mg/kg/day	Crossover	1 week	157	9.0

Note: AMP=amphetamine; BID = twice daily; dMPH= dexmethylphenidate; EqXL=Equasym XL; IR = immediate release; MAS=mixed amphetamine salts; MPH=methylphenidate; MR = modified-release; MTS = methylphenidate transdermal system; OROS = Osmotic Controlled-Release Oral Delivery System; TID = three times daily; XR/ER= extended-release.

Figure Legends:

Figure 1. Selection of studies. Note: ADHD = attention-deficit/hyperactivity disorder.

Figure 2.Relative risk of tics with psychostimulants compared to placebo. Note: Figure 2 depicts a forest plot comparing the relative risk of tics in participants treated with psychostimulants compared to placebo in short-term, randomized-controlled trials. Meta-analysis demonstrated no significant difference in the risk of tics with stimulants compared to placebo (risk ratio=0.99 [95% CI: 0.78, 1.27], z=-0.05, p=.96).

Figure 3. Absolute risk difference of tics between psychostimulants and placebo. Note: Figure 3 depicts a forest plot depicting the absolute risk difference of tics in participants treated with psychostimulants compared to placebo in short-term, randomized-controlled trials. Meta-analysis demonstrated no significant difference in the risk of tics with stimulants compared to placebo (absolute risk difference=0.001 [95% CI: -0.009, 0.011], z=0.18, p=.86).