Published in final edited form as:

Eur Neuropsychopharmacol. 2013 June ; 23(6): 534–541. doi:10.1016/j.euroneuro.2012.06.011.

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

Eric Mick, ScD^{a,b}, David D. McManus, MD^{a,c}, and Robert J. Goldberg, PhD^a

^aDepartment of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA

^bDepartment of Psychiatry, University of Massachusetts Medical School, Worcester, MA

^cDivision of Cardiovascular Medicine in the Department of Medicine at the University of Massachusetts Medical School, Worcester, MA

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

© 2012 Elsevier B.V. and European College of Neuropsychopharmacology. All rights reserved.

Corresponding Author: Eric Mick ScD; University of Massachusetts Medical School, Department of Quantitative Health Sciences, 55 Lake Avenue North – AC7-041, Worcester, MA, 01655; eric.mick@umassmed.edu; 508-856-8824.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

None

All authors declare that they have no conflicts of interest.

All authors have contributed to and have approved the final manuscript. Dr. Mick designed this study, performed the literature review and conducted all meta-analyses. Dr. Mick generated the first draft which was edited by Drs. McManus and Goldberg who provided further interpretation of these results.

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 msec), QRS interval (> 120 msec), PR interval (> 200 msec) and the number of trial discontinuations attributed to cardiovascular events by study investigators.

Faraone et al (2009) identified 12 randomized placebo controlled trials of CNS stimulants for aADHD published between 1979 and 2008 (Wender et al., 1985, Spencer et al., 1995, Taylor and Russo, 2000, Spencer et al., 2001, Kooij et al., 2004, Spencer et al., 2005, Biederman et al., 2006, Weisler et al., 2006, Weiss and Hechtman, 2006, Reimherr et al., 2007, Spencer et al., 2007, Adler et al., 2008) in a meta-analysis of clinical response and Hamner et al (2011) identified three additional trials published between 2008 and 2010 (Adler et al., 2008, Adler et al., 2009b, Rosler et al., 2009). Our review identified an additional five studies (Medori et al., 2008, Biederman et al., 2010, Casas et al., 2011, Retz et al., 2012, Biederman et al., 2012), resulting in a total of 20 studies published between 1979 to 2012 for inclusion in our meta-analysis.

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

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% ≥ 140 mmHg), DBP (21% ≥ 90 mmHg), 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 ≥ 140 mmHg, 19% DBP ≥ 90 mmHg) 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.

Acknowledgments

The authors were supported by the following NIH grants R01HL035434 (Goldberg, Mick), R01HL105268 (Goldberg, McManus), R01HL69874 (Goldberg, McManus), and P30HD004147 (Mick). The individual NIH institutions represented had no further role in study design; in the collection, analysis or interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References

- Adler LA, Goodman DW, Kollins SH, Weisler RH, Krishnan S, Zhang Y, Biederman J. Double-blind, placebo-controlled study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. *The Journal of Clinical Psychiatry*. 2008; 69:1364–73. [PubMed: 19012818]
- Adler LA, Weisler RH, Goodman DW, Hamdani M, Niebler GE. Short-term effects of lisdexamfetamine dimesylate on cardiovascular parameters in a 4-week clinical trial in adults with attention-deficit/hyperactivity disorder. *The Journal of Clinical Psychiatry*. 2009a; 70:1652–61. [PubMed: 20141706]
- Adler LA, Zimmerman B, Starr HL, Silber S, Palumbo J, Orman C, Spencer T. Efficacy and safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, double-blind, parallel group, dose-escalation study. *Journal of Clinical Psychopharmacology*. 2009b; 29:239–47. [PubMed: 19440077]
- Akinbami LJ, Liu X, Pastor PN, Reuben CA. Attention deficit hyperactivity disorder among children aged 5-17 years in the United States, 1998-2009. *NCHS Data Brief*. 2011:1–8.
- Biederman J, Fried R, Hammerness P, Surman C, Mehler B, Petty CR, Faraone SV, Miller C, Bourgeois M, Meller B, Godfrey KM, Reimer B. The effects of lisdexamfetamine dimesylate on the

- driving performance of young adults with ADHD: A randomized, double-blind, placebo-controlled study using a validated driving simulator paradigm. *Journal of Psychiatric Research*. 2012
- Biederman J, Mick E, Surman C, Doyle R, Hammerness P, Harpold T, Dunkel S, Dougherty M, Aleardi M, Spencer T. A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2006; 59:829–35. [PubMed: 16373066]
- Biederman J, Mick E, Surman C, Doyle R, Hammerness P, Kotarski M, Spencer T. A randomized, 3-phase, 34-week, double-blind, long-term efficacy study of osmotic-release oral system-methylphenidate in adults with attention-deficit/hyperactivity disorder. *Journal of Clinical Psychopharmacology*. 2010; 30:549–53. [PubMed: 20814332]
- Biederman J, Mick EO, Surman C, Doyle R, Hammerness P, Michel E, Martin J, Spencer TJ. Comparative acute efficacy and tolerability of OROS and immediate release formulations of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. *BMC Psychiatry*. 2007; 7:49. [PubMed: 17868455]
- Casas M, Rosler M, Sandra Kooij JJ, Ginsberg Y, Ramos-Quiroga JA, Heger S, Berwaerts J, Dejonckheere J, Van Der Vorst E, Schauble B. Efficacy and safety of prolonged-release OROS methylphenidate in adults with attention deficit/hyperactivity disorder: A 13-week, randomized, double-blind, placebo-controlled, fixed-dose study. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*. 2011
- Cooney MT, Vartiainen E, Laatikainen T, Juolevi A, Dudina A, Graham IM. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. *American Heart Journal*. 2010; 159:612–619. e3. [PubMed: 20362720]
- Cooper WO, Habel LA, Sox CM, Chan KA, Arbogast PG, Cheetham TC, Murray KT, Quinn VP, Stein CM, Callahan ST, Fireman BH, Fish FA, Kirshner HS, O'duffy A, Connell FA, Ray WA. ADHD drugs and serious cardiovascular events in children and young adults. *The New England Journal of Medicine*. 2011; 365:1896–904. [PubMed: 22043968]
- De Zwaan M, Gruss B, Muller A, Philipsen A, Graap H, Martin A, Glaesmer H, Hilbert A. Association between obesity and adult attention-deficit/hyperactivity disorder in a German community-based sample. *Obesity Facts*. 2011; 4:204–11. [PubMed: 21701236]
- Denchev P, Kaltman JR, Schoenbaum M, Vitiello B. Modeled economic evaluation of alternative strategies to reduce sudden cardiac death among children treated for attention deficit/hyperactivity disorder. *Circulation*. 2010; 121:1329–37. [PubMed: 20212277]
- Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine*. 2006; 36:159–65. [PubMed: 16420712]
- Faraone SV, Glatt SJ. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. *Journal of Clinical Psychiatry*. 2009; 71:754–763. [PubMed: 20051220]
- Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet*. 2008; 372:817–21. [PubMed: 18757091]
- Franke B, Faraone SV, Asherson P, Buitelaar J, Bau CH, Ramos-Quiroga JA, Mick E, Grevet EH, Johansson S, Haavik J, Lesch KP, Cormand B, Reif A. The genetics of attention deficit/hyperactivity disorder in adults, a review. *Molecular Psychiatry*. 2011
- Gerhard T, Winterstein AG, Olfson M, Huang C, Saidi A, Crystal S. Pre-existing cardiovascular conditions and pharmacological treatment of adult ADHD. *Pharmacoepidemiology and drug safety*. 2010; 19:457–64. [PubMed: 20232490]
- Gould MS, Walsh BT, Munfakh JL, Kleinman M, Duan N, Olfson M, Greenhill L, Cooper T. Sudden death and use of stimulant medications in youths. *American Journal of Psychiatry*. 2009; 166:992–1001. [PubMed: 19528194]
- Habel LA, Cooper WO, Sox CM, Chan KA, Fireman BH, Arbogast PG, Cheetham TC, Quinn VP, Dublin S, Boudreau DM, Andrade SE, Pawloski PA, Raebel MA, Smith DH, Achacoso N, Uratsu C, Go AS, Sidney S, Nguyen-Huynh MN, Ray WA, Selby JV. ADHD medications and risk of

- serious cardiovascular events in young and middle-aged adults. *JAMA*. 2011; 306:2673–83. [PubMed: 22161946]
- Hammerness P, Zusman R, Systrom D, Surman C, Baggish A, Schillinger M, Shelley-Abrahamson R, Wilens TE. A cardiopulmonary study of lisdexamfetamine in adults with attention-deficit/hyperactivity disorder. *The world journal of biological psychiatry: the official journal of the World Federation of Societies of Biological Psychiatry*. 2012
- Hammerness PG, Surman CB, Chilton A. Adult attention-deficit/hyperactivity disorder treatment and cardiovascular implications. *Current Psychiatry Reports*. 2011; 13:357–63. [PubMed: 21698412]
- Harbord RM, Higgins JPT. Meta-regression in Stata. *The Stata Journal*. 2008; 8:493–519.
- Hozawa A, Ohkubo T, Kikuya M, Ugajin T, Yamaguchi J, Asayama K, Metoki H, Ohmori K, Hoshi H, Hashimoto J, Satoh H, Tsuji I, Imai Y. Prognostic value of home heart rate for cardiovascular mortality in the general population: the Ohasama study. *American Journal of Hypertension*. 2004; 17:1005–10. [PubMed: 15533725]
- Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, Faraone SV, Greenhill LL, Howes MJ, Secnik K, Spencer T, Ustun TB, Walters EE, Zaslavsky AM. The prevalence and correlates of adult ADHD in the United States: Results from the national comorbidity survey replication. *American Journal of Psychiatry*. 2006; 163:716–723. [PubMed: 16585449]
- Kooij JJ, Burger H, Boonstra AM, Van Der Linden PD, Kalma LE, Buitelaar JK. Efficacy and safety of methylphenidate in 45 adults with attention-deficit/hyperactivity disorder. A randomized placebo-controlled double-blind cross-over trial. *Psychological Medicine*. 2004; 34:973–82. [PubMed: 15554568]
- Matthies S, Holzner S, Feige B, Scheel C, Perlov E, Ebert D, Tebartz Van Elst L, Philipsen A. ADHD as a Serious Risk Factor for Early Smoking and Nicotine Dependence in Adulthood. *Journal of Attention Disorders*. 2012
- Mccarthy S, Cranswick N, Potts L, Taylor E, Wong IC. Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: a retrospective cohort study of children, adolescents and young adults using the general practice research database. *Drug safety: an international journal of medical toxicology and drug experience*. 2009; 32:1089–96. [PubMed: 19810780]
- Medco 2011. America's State of Mind. <http://medco.mediaroom.com>
- Medori R, Ramos-Quiroga JA, Casas M, Kooij JJ, Niemela A, Trott GE, Lee E, Buitelaar JK. A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2008; 63:981–9. [PubMed: 18206857]
- Perret-Guillaume C, Joly L, Benetos A. Heart rate as a risk factor for cardiovascular disease. *Progress in Cardiovascular Diseases*. 2009; 52:6–10. [PubMed: 19615487]
- Polanczyk G, De Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *The American Journal of Psychiatry*. 2007; 164:942–8. [PubMed: 17541055]
- Reimherr FW, Williams ED, Strong RE, Mestas R, Soni P, Marchant BK. A double-blind, placebo-controlled, crossover study of osmotic release oral system methylphenidate in adults with ADHD with assessment of oppositional and emotional dimensions of the disorder. *The Journal of Clinical Psychiatry*. 2007; 68:93–101. [PubMed: 17284136]
- Retz W, Rosler M, Ose C, Scherag A, Alm B, Philipsen A, Fischer R, Ammer R. Multiscale assessment of treatment efficacy in adults with ADHD: A randomized placebo-controlled, multi-centre study with extended-release methylphenidate. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*. 2012; 13:48–59. [PubMed: 21155632]
- Rosler M, Fischer R, Ammer R, Ose C, Retz W. A randomised, placebo-controlled, 24-week, study of low-dose extended-release methylphenidate in adults with attention-deficit/hyperactivity disorder. *European Archives of Psychiatry and Clinical Neuroscience*. 2009; 259:120–9. [PubMed: 19165529]

- Schelleman H, Bilker WB, Strom BL, Kimmel SE, Newcomb C, Guevara JP, Daniel GW, Cziraky MJ, Hennessy S. Cardiovascular events and death in children exposed and unexposed to ADHD agents. *Pediatrics*. 2011; 127:1102–10. [PubMed: 21576311]
- Sharp S, Sterne J. New syntax and output for the meta-analysis command. *Stata Technical Bulletin*. 1998; 42:6–8.
- Simon V, Czobor P, Balint S, Meszaros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *The British Journal of Psychiatry*. 2009; 194:204–11. [PubMed: 19252145]
- Spencer T, Biederman J, Wilens T, Doyle R, Surman C, Prince J, Mick E, Aleardi M, Herzig K, Faraone S. A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2005; 57:456–63. [PubMed: 15737659]
- Spencer T, Biederman J, Wilens T, Faraone S, Prince J, Gerard K, Doyle R, Parekh A, Kagan J, Bearman SK. Efficacy of a mixed amphetamine salts compound in adults with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*. 2001; 58:775–82. [PubMed: 11483144]
- Spencer T, Wilens T, Biederman J, Faraone SV, Ablon JS, Lapey K. A double-blind, crossover comparison of methylphenidate and placebo in adults with childhood-onset attention-deficit hyperactivity disorder. *Archives of General Psychiatry*. 1995; 52:434–43. [PubMed: 7771913]
- Spencer TJ, Adler LA, McGough JJ, Muniz R, Jiang H, Pestreich L. Efficacy and safety of dexamethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2007; 61:1380–7. [PubMed: 17137560]
- Taylor FB, Russo J. Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults. *Journal of Child and Adolescent Psychopharmacology*. 2000; 10:311–20. [PubMed: 11191692]
- Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Statistics in Medicine*. 1999; 18:2693–708. [PubMed: 10521860]
- Weisler RH, Biederman J, Spencer TJ, Wilens TE, Faraone SV, Chrisman AK, Read SC, Tulloch SJ. Mixed amphetamine salts extended-release in the treatment of adult ADHD: a randomized, controlled trial. *CNS Spectrums*. 2006; 11:625–39. [PubMed: 16871129]
- Weiss M, Hechtman L. A randomized double-blind trial of paroxetine and/or dextroamphetamine and problem-focused therapy for attention-deficit/hyperactivity disorder in adults. *The Journal of Clinical Psychiatry*. 2006; 67:611–9. [PubMed: 16669726]
- Wender PH, Reimherr FW, Wood D, Ward M. A controlled study of methylphenidate in the treatment of attention deficit disorder, residual type, in adults. *The American Journal of Psychiatry*. 1985; 142:547–52. [PubMed: 3885760]
- Wilens TE, Martelon M, Joshi G, Bateman C, Fried R, Petty C, Biederman J. Does ADHD predict substance-use disorders? A 10-year follow-up study of young adults with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2011; 50:543–53. [PubMed: 21621138]
- Winterstein AG, Gerhard T, Shuster J, Johnson M, Zito JM, Saidi A. Cardiac safety of central nervous system stimulants in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics*. 2007; 120:e1494–501. [PubMed: 18055666]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 2
Heart Rate, blood pressure and ECG findings extracted from aADHD CNS stimulant trials

Study	Drug Group	Heart Rate (bpm)	Systolic BP (mmHg)	Diastolic BP (mmHg)	QTc Interval (msec)	QRS Interval (msec)	PR Interval (msec)
		Mean±SE	Mean±SE	Mean±SE	Mean±SE	Mean±SE	Mean±SE
Weisler (2006)	Placebo	1.9±1.3	-1.9±1.3	NR	-2.8±2.5	NR	NR
	MAS-XR	5.2±0.7	1.7±1.2	NR	4.5±1.8	NR	NR
Spencer (2007)	PBO	-1.4±1.3	-1.7±1.6	0.3±1.1	NR	NR	NR
	d-MPH-ER	4.4±0.8	0.5±0.9	1.0±0.6	NR	NR	NR
Biederman (2007)	Placebo	-4.7±1.1	-1.2±1.1	-1.5±0.8	0.5±1.7	0.5±0.8	-1.1±1.3
	OROS-MPH	4.5±1.3	3.5±1.4	4.0±1.0	1.9±1.9	-1.2±0.7	-1.2±1.4
	MPH-tid	5.9±1.3	2.0±1.2	2.1±0.9	6.1±1.6	-1.2±1.0	-2.5±1.2
Medori (2008)	Placebo	2.7±1.7	1.1±2.4	-1.8±1.7	-	-	-
	OROS-MPH	5.5±1.1	1.0±1.2	-0.2±0.9	-	-	-
Adler (2008)	Placebo	0.0±1.1	-0.5±1.0	1.1±0.1	-0.3±1.9	0.0±0.7	NR
	LDX	4.1±0.5	0.8±0.4	1.2±0.3	1.6±1.8	-	NR
					0.03±0.3		
Adler (2009)	Placebo	-1.6±0.8	-0.5±0.9	0.4±0.7	NR	NR	NR
	OROS-MPH	6.3±0.9	-1.2±0.8	1.1±0.6	NR	NR	NR
Rosler (2009)	Placebo	1.0±1.8	2.0±2.4	0.0±1.5	-	-	-
	MPH-ER	4.0±1.6	3.0±1.2	0.0±0.8	-	-	-
Casas (2011)	Placebo	1.0±1.1	-2.0±1.2	0.4±0.9	NR	NR	NR
	OROS-MPH	4.3±0.9	1.6±0.9	1.1±0.7	NR	NR	NR
Retz (2012)	Placebo	1.0±1.9	2.0±1.2	-2.0±1.6	-	-	-
	OROS-MPH	2.0±2.0	1.0±1.4	3.0±1.7	-	-	-
Biederman (2012)	Placebo	-0.6±2.2	-1.7±2.5	-2.3±2.2	0.6±2.7	-0.2±0.8	0.1±2.2
	LDX	15.9±2.9	4.2±2.9	2.9±1.9	9.7±2.0	0.8±0.9	-4.9±2.0

Study	Drug Group	Heart Rate (bpm)	Systolic BP (mmHg)	Diastolic BP (mmHg)	QTc Interval (msec)	QRS Interval (msec)	PR Interval (msec)
Pooled Estimate	Placebo	Mean±SE -0.5±0.7	Mean±SE -0.9±0.4	Mean±SE 0.2±0.4	Mean±SE -	Mean±SE -	Mean±SE -
	CNS Stimulant	Mean±SE 5.0±0.5 ^a	Mean±SE 1.2±0.4 ^b	Mean±SE 1.2±0.3 ^c	Mean±SE -	Mean±SE -	Mean±SE -

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

^a(p<0.001)

^b(p=0.004)

^c(p<0.001).