Risk of Irritability With Psychostimulant Treatment in Children With ADHD:
A Meta-Analysis

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ABSTRACT

Objective: Irritability is listed as a common side effect of psychostimulant medications. However, psychostimulants have been demonstrated as an effective treatment in reducing irritability and aggression in children with attention-deficit/hyperactivity disorder (ADHD). The goal of this study was to quantify the risk of irritability as a side effect of psychostimulant treatment for ADHD.

Data Sources and Study Selection: A PubMed search was conducted on August 18, 2013, to identify all double-blind, randomized, placebo-controlled trials published in English examining the efficacy of psychostimulant medications in the treatment of children with ADHD. Trials were excluded if (1) they required additional psychiatric or medical comorbidity in addition to ADHD, (2) they involved fewer than 20 subjects (parallel group trials), or (3) children received psychostimulant medication for less than 1 week.

Data Extraction: A fixed-effects meta-analysis was used to examine the risk ratio of irritability reported as a side effect in children treated with psychostimulants compared to placebo. Stratified subgroup analysis and meta-regression were used to examine the effects of stimulant type, dosage, duration of use, and trial design on the measured risk of irritability.

Results: From 92 potentially eligible trials, the meta-analysis identified 32 trials involving 3,664 children with ADHD that reported data on irritability as a side effect. The relative risk of irritability significantly differed between psychostimulant classes (test for subgroup differences $\chi^2_1 = 7.6$, $P = .006$). Methylphenidate derivatives were associated with a significantly decreased risk of irritability compared to placebo (risk ratio [RR] = 0.89 [95% CI, 0.82 to 0.96], $z = -2.87$, $P = .004$, k = 32, $I^2 = 50\%$), whereas amphetamine derivatives were associated with a significantly increased risk of irritability (RR = 2.90 [95% CI, 1.26 to 6.71], $z = 2.5$, $P = .01$, k = 5, $I^2 = 0\%$).

Conclusions: This meta-analysis suggests an increased risk of irritability may be confined to amphetamine-derived psychostimulants. Future meta-analyses examining the effects of amphetamine and methylphenidate derivatives on irritability as a continuous measure, as well as head-to-head trials between methylphenidate and amphetamine derivatives examining effects on irritability, will be important to replicate the findings of this meta-analysis.

J Clin Psychiatry 2017;78(6):e648–e655
https://doi.org/10.4088/JCP.15r10601

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Irritability is a common and impairing problem that cuts across a range of formal psychiatric diagnoses, including major depression, anxiety disorders, bipolar disorder, and disruptive behavioral disorders such as oppositional defiant disorder and attention-deficit/hyperactivity disorder (ADHD).[1] Irritability is associated with decreased self-esteem, emotional difficulties, impeded family functioning, and worse quality of life in childhood.[2] Furthermore, childhood irritability is predictive of depression later in life.[3,4] Irritable mood has gained recognition as a significant child mental health issue with the introduction of disruptive mood dysregulation disorder in DSM-5, of which the core feature is "chronic, severe persistent irritability."[5]

Clinically, the assessment and treatment of irritability is complicated by 2 factors. First, significant irritability is present in 25%–45% of children with ADHD.[6] In epidemiologic studies,[4] irritability is 10-fold more common in children with ADHD compared to healthy controls. Second, psychostimulant medications, which are the most common and effective treatment for ADHD, have unclear effects on irritability symptoms. While irritability is documented as a common side effect of psychostimulant medications, it is not well understood how psychostimulant medications affect irritability symptoms that are not a side effect of medication. Nonetheless, meta-analyses[7,8] suggest that psychostimulant medications are also among the most effective treatments for aggression in children and adolescents with ADHD. Psychostimulants have been utilized as a first-line treatment for aggression and/or irritability in previous studies.[9] Furthermore, the Multimodal Treatment Study of Children With ADHD[10] suggested that the medication management condition, primarily involving evidence-based psychostimulant treatment, was superior to the behavioral treatment condition in reducing irritability symptoms in children with ADHD during 14 months of treatment.

Since the role of psychostimulants in ameliorating or exacerbating irritability in children with ADHD is unclear, we have used the available evidence base to elucidate the relationship between irritability and psychostimulant treatment. More specifically, the goal of this meta-analysis was to examine the effects of psychostimulant medications on irritability in randomized, placebo-controlled trials in children with ADHD. We also examined the effects of psychostimulant type (methylphenidate vs amphetamine

Clinical Points

- Irritability is a commonly reported side effect of psychostimulant medications. Current data are unclear as to whether irritability is a side effect associated with psychostimulant treatment or simply a common event unrelated to medication reported in children with attention-deficit/hyperactivity disorder (ADHD).
- Overall, psychostimulant medications were associated with a significantly decreased risk of irritability in children with ADHD compared to placebo.
- Methylphenidate derivatives were associated with a reduced risk of irritability when compared to placebo, whereas amphetamine derivatives were associated with an increased risk of irritability compared to placebo.

derivatives), duration of action, and dose on the likelihood of experiencing irritability in children with ADHD.

METHODS

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 *hyperactive** 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 was limited to randomized controlled trials. The references of included articles, review articles, and meta-analyses 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 2 reviewers to determine inclusion in this meta-analysis. Eligibility for the study was based upon analysis of the full articles for the following criteria: (1) studies were randomized, double-blind, placebo-controlled clinical trials comparing psychostimulant medications (methylphenidate and amphetamine derivatives); (2) participants included were children and adolescents younger than 18 years of age diagnosed with ADHD or hyperkinetic disorder by explicit criteria, ie, *DSM* or *ICD* criteria; and (3) psychostimulants were taken for at least 7 days continuously. We required at least 7 days of stimulant treatment because we believe a priori that this was the minimum length of stimulant treatment that would be needed to detect changes in irritability symptoms. Studies were excluded if (1) they were not published in English, (2) the study population required that participants have an additional primary comorbidity (ie, mental retardation, pervasive developmental disorder, oppositional defiant disorder, tics, or anxiety) in addition to ADHD, (3) there were fewer than 10 subjects (crossover design) or fewer than 20 subjects (parallel design), or (4) the primary goal of the trial was not treatment for ADHD (eg, studies primarily concerned with neuroimaging or neuropsychological measures were excluded).

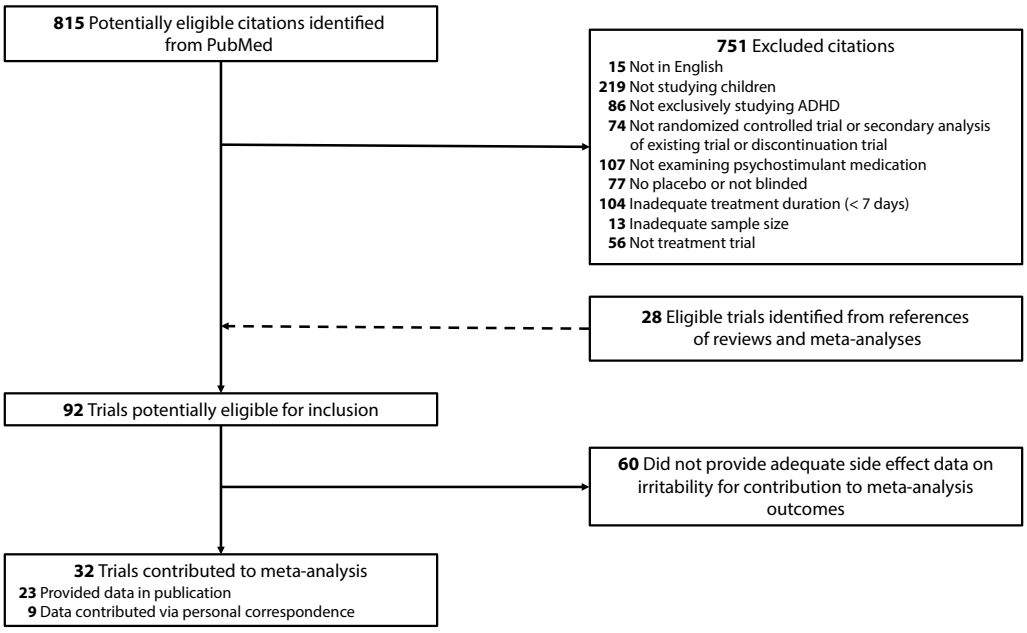
Meta-Analytic Procedures

Data extraction was performed by 4 independent reviewers working in teams of 2 on specially designed Microsoft Excel spreadsheets. Our primary outcome measure was the proportion of children reporting irritability as a side effect of medication. When possible, clinician-rated side effect measures (typically spontaneous report) were utilized as the main outcome measure. When this information was unavailable, participant-rated or parent-rated side effect measures were used. Reviewers additionally gathered data on trial medication, trial duration, maximum daily medication dose, duration of active treatment, number of participants, mean age of participants, and trial design (crossover or parallel-group). Any disagreement between reviewers was mitigated through discussion and, when possible, the procurement of more information from the study investigators. When agreement could not be attained between initial reviewers, the senior investigator resolved all disputes. When information about frequency of irritability as a side effect was not available in the original article, the corresponding author was contacted for further information. We also planned to conduct an analysis examining the risk of irritability with psychostimulants stratified by age group (school age vs preschool versus adolescents) but were unable to because of the dearth of trials performed exclusively in preschool or adolescent populations.

All statistical analysis was completed in Comprehensive Meta-Analysis Version 3 (Biostat Inc, Englewood, New Jersey). For our outcome measures of interest, proportion of subjects experiencing new-onset or worsening irritability was analyzed using pooled risk ratio (RR). For all outcome measures, 95% confidence intervals (CIs) were calculated. A fixed-effects model for meta-analysis was used, as well as a random-effects model in sensitivity analysis. We chose to use a fixed-effects model as the primary statistical model a priori as we believed that there was likely to be a strong possibility of selective reporting of side effect data in stimulant trials. When there is selective publication of data, fixed-effects models are typically more conservative. Publication bias was reviewed by entering data from included trials into a funnel plot (trial effect size plotted against sample size). Additionally, publication bias was evaluated utilizing the Egger test.

For secondary analyses, several subgroup analyses and meta-regressions were performed. Stratified subgroup analyses were conducted based on (1) type of psychostimulant (methylphenidate vs amphetamine derivatives), (2) duration of action of medications (long-acting or short-acting psychostimulants), (3) trial design (crossover vs parallel-group trials), and (4) rater of irritability as a side effect (clinician vs nonclinician recorder). We utilized the test for subgroup differences (between-group heterogeneity χ^2) in the fixed-effects model of comprehensive meta-analysis to test for subgroup differences. We used meta-regression

Figure 1. Selection of Included Trials



Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

to analyze the effect of (1) total daily psychostimulant dosage in methylphenidate equivalents, (2) length of active psychostimulant treatment, and (3) mean age of participants on the risk of developing irritability with psychostimulants compared to placebo. Dosages of all psychostimulant medications were converted to methylphenidate immediate-release equivalent doses (eg, methylphenidate 10 mg = 5 mg of mixed amphetamine salts). All daily doses of psychostimulants were converted into methylphenidate equivalents using previously described methodology.[11] Our threshold for statistical significance was $P < .05$ for the primary analysis, 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 92 trials were eligible for potential inclusion. Of these 92 trials, only 32 trials reported irritability as a side effect of psychostimulant medication. The characteristics of included trials are depicted in Table 1. Our meta-analysis included data from 32 trials involving 3,664 children with ADHD.[12–43]

Irritability With Psychostimulants

Figure 2 depicts the forest plot examining the risk of irritability with psychostimulant treatment compared to placebo. Meta-analysis demonstrated a significantly decreased risk of irritability when utilizing psychostimulant medication as compared to placebo (RR = 0.90 [95% CI, 0.83 to 0.97], $z = -2.61$, $P = .009$). There was a moderate amount of heterogeneity between trials ($I^2 = 50\%$, $P < .001$) but no evidence of publication bias between trials (Egger $P = .30$). When a random-effects model, rather than a fixed-effects model, was used in sensitivity analysis, psychostimulant use was still associated with reduced irritability, but the outcome was no longer statistically significant (RR = 0.94 [95% CI, 0.79 to 1.13], $z = -0.66$, $P = .51$).

Type of Psychostimulant

Stratified subgroup analysis demonstrated a significant difference between psychostimulant classes with regard to risk of irritability (Figure 2) (test for subgroup differences: $\chi^2_1 = 7.6$, $P = .006$). Methylphenidate derivatives (RR = 0.89 [95% CI, 0.82 to 0.96], $z = -2.87$, $P = .004$, k = 32, $I^2 = 50\%$) were associated with a significantly decreased risk of irritability, while amphetamine derivatives (RR = 2.90 [95% CI, 1.26 to 6.71], $z = 2.5$, $P = .01$, k = 5, $I^2 = 0\%$) were associated with increased risk of irritability. The difference between psychostimulant medication classes remained significant when dose of psychostimulants was controlled for in the meta-analysis.

Duration of Action of Psychostimulants

No significant association was found between duration of action of psychostimulant medications and risk of irritability (test for subgroup differences: $\chi^2_1 = 0.4$, $P = .53$). Long-acting stimulants (RR = 0.96 [95% CI, 0.77 to 1.19], $z = -0.37$, $P = .71$, k = 15, $I^2 = 29\%$) were associated with a risk of irritability similar to that of short-acting stimulants (RR = 0.89 [95% CI, 0.82 to 0.97], $z = -2.58$, $P = .01$, k = 21, $I^2 = 61\%$).

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

Author[a]	Year	Medication	Stimulant Class	Duration of Action	Maximum Dose/d	Design	Duration of Active Treatment	N	Mean Age, y
Greenberg[14]	1972	dAMP	AMP	Short	25 mg	Parallel	8 wk	76	8.7
Rapoport[15]	1974	MPH	MPH	Short	30 mg	Parallel	6 wk	47	9.0
Werry[16]	1974	MPH IR	MPH	Short	1 mg/kg	Crossover	4 wk	37	8.9
Gittelman-Klein[17]	1976	MPH IR	MPH	Short	60 mg	Parallel	4 wk	80	8.6
Conners[18]	1980	MPH IR	MPH	Short	60 mg	Parallel	8 wk	60	7.9
Werry[19]	1980	MPH IR	MPH	Short	0.4 mg/kg	Crossover	3–4 wk	30	8.4
Rapport[29]	1985	MPH IR	MPH	Short	15 mg	Crossover	1 wk	12	6–10
Barkley[20]	1990	MPH IR	MPH	Short	1 mg/kg	Crossover	7–10 d	82	8.2
Klorman[21]	1990	MPH IR	MPH	Short	40 mg	Crossover	3 wk	48	14.1
Fitzpatrick[22]	1992	MPH LA	MPH	Long	20 mg	Crossover	2 wk	19	8.7
		MPH IR	MPH	Short	20 mg				
Ahmann[12]	1993	MPH IR	MPH	Short	1.5 mg/kg	Crossover	7 d	206	9.1
Buitelaar[23]	1996	MPH IR	MPH	Short	20 mg	Parallel	4 wk	52	9.2
Stein[28]	1996	MPH IR	MPH	Short	60 mg	Crossover	1 wk	25	8.0
Firestone[24]	1998	MPH IR	MPH	Short	1 mg/kg	Crossover	7–10 d	32	4.8
Pliszka[25]	2000	MPH IR	MPH	Short	50 mg	Parallel	3 wk	58	8.2
		MAS IR	AMP	Short	30 mg				
		MPH IR	MPH	Short	45 mg				
		MPH IR	MPH	Short	45 mg				
Greenhill[26]	2002	MPH MR	MPH	Long	60 mg	Parallel	3 wk	316	9.0
Stein[27]	2003	OROS MPH	MPH	Long	54 mg	Crossover	7 d	47	9.0
Swanson[30]	2004	MPH ER	MPH	Long	60 mg	Crossover	7 d	184	9.6
		MPH ER	MPH	Long	54 mg				
Findling[31]	2006	EqXL	MPH	Long	60 mg	Parallel	3 wk	318	9.5
		MPH IR	MPH	Short	60 mg				
Gorman[32]	2006	MPH IR	MPH	Short	50 mg	Crossover	3 wk	41	9.1
Greenhill[33]	2006	dMPH ER	MPH	Long	30 mg	Parallel	7 wk	100	10.0
Wigal[34]	2006	MPH IR	MPH	Short	22.5 mg	Crossover	7 d	165	3–5
Biederman[13]	2007	LDX	AMP	Long	70 mg	Parallel	4 wk	290	9.0
Newcorn[35]	2008	OROS MPH	MPH	Long	54 mg	Parallel	6 wk	293	10.2
Schachar[36]	2008	MPH IR	MPH	Short	1.2 mg/kg	Crossover	7 d	17	11.3
Childress[37]	2009	dMPH ER	MPH	Long	30 mg	Parallel	5 wk	245	9.0
Solanto[38]	2009	MPH IR	MPH	Short	50 mg	Crossover	1 wk	25	8.8
Wigal[39]	2009	LDX	AMP	Long	70 mg	Crossover	7 d	115	10.1
Schulz[40]	2010	MPH ER	MPH	Long	20 mg	Crossover	7 d	147	10.2
		MPH ER	MPH	Long	20 mg				
Wilens[41]	2010	MTS	MPH	Short	20 mg	Crossover	2 wk	30	9.2
Findling[42]	2011	LDX	AMP	Long	70 mg	Parallel	4 wk	310	14.6
Lee[43]	2011	MPH IR	MPH	Short	0.5 mg/kg	Crossover	1 wk	157	9.0

[a]Name of only the first author listed for each study.
Abbreviations: AMP = amphetamine, dAMP = dextroamphetamine, dMPH = dexmethylphenidate, EqXL = Equasym XL, IR = immediate release, LA = long-acting, LDX = lisdexamfetamine, MAS = mixed amphetamine salts, MPH = methylphenidate, MR = modified release, MTS = methylphenidate transdermal system, OROS = osmotic controlled-release oral delivery system, XR/ER = extended release.

Dose of Psychostimulant Medications

A significant negative association was found between dose of psychostimulant utilized in methylphenidate equivalent doses and risk of irritability (β = −0.0034 [95% CI, −0.0059 to −0.0008], $z = -2.55$, $P = .011$). The association between dose of psychostimulant utilized and risk of irritability was not statistically significant when the relationship was examined within psychostimulant medication classes. There was a nonsignificant negative association between dose and risk of irritability within trials involving methylphenidate derivatives (β = −0.0022 [95% CI, −0.0071 to 0.0028], $z = -0.86$, $P = .39$) and a nonsignificant positive association within trials involving amphetamine derivatives (β = .0037 [95% CI, −0.0448 to 0.0523], $z = 0.15$, $P = .88$).

Duration of Active Psychostimulant Use

A significant association was found between duration of active psychostimulant use and risk of irritability (β = .018 [95% CI, 0.007 to 0.029], $z = -3.27$, $P = .001$). Longer use of psychostimulant treatment in trials was associated with increased risk of irritability relative to placebo within the time frame of 1–8 weeks of psychostimulant treatment.

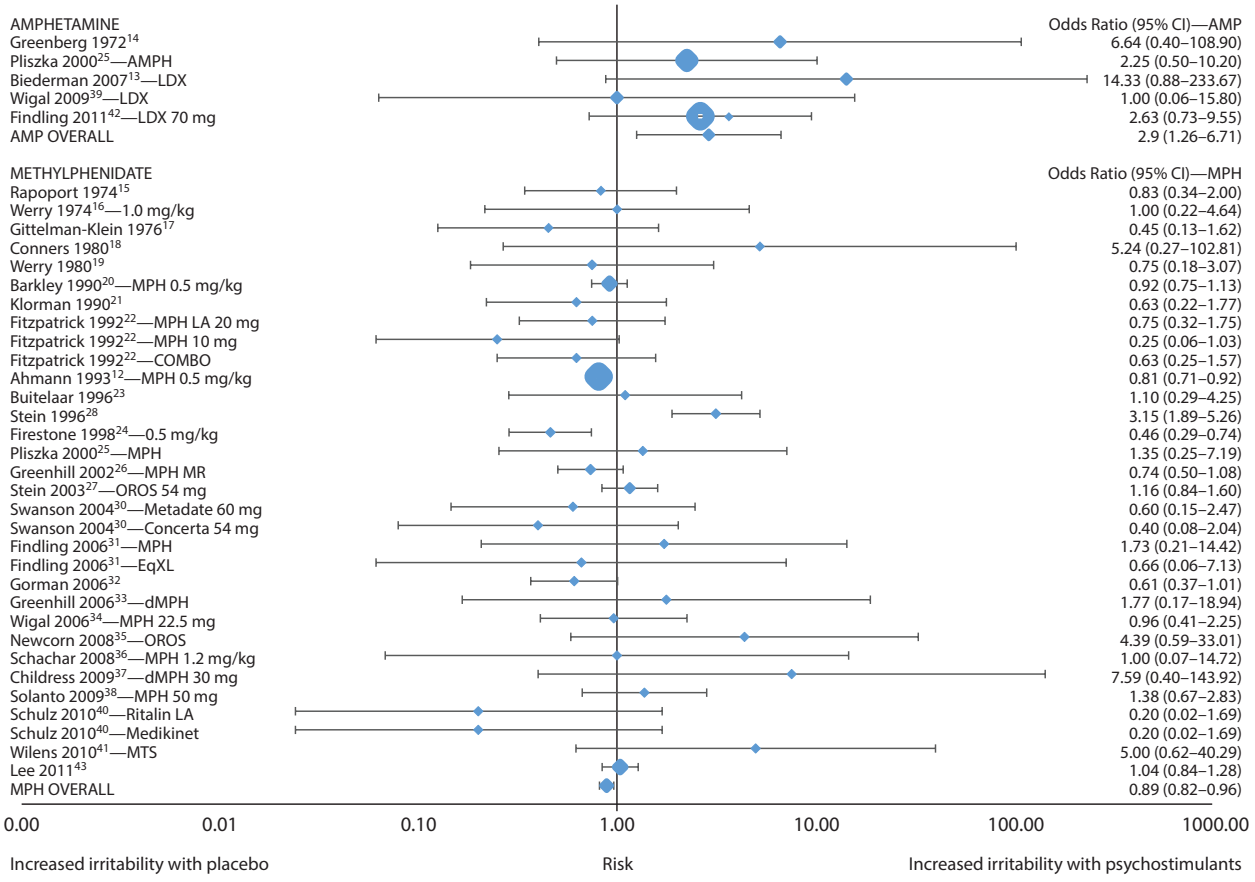
Mean Age of Participants

No significant association was found between mean age of participants in trials and risk of irritability (β = .055 [95% CI, −0.03 to 0.14], $z = 1.26$, $P = .21$). There was no significant association between age and risk of irritability within either of the psychostimulant classes.

Trial Design

No significant association was found between the trial design and measured risk of psychostimulant medications (test for subgroup differences $\chi^2_1 = 0.4$, $P = .53$). Parallel-design studies (RR = 0.98 [95% CI, 0.74 to 1.31], $z = -0.1$, $P = .89$) were associated with a similar risk of irritability as

Figure 2. Risk of Irritability in Methylphenidate and Amphetamine Derivatives[a,b]



[a]Name of only the first author listed for each study.
[b]Meta-analysis demonstrated a significantly reduced risk of irritability on psychostimulants compared to placebo (RR = 0.90 [95% CI, 0.83–0.97], $z = -2.61$, $P = .009$). The relative risk of irritability significantly differed between psychostimulant classes (test for subgroup differences $\chi^2_1 = 7.6$, $P = .006$). Methylphenidate derivatives were associated with a significantly decreased risk of irritability compared to placebo (RR = 0.89 [95% CI, 0.82–0.96], $z = -2.87$, $P = .004$, k = 32, $I^2 = 50\%$), whereas amphetamine derivatives were associated with a significantly increased risk of irritability (RR = 2.90 [95% CI, 1.26–6.71], $z = 2.5$, $P = .01$, k = 5, $I^2 = 0\%$). The size of the circle representing each trial is proportional to its weight in the meta-analysis.
Abbreviations: AMP = amphetamine, COMBO = combination of standard and LA methylphenidate, dMPH = dexmethylphenidate, EqXL = Equasym XL, IR = immediate release, LA = long-acting, LDX = lisdexamfetamine, MAS = mixed amphetamine salts, MPH = methylphenidate, MR = modified release; MTS = methylphenidate transdermal system, OROS = osmotic controlled-release oral delivery system, RR = risk ratio.

crossover studies (RR = 0.89 [95% CI, 0.82 to 0.97], $z = -2.68$, $P = .007$).

Rater of Irritability as a Side Effect

No significant association was found between who was rating irritability as a side effect and measured risk of psychostimulant medications (test for subgroup differences $\chi^2_1 = 0.1$, $P = .92$). Trials utilizing clinician raters of irritability (RR = 0.89 [95% CI, 0.70 to 1.13], $z = -1.0$, $P = .33$) demonstrated a similar risk of irritability as compared with trials utilizing non-clinician raters (eg, parents and teachers) (RR = 0.90 [95% CI, 0.82 to 0.98], $z = -2.4$, $P = .02$).

DISCUSSION

This meta-analysis demonstrated a reduced risk of irritability in children with ADHD receiving methylphenidate treatment as compared with placebo. This result is consistent with previous clinical trial data examining irritability as an outcome in children with ADHD[10] and also with previous meta-analyses that have demonstrated a reduction of aggression symptoms when children with ADHD are treated with psychostimulants.[7,8] However, we also unexpectedly demonstrated a significant difference in risk of irritability by stimulant class. Specifically, amphetamine-derivative psychostimulants were associated with a significantly increased risk of irritability, whereas methylphenidate derivatives were associated with reduced risk of irritability compared to placebo. Previous head-to-head trials have suggested greater reductions in irritability with methylphenidate compared to dexamphetamine treatment.[44]

Although methylphenidate and amphetamine derivatives produce similar behavioral effects, the neurochemical actions of the two types of psychostimulants differ.[45] The differential effects of methylphenidate versus amphetamine derivatives in causing irritability may be explained by differences in their mechanism of action. Administration of

both amphetamine and methylphenidate results in increased biogenic amine neurotransmitters (dopamine, serotonin, and norepinephrine) at the level of the synapse.[46] However, the biological mechanism by which psychostimulants produce these effects differs, and accordingly, these medications cause different relative effects on biogenic amine neurotransmitters.[46] Methylphenidate is a pure reuptake inhibitor of catecholamines with no presynaptic effects, whereas amphetamines also have presynaptic activity causing the release of dopamine and norepinephrine from the presynaptic synapse.[47,48] Dose-dependent effects on dopamine, norepinephrine, and serotonin are much greater in amphetamine compared to methylphenidate.[46] Amphetamines inhibit serotonin transporter functioning at higher doses, whereas methylphenidate does not.[49] Serotonin is also hypothesized to play an important role in aggressive behavior, forming the "serotonin hypothesis" for aggression.[50] Specific evidence supporting the important role of serotonin in impulsive aggression includes correlation between low serotonin levels and aggressive behaviors in humans and rats as well as evidence for decreased aggressive behavior with treatment with selective serotonin reuptake inhibitors.[50] Increases of dopamine and norepinephrine are also hypothesized to increase impulsive aggression and irritability.[51] Rodent models have demonstrated the importance of the mesolimbic dopamine system in the preparation and execution of aggressive acts.[51] Pharmacologically induced dopamine increases, often using amphetamines, lead to heightened aggression in rodent models (such as after frustrative nonreward or during opiate withdrawal).[52–55] Evidence for the importance of a role of dopamine in human aggressive behaviors comes from positron emission tomography imaging with the demonstration of decreased striatal D_1 receptors in depressed patients with anger attacks.[56]

Although differences in biological mechanism of action is one possible explanation for the divergent measured effects between amphetamine- and methylphenidate-derived psychostimulants on irritability, there exist some other possible explanations. Specifically, there was most likely not a standardized definition of irritability across trials. Measurement of irritability as a side effect is not standardized across clinical trials. Differences in how, when, and in whom irritability as a side effect is specifically probed in assessments might cause differences in the measured risk of irritability between trials. For instance, parents of children taking psychostimulant medications typically complain about 2 different types of irritability—(1) irritability that is temporally associated with taking the stimulant and (2) irritability occurring as the psychostimulant wears off. Given the limitation of measuring irritability as a side effect rating, we cannot be sure whether each trial was measuring either or both of these potential relationships of irritability with psychostimulants. As most of these trials are industry-sponsored trials, it is highly likely that irritability as a side effect was measured similarly within each individual pharmaceutical medication but differently between medications. This phenomenon might cause different measured risk of irritability between drug classes.

Given the potential clinical relevance of this meta-analysis, it is important to take stock of its limitations. Although there are a large number of randomized controlled trials of psychostimulants, there were only a limited number of randomized, placebo-controlled trials of psychostimulants in children with ADHD that actually reported irritability as a side effect. Specifically, only 32 of 92 potentially eligible psychostimulant trials actually reported irritability as a side effect (or we were able to obtain the data by contacting study authors). Although the meta-analysis was still quite well-powered to detect differences between treatments, there remains the possibility of publication or reporting bias in our meta-analysis. Because many trials report side effect data only if events occur above a certain frequency in the sample or if there was a statistically significant difference between groups, the selective presentation of irritability side effect data raises the possibility of bias, which may exaggerate differences in risk between groups. Partially arguing against this phenomenon is that there was no evidence of publication or reporting bias using both qualitative (funnel plot) and quantitative evaluation (Egger test). Funnel plot asymmetry would be expected in the meta-analysis if side effects were being selectively reported based on statistical significance (but we would not observe funnel plot asymmetry if the selective reporting was based on side effect frequency). Another limitation is that many more studies assessed methylphenidate (27 studies) than amphetamine derivatives (5 studies), limiting our power to detect treatment effects and heterogeneity in the amphetamine-derived psychostimulant group. Additionally, the relatively disproportionate number of methylphenidate compared to amphetamine trials leads to an overweighting of the effects of methylphenidate (compared to those of amphetamines) when examining the total effect of psychostimulants as a class on irritability.

Quite unexpectedly, meta-analysis demonstrated that amphetamine derivatives were associated with an increased risk of irritability when compared to placebo and that methylphenidate derivatives were associated with a reduced risk of irritability when compared to placebo in children with ADHD. These results provide preliminary evidence that could inform the treatment of children with ADHD. For clinicians, the findings of this meta-analysis highlight the need to assess irritability prior to initiation of psychostimulant treatment in order to differentiate medication-induced side effects from baseline symptoms associated with ADHD. Additionally, it appears that methylphenidate-derived psychostimulants may be a better treatment option in children with ADHD and irritability. Moreover, based on the data in this meta-analysis, if a child develops irritability after starting an amphetamine-derived psychostimulant, switching to a methylphenidate-derived psychostimulant seems prudent. However, the actual reduction in risk of irritability associated with methylphenidate use (compared to placebo), although statistically significant, was small, suggesting that if irritability is the primary symptom to be

targeted with pharmacologic treatment, methylphenidate might not be the best initial choice compared to other available pharmacologic agents. These results are preliminary and require replication.

An initial step might be a meta-analysis examining differences between psychostimulant medication classes on irritability as continuous (eg, using rating scales) rather than dichotomous outcome (eg, side effect ratings) to determine if similar trends are observed. Another useful research strategy may be to examine the association between psychostimulants and other mood symptoms associated with irritability. Future research involving head-to-head methylphenidate-versus-amphetamine trials in children with ADHD are needed to further explore and confirm the potentially differential effect these medication classes have on irritability.

Submitted: December 18, 2015; accepted October 4, 2016.

Potential conflicts of interest: None.

Funding/support: The authors acknowledge the support of the National Institutes of Health (NIH)1K23MH091240, the Tourette Syndrome Association, NARSAD, the Patterson Foundation, and UL1 RR024139 from the National Center for Research Resources, a component of the National Institutes of Health, and NIH roadmap for Medical Research (all to M.H.B.).

Role of the sponsor: The funders had no role in the design, conduct, or reporting of this study.

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