Meta-Analyses of Increased Heart Rate and Blood Pressure Associated with CNS Stimulant Treatment of ADHD in Adults

Eric Mick, ScD, David D. McManus, MD, and Robert J. Goldberg, PhD

Abstract

Compared to children, adults with ADHD are at greater risk for developing adverse cardiovascular related outcomes and, if treated, may be likely to carry a greater burden of exposure to stimulant medications. The goal of this report is to critically review the available literature relevant to the cardiovascular safety of CNS stimulants for adult ADHD (aADHD). Twenty potential clinical trials of a CNS stimulant for aADHD have been published between 1979 and 2012. Of these, ten presented sufficient data to estimate the relative change in various cardiovascular parameters associated with ADHD treatment modalities. These trials were predominantly focused on long-acting stimulant preparations for acute symptom reduction (median duration = 6 weeks, range: 4 – 24 weeks) and enrolled relatively young subjects (median age = 36 years, range: 22 – 40). Using random effects meta-analysis, we found that subjects randomized to CNS stimulant treatment demonstrated a statistically significant increased resting heart rate [+5.7 bpm (3.6, 7.8), p<0.001] and systolic blood pressure findings [+2.0 mmHg (0.8, 3.2), p=0.005] compared with subjects randomized to placebo. There was a statistically significant increased risk for a resting heart rate >90 bpm [4.2% (n=50) vs. 1.7% (n=8), OR = 2.75 (1.3, 6.7), p=0.006] associated with CNS stimulant treatment. In light of prognostic value of resting heart rate with regard to cardiovascular morbidity in epidemiological studies, future research of adults with ADHD should focus on the potential clinical impact of the increase in heart rate observed in this meta-analysis.

Keywords

ADHD; CNS Stimulants; elevated heart rate; blood pressure; adult
Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder in children with worldwide prevalence estimates of approximately 3-10% (Akinbami et al., 2011, Polanczyk et al., 2007). Follow-up studies of children with this disorder have demonstrated that the symptoms of ADHD and its associated impairment persist into adulthood in approximately 30 to 50% of persons diagnosed with ADHD (Kessler et al., 2006, Faraone et al., 2006, Simon et al., 2009); it is estimated that 4-5% of American adults have this disorder. As the recognition that ADHD may persist into adulthood has gained greater acceptance, there has been a coincident increase in the use of CNS stimulants in adults with ADHD. For example, nearly 2% of American adults 20-44 years old were using stimulant medications for ADHD in 2010 representing marked increases in use among men (+188%) and women (+265%) over the prior decade (Medco, 2011). Faraone and Glatt (2009) conducted a meta analysis of aADHD pharmacotherapy and concluded that both short- and long- acting CNS stimulants were effective (effect sizes of 0.96 and 0.73, respectively) in treating the over-activity, impulsivity, and inattention characteristic of patients with ADHD.

Despite their increasing use and documented efficacy, CNS stimulant pharmacotherapy has remained controversial due to safety concerns, including the potential for abuse and adverse cardiovascular side effects. In children, a case-control study suggested that stimulant exposure was associated with a 7-fold increased risk of sudden unexplained death as 1.8% of children with sudden unexplained death compared with 0.4% of children dying in a car accident had been exposed to methylphenidate (Gould et al., 2009). Subsequent studies of large claims databases failed to identify an increased risk for serious cardiovascular events associated with the use of CNS stimulants and concluded that the absolute and relative risks associated with these medications are exceedingly small in children (Winterstein et al., 2007, McCarthy et al., 2009, Schelleman et al., 2011, Cooper et al., 2011).

Estimates of cardiovascular safety of CNS stimulants in children cannot be directly generalized to adults with ADHD, however. In general, adults have accumulated more cardiovascular disease risk factors with subsequently higher incidence rates in each decade of life. It is also noteworthy that adults with ADHD are at and even greater risk for developing unhealthy lifestyle practices and cardiovascular risk factors, such as obesity, early initiation of tobacco use, and a greater probability of chronic substance misuse (Franke et al., 2011, de Zwaan et al., 2011, Wilens et al., 2011, Matthies et al., 2012). Therefore, pharmacotherapy for aADHD results in exposure to CNS stimulants during a period of greater risk of cardiovascular disease.

The goal of this report is to critically review the available literature relevant to the cardiovascular safety of stimulants for aADHD. In this summary overview, we update previous literature reviews and conduct a formal meta-analysis of the effects of CNS stimulants in adults on several pathophysiologic cardiovascular parameters based on data from placebo-controlled trials conducted in adults with ADHD.

Experimental Procedures

Literature Search

Since there have been recent reviews of cardiovascular safety (Hammerness et al., 2011) and meta-analyses of clinical response (Faraone and Glatt, 2009) of the aADHD treatment literature, we conducted a systematic search of literature published since 2010 through PubMed using the search terms ADHD, adult, clinical trial, and stimulant. We extracted the following information from each article: 1) drug name and dose; 2) baseline, endpoint and
change values for systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate; and 3) any available electrocardiogram (ECG) parameters. We also recorded the number of treatment emergent outliers (as defined in the publications) for pulse (≥ 90 bpm), SBP (≥ 140 mmHg), DBP (≥ 90 mmHg), QTc interval (≥ 460 msecs), QRS interval (≥ 20 msecs), PR interval (≥ 200 msecs) and the number of trial discontinuations attributed to cardiovascular events by study investigators.


Of the 20 potential CNS stimulant trials, ten presented sufficient data to estimate the relative change in various cardiovascular parameters associated with ADHD treatment modalities. Two studies did not assess blood pressure (Wender et al., 1985, Taylor and Russo, 2000), four cross-over studies did not present data needed to estimate change scores (Spencer et al., 1995, Spencer et al., 2001, Kooij et al., 2004, Reimherr et al., 2007), and one study failed to report information needed to calculate change scores and standard errors (Weiss and Hechtman, 2006). Two study samples contributed to multiple publications (Spencer et al., 2005, Biederman et al., 2006, Biederman et al., 2010) but in only a direct comparison of the active treatments (OROS-MPH and MPH-tid) (Biederman et al., 2007) against a pooled placebo group was the data presented with enough detail to included in our meta-analysis.

Six studies employed optimal response dose titration (Spencer et al., 2005, Adler et al., 2009a, Rosler et al., 2009, Biederman et al., 2010, Retz et al., 2012, Biederman et al., 2012) and four studies employed a forced-dose titration (Weisler et al., 2006, Spencer et al., 2007, Medori et al., 2008, Adler et al., 2008, Casas et al., 2011) with subjects randomized to low, middle, or high dose treatment (18-, 36-, 54-, or 72-mg for OROS-MPH; 20-, 30-, or 40-mg d-MPH-ER; and 30-, 50-, and 70-mg for LDX). For these fixed dose titration studies, we calculated a weighted mean total group change score from the dose group stratifications presented in the original published reports.

**Statistical Analysis**

We extracted and analyzed the change from baseline values at the time of trial entry in cardiovascular parameters in adults with ADHD randomized to treatment with either an active CNS stimulant or to placebo. We used random-effects meta-analysis to estimate change in these variables pooled within the active and placebo groups and used random-effects meta-analytic regression models to estimate the magnitude and statistical significance of the change scores in the active relative to placebo treated groups (Sharp and Sterne, 1998, Thompson and Sharp, 1999, Harbord and Higgins, 2008). Both the meta-analysis pooled estimates and the meta-analytic regressions were weighted by the reciprocal of the variance of change scores. To summarize the prevalence of clinical outliers and cardiovascular events precipitating trial discontinuation, we estimated pooled event rates by summing the number of reported outliers across all studies and dividing by the cumulative sample size rather than attempting to pool rate ratios which may have been undetermined in individual samples due to sparse data.
Results

The ten randomized, placebo-controlled clinical trials of CNS stimulants for aADHD included in this meta-analysis are listed in Table 1. All studies meeting our inclusion criteria were published after 2005 and focused predominantly on preparations designed to provide day-long coverage with a single dose. The one exception was a study of immediate release methylphenidate (Spencer et al., 2005) that required three daily doses and effectively provided the same coverage as a long-acting preparation (Biederman et al., 2007). Three studies employed amphetamines with the remaining majority studying methylphenidate (Table 1). Study samples were relatively homogeneous with respect to age (median age =36 years, range: 22 – 40) and sex (median % male was 55%, range 38-68%). Most trials were focused on assessment of acute symptom reduction; the median study duration was 6 weeks (range: 4 – 24 weeks).

Only studies that provided sufficient detail to calculate the mean change from baseline for vital signs (pulse and blood pressure) in placebo and CNS stimulant treated groups were included in this meta-analysis. The change scores extracted from the 10 identified publications are presented in Table 2. Electrocardiographic data, however, were less frequently reported, with only two studies (Biederman et al., 2007, Biederman et al., 2012) presenting QRS, QTc, and PR intervals in both placebo and active treatment groups at multiple time points. The remaining trials, however, reported limited ECG data or only those values that were found to be significantly different between the active and placebo treated groups. Given the incomplete presentation of detailed ECG data, we did not attempt to estimate a pooled mean change in any electrocardiographic parameters in relation to CNS stimulant exposure.

The results from the random-effect meta-analyses of the change in heart rate, SBP, and DBP in placebo and active medication groups are presented in Table 2. Findings were relatively consistent across studies with only heart rate (Q=27.7, p=0.001) and DBP (Q=16.7, p=0.02) in the placebo groups demonstrating significant evidence of between study heterogeneity (p>0.05 for SBP in placebo and for all measures in the CNS stimulant treated groups). There was no statistically significant change from baseline for any of the cardiovascular measures in the placebo groups, but there was a statistically significant increase in heart rate, SBP, and DBP observed in the meta-analysis of the CNS stimulant groups (Table 2).

The difference between the CNS stimulant and placebo groups was statistically significant for heart rate [beta = 5.7 (3.6, 7.8), p<0.001] and SBP [beta = 2.0 (0.8, 3.2), p=0.005], but not for DBP [beta = 1.0 (-0.1, 2.1), p=0.1]. For the four studies that utilized a fixed, forced-titration dosing protocol we estimated the mean change from baseline in the total sample. Because the pooled sample was comprised of subjects on low therapeutic doses, change observed in the total sample may under-estimate the cardiovascular response to CNS stimulants. Using meta-analysis regression models, we found that dose-titration schedule (i.e. fixed vs. optimal in the CNS stimulant groups) was not statistically significantly associated with our estimate of change in heart rate [beta = −0.75 (−2.23, 0.75), p=0.3], SBP [beta = −0.42 (−2.6, 1.75), p=0.7] or DBP [beta = −0.58 (−2.25, 1.06), p=0.4].

All studies documented the rate of subject discontinuation due to adverse effects and eight characterized the type of adverse event. In none of the studies reviewed were any serious cardiovascular events (e.g., myocardial infarction, atrial fibrillation, sudden cardiac death, heart failure) reported, and the rate of drug discontinuation due to cardiovascular symptoms was not different between study drug treated (22 of 1514, 1.5%) and subjects treated with placebo [5 of 630, 0.8% p=0.2]. Clinically significant outliers for heart rate (≥90 bpm), SBP (≥140 mmHg), and DBP (≥90 mmHg) were reported in six trials (Adler et al., 2008, Adler et
Biederman et al., 2009b, Biederman et al., 2007, Casas et al., 2011, Spencer et al., 2007, Weisler et al., 2006) with a cumulative sample of 504 subjects on placebo and 1,178 subjects treated with a CNS stimulant. There was no difference in the risk of clinically elevated SBP [5.7% (n=67) vs. 5.5% (n=27), OR = 1.1 (0.7, 1.8), p=0.8] or DBP [5.7% (n=67) vs. 4.5% (n=23), OR = 1.3 (0.8, 2.1), p=0.3] between the pooled placebo and CNS stimulant groups. On the other hand, there was a statistically significant increased risk for an elevated heart rate [4.2% (n=50) vs. 1.7% (n=8), OR = 2.75 (1.3, 6.7), p=0.006] associated with randomization to CNS stimulant treatment.

Discussion

In this meta-analysis of published clinical trials, we provide a contemporary estimate of change in blood pressure and pulse findings associated with CNS stimulant use for aADHD. In 2665 patients from 10 trials, we observed that use of CNS stimulants were associated with an increase in heart rate of approximately 5 bpm and an increase in systolic or diastolic blood pressure of 1.2 mmHg. We also noted a low overall risk (≤5%) of clinically significant cardiovascular events, including tachycardia or hypertension. Our meta-analysis is consistent with previous literature reviews (Hammerness et al., 2011) and pharmaco-epidemiological studies (Cooper et al., 2011, Habel et al., 2011) summarizing the cardiovascular impact of CNS stimulant treatment for adults with aADHD.

Although relatively small in magnitude, the statistically significant heart rate increase of 5.7 (3.6, 7.8) bpm associated with CNS stimulants may be clinically significant. Epidemiological studies of general and patient populations have demonstrated that elevated resting heart rate is a significant independent predictor of mortality and a shorter life expectancy (Cooney et al., 2010, Perret-Guillaume et al., 2009). For example, a systematic review of the literature estimated that heart rate increases of 10 bpm are associated with a 20% increased risk of cardiac death (Perret-Guillaume et al., 2009). In a more recent study, 15 bpm increases in heart rate were found to increase the rate of cardiovascular disease mortality by 23 to 50% in men and women (Cooney et al., 2010). Heart rate increases on par with those observed with CNS stimulant treatment for aADHD have been associated with a 17% increased cardiovascular mortality in the Ohasama study (Hozawa et al., 2004) and an 8% increase in cardiovascular mortality among patients with coronary artery disease (Fox et al., 2008).

Cardiovascular complications, morbidity, and mortality are predominantly observed in individuals with a resting heart rate of more than 80 bpm (Perret-Guillaume et al., 2009). This likely relates to an relative imbalance between sympathetic and parasympathetic cardiac inputs, leading to increased myocardial excitability and conductance. Patients with increased sympathetic nervous system activity are at higher risk for clinically significant cardiac arrhythmias, myocardial ischemia, and stroke (Cooney et al., 2010). Although we estimate that a minority (4.2%) of adults with ADHD exposed to CNS stimulants recorded heart rates in excess of 90 bpm, the incidence of borderline tachycardia (i.e. 80-85 bpm) (Perret-Guillaume et al., 2009) is not known. Moreover, a recent pilot study of lisdexamfetamine in 15 patients with aADHD found suggestive evidence of reduced heart rate recovery at one minute past maximum exertion on cardiopulmonary exercise testing (Hammerness et al., 2012). Considering the consistent increase in heart rate associated with CNS stimulants, future studies should consider heart rates surpassing this lower limit as clinical outliers in evaluating the cardiovascular disease related effects of CNS stimulants.

It is important to note, however, that the studies used to estimate risks from CNS stimulant exposure sampled specific and relatively narrow populations of healthy individuals at low risk for cardiovascular events. At a minimum, these trials excluded subjects with clinically
significant medical conditions or abnormal laboratory values at baseline (Biederman et al., 2007, Rosler et al., 2009, Retz et al., 2012) or for whom CNS stimulant treatment may have been destabilizing or posed additional risk (Spencer et al., 2007). Other studies specified that, beyond being in good physical health, subjects must have normal ECG and blood pressure measurements at baseline (Weisler et al., 2006), in addition to no history of hypertension or structural cardiac abnormality (Adler et al., 2008, Adler et al., 2009b, Medori et al., 2008, Biederman et al., 2012) or no significant cardiac illness (e.g. stroke, myocardial infarction, angina pectoris, cardiac arrhythmias) in the preceding six months (Casas et al., 2011, Medori et al., 2008).

One possible exception is the large European study of OROS-MPH (Medori et al., 2008) that, despite the stated exclusion criteria, enrolled some subjects with an elevated SBP (16% ≥ 140mmHg), DBP (21% ≥ 90mmHg), or heart rate (4% ≥ 90 bpm) at initial evaluation. The prevalence of these outliers in individuals who completed the trial was either stable (16% SBP ≥140mmHg, 19% DBP ≥90mmHg) or increased (11% heart rate> 90 bpm), but the presented data were not sufficient to determine if these were ongoing or incident elevations of these important physiologic parameters. Thus, the current body of data from randomized clinical trials of CNS stimulants for aADHD does not provide any guidance regarding the absolute or relative risk of various cardiovascular events in a less healthy population treated with CNS stimulants.

In order to further study the potential risk of sudden death in children from CNS stimulant exposure (Gould et al., 2009), several pharmacoepidemiological investigations have recently been conducted using data from a large, representative sample of young and middle aged adults treated with CNS stimulants (Cooper et al., 2011, Habel et al., 2011). In a sample of more than 150,000 adults (25 to 64 years old) treated with CNS stimulants, the incidence (per 1,000 person-years) of myocardial infarction was 1.34, of sudden cardiac death was 0.3, and of stroke was 0.56 (Habel et al., 2011). Current CNS stimulant users were significantly less likely (RR =0.83, 95% CI = 0.72-0.96) to have developed a serious cardiovascular event than non-users, but this protective effect was considered most likely to be biased by a “healthy user effect” (Habel et al., 2011). This is consistent with research conducted in the Thomson MarketScan Commercial Claims and Encounters Database that found 10% of aADHD patients seeking treatment presented with pre-existing cardiovascular conditions and that patients with cardiovascular comorbidities were less likely to be prescribed CNS stimulants (Gerhard et al., 2010). Although these samples are less selected than those participating in randomized clinical trials where more narrowly defined inclusion and exclusion criteria are placed on the study population, the exposed study sample is, again, more healthy than the general aADHD population.

Other factors to consider in understanding the risk estimates for serious adverse cardiovascular events associated with CNS stimulant use in adults include age at exposure, the duration of exposure, and the period of exposure. For example, subjects exposed to CNS stimulants were relatively young (median age of 42 years) and exposed for a short time interval (median duration of 0.33 years). It may also be noteworthy that the catchment window (1986 to 2005) for these large safety studies (Cooper et al., 2011, Habel et al., 2011) predominantly covered a time period prior to the first FDA approval of CNS stimulant treatment for aADHD in 2004. As more treatments are approved and prescribers become more comfortable treating aADHD, it’s likely that a broader - perhaps less healthy - populations will be exposed to CNS stimulants. Therefore, although the recent results of pharmacoepidemiological studies are encouraging with regard to the low absolute risk of serious cardiovascular events associated with these medications in aADHD, firm conclusions regarding the overall cardiovascular safety of these agents cannot currently be made for patients at varying risk for CVD or in relation to chronic treatment exposure.
There is remarkably little data available to guide and inform clinical practice in the many patients with aADHD and concomitant cardiovascular disease and/or risk factors. Clinical recommendations currently include measuring vital signs and assessing a prospective patient’s personal and family history for cardiovascular disease prior to prescribing CNS stimulants (Hammerness et al., 2011). Change in ECG parameters was inconsistently reported in the aADHD trials we reviewed here but clinically significant outliers were either not observed (Adler et al., 2008, Adler et al., 2009b, Casas et al., 2011, Spencer et al., 2007, Weisler et al., 2006), or were uncommon (i.e. <2%) (Biederman et al., 2010). Since universal ECG prescreening has not been shown to be cost effective for preventing sudden cardiac death in children with ADHD (Denchev et al., 2010), or in young individuals in general, ECG screening and cardiologist referrals are recommended only for aADHD subjects with a positive history of structural cardiac abnormalities (Adler et al., 2009a, Hammerness et al., 2011).

This meta-analysis and literature review highlights the dearth of information currently available regarding the cardiovascular safety of CNS stimulant therapy in adults with ADHD. Numerous large clinical trials have been published concluding that the magnitude of change in several important cardiovascular parameters is observable but of little clinical significance. These studies, however, were not designed or adequately powered to study cardiovascular risks and enrolled young, healthy adults selected primarily to ensure their safety during the trial. Although large pharmaco-epidemiological studies demonstrate that the risk of serious cardiovascular events is small among CNS stimulant treated patients, there is limited information available to quantify the risks of common cardiovascular diseases that may be influenced by chronic use of CNS stimulants in middle-aged or elderly men and women. Considering the emerging evidence that increased heart rate is a significant risk factor for cardiovascular morbidity and mortality, the long-term use of the CNS stimulants should be followed closely to monitor changes in the risk for cardiovascular events among adults with ADHD.

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References


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## Table 1

Randomized, placebo-controlled trials of CNS stimulants for ADHD included in meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Group</th>
<th>N</th>
<th>% Male</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weisler (2006)</td>
<td>Placebo</td>
<td>60</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAS-XR</td>
<td>188</td>
<td>50</td>
<td>40*</td>
</tr>
<tr>
<td>Spencer (2007)</td>
<td>PBO</td>
<td>53</td>
<td>56</td>
<td>30*</td>
</tr>
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<td>Biederman (2007)</td>
<td>Placebo</td>
<td>116</td>
<td>50</td>
<td>80.9</td>
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<tr>
<td>Medori (2008)</td>
<td>Placebo</td>
<td>96</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Adler (2008)</td>
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<td>52</td>
<td></td>
</tr>
<tr>
<td>Adler (2009)</td>
<td>Placebo</td>
<td>116</td>
<td>55</td>
<td></td>
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<td>Roder (2009)</td>
<td>Placebo</td>
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<td>50</td>
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<tr>
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<td>97</td>
<td>53</td>
<td></td>
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<tr>
<td>Retz (2012)</td>
<td>Placebo</td>
<td>78</td>
<td>56</td>
<td></td>
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<tr>
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<td>Placebo</td>
<td>30</td>
<td>62</td>
<td>NR</td>
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MAS-XR (mixed amphetamine salts, extended release), d-MPH-ER (dexmethylphenidate extended-release), OROS-MPH (osmotic release oral system methylphenidate), IR-MPH (immediate release methylphenidate), LDX (lisdexamphetamine).
### Table 2

Heart Rate, blood pressure and ECG findings extracted from ADHD CNS stimulant trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug Group</th>
<th>Heart Rate (bpm)</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
<th>QTc Interval (msec)</th>
<th>QRS Interval (msec)</th>
<th>PR Interval (msec)</th>
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<td></td>
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<td>Mean±S E</td>
<td>Mean±S E</td>
<td>Mean±S E</td>
<td>Mean±S E</td>
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<td>Placebo</td>
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<td>−2.8±2.5</td>
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<td>NR</td>
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<td></td>
<td>MAS-XR</td>
<td>5.2±0.7</td>
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<td>NR</td>
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<td>Spencer (2007)</td>
<td>PBO</td>
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<td></td>
<td>d-MPH-ER</td>
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<td>0.5±0.9</td>
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<td>NR</td>
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<td>−1.2±1.1</td>
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<tr>
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<td>OROS-MPH</td>
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<td>2.0±1.2</td>
<td>−2.0±1.6</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>OROS-MPH</td>
<td>2.0±2.0</td>
<td>1.0±4.1</td>
<td>3.0±1.7</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Biederman (2012)</td>
<td>Placebo</td>
<td>−0.6±2.2</td>
<td>−1.7±2.5</td>
<td>−2.3±2.2</td>
<td>0.6±2.7</td>
<td>−0.2±0.8</td>
<td>0.1±2.2</td>
</tr>
<tr>
<td></td>
<td>LDX</td>
<td>15.9±2.9</td>
<td>4.2±2.9</td>
<td>2.9±1.9</td>
<td>9.7±2.0</td>
<td>0.8±0.9</td>
<td>−4.9±2.0</td>
</tr>
<tr>
<td>Study</td>
<td>Drug Group</td>
<td>Heart Rate (bpm) Mean±SE</td>
<td>Systolic BP (mmHg) Mean±SE</td>
<td>Diastolic BP (mmHg) Mean±SE</td>
<td>QTc Interval (msec) Mean±SE</td>
<td>QRS Interval (msec) Mean±SE</td>
<td>PR Interval (msec) Mean±SE</td>
</tr>
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<td>---------------</td>
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</tr>
<tr>
<td>Pooled Estimate</td>
<td>Placebo</td>
<td>-0.5±0.7</td>
<td>-0.9±0.4</td>
<td>0.2±0.4</td>
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</tr>
<tr>
<td></td>
<td>CNS Stimulant</td>
<td>5.0±0.5\textsuperscript{a}</td>
<td>1.2±0.4\textsuperscript{b}</td>
<td>1.2±0.3\textsuperscript{c}</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

MAS-XR (mixed amphetamine salts, extended release), d-MPH-ER (dextroamphetamine extended-release), OROS-MPH (osmotic release oral system methylphenidate), IR-MPH (immediate release methylphenidate), LDX (lisdexamfetamine), MPH-ER (extended release methylphenidate). Statistically significant change scores within treatment group:

\textsuperscript{a} (p < 0.001)

\textsuperscript{b} (p = 0.004)

\textsuperscript{c} (p < 0.001).