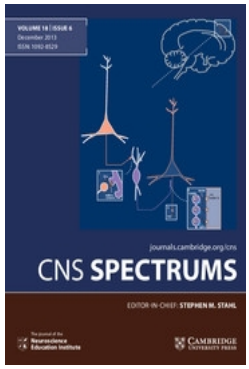

Psychopharmacology and psychotherapy for the treatment of adults with ADHD—a systematic review of available meta-analyses

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INVITED REVIEW

Psychopharmacology and psychotherapy for the treatment of adults with ADHD—a systematic review of available meta-analyses

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Objective/Introduction. Attention-deficit/hyperactivity disorder (ADHD) in adult life is a prevalent condition. We systematically reviewed the literature available by searching for meta-analyses assessing pharmacological and psychosocial interventions for adults with ADHD.

Methods. Using wide-ranging search terms, we retrieved 191 titles from the PubMed and Cochrane databases. Two independent evaluators judged all abstracts. Only meta-analyses about the treatment of adults with ADHD were included. Information from meta-analyses found was systematically extracted by 3 independent evaluators.

Results. Eight meta-analyses were identified. Results from those meta-analyses suggest that stimulants are effective in decreasing ADHD symptoms on a short-term basis with a medium to large effect size (ES). Short-acting stimulants might be superior to long-acting stimulants, but no data on difference in adherence are available for the comparison of these two types of formulation. Bupropion is superior to placebo but less effective than stimulants. No conclusions about the impact of psychosocial interventions can be drawn based on meta-analyses so far.

Discussion. The efficacy of stimulants in reducing ADHD symptoms for adults is well documented in meta-analyses, but there is a concerning lack of meta-analysis about other treatment interventions.

Conclusion. The available meta-analytic literature does not cover questions of essential clinical relevance for adults with ADHD.

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Key words: ADHD, adults, inattention, stimulants, treatment.

Clinical Implications

- Meta-analyses are considered to provide a good level of evidence and are frequently used to ground treatment recommendation. It is possible, however, that important topics of clinical relevance for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adults are not yet covered by meta-analyses. It is important to identify clinically relevant questions covered and not covered by meta-analyses to plan future clinical trials and meta-analyses.
- There are, to date, 8 meta-analyses computing effect size (ES) of different interventions for the treatment of adult ADHD.
- Stimulants are effective on a short-term basis with a medium to large ES. Bupropion is superior to placebo but less effective than stimulants. Pooled estimation for the ES of other drugs is not described in meta-analyses. No high quality meta-analyses for psychosocial interventions were identified.
- Many questions of crucial importance for the treatment of adults with ADHD are not covered by available meta-analyses.

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Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common mental disorders in childhood[1]. Although childhood ADHD is one of the most studied psychiatric conditions worldwide[2], far less attention has been given to adult ADHD, a concerning reality given the fact that at least half of those children affected will carry symptoms and associated functional deficit to adult life[4].

Although the prevalence of adult ADHD is not yet well established, there is some evidence that at least 2% of the adult population suffers from the disorder[5,6,7]. A pooled estimation of studies from non-representative samples of the population found a prevalence of 2.5% (2.1–3.1)[5]; a study approaching a representative community based population but using indirect estimation found an even higher prevalence of around 4.4% in the USA[6] and a rate of 5.2%[7] for cross-national data.

The number of adults affected contrasts markedly with the imbalance of available literature about children and adult ADHD; hundreds of clinical trials have already been conducted to test different interventions for children with ADHD, and at least 17 meta-analyses have been published on this topic.[8–24] Nevertheless, empirically based information about the treatment of adults with ADHD is considerably less frequent in the literature. A systematic review of guidelines for the treatment of ADHD available until 2011 found 13 guidelines.[25] Among those, only 1 was exclusively dedicated to the treatment of adults, but its quality was compromised by serious methodological problems.[26] Three other guidelines address the treatment of adults and children,[27–29] and all the others are dedicated to the treatment of only children with ADHD. Most guidelines suggest stimulants as first-line treatments for adults with ADHD, but recommendations are more vague and divergent for psychotherapy and other drugs. These kinds of recommendations contrast with those for children with ADHD, for whom psychosocial interventions are frequently recommended as first line treatments, either alone or in combination with pharmacotherapy.[28,30,31]

Although meta-analyses have several important limitations, many treatment guidelines have used meta-analyses as the ultimate level of evidence in the past few years. This approach can lead to distorted recommendations based on which topics are covered by meta-analysis. Because the scientific literature about ADHD has grown exponentially in the past few decades,[2] the large number of studies available makes meta-analysis a suitable approach for the systematization of available data on this topic. It is possible, however, that important clinical questions have not been explored in meta-analyses. We systematically reviewed the literature, searching for meta-analyses about the treatment of adult ADHD to verify to what extent clinically relevant questions about the treatment of adults with the disorder can be answered by available meta-analyses. The identification of clinically relevant questions covered and not covered by meta-analyses can help to plan future clinical trials and meta-analyses in this field, and in addition can provide evidence-based information for treatment recommendations.

Methods

Relevant publications were identified by searching the PubMed and Cochrane databases using the following search keywords: "ADHD" and ["pharmacotherapy" or "stimulants" or "antidepressant" or "atomoxetine" or "modafinil" or "alpha-2 agonists" or "psychosocial" or "psychotherapy" or "school based intervention" or "behavioral therapy" or "cognitive therapy" or "cognitive training" or "complementary therapy" or "alternative therapy"]. No limit for date was set. The matches were restricted to publication type, and only reviews were retrieved. This search resulted in 191 titles. Abstracts for those 191 titles were independently reviewed by two evaluators (authors FST and KMF). Articles were included in this systematic review if (1) they described the results of a meta-analysis for the treatment of ADHD, (2) at least 1 study included in the meta-analysis was conducted in the adult population (age older than 18 years), (3) the intervention tested was a drug or a psychosocial treatment, and (4) the article was available in the English language. If the authors were aware of any other studies fulfilling these criteria that were not retrieved using the search strategy, those were also included. Reviews of reference lists of all articles included were also performed.

Information of interest was extracted from the manuscript independently by 3 of the authors (FST, KMF, and TSM), and 1 of the authors (TSM) congregated all information that was collected. The following information was extracted: first author name and year of publication, number of studies included, total sample size, age of patients included, proportion of males, inclusions and exclusion criteria, interventions under comparison for the calculation of effect size (ES), duration of the trials included, sources and dates of search, overall quality of studies included, and main results in regard to ES for the main outcomes considered. When publication bias was identified (regularly using funnel plots), corrected ES was preferred. Evaluators were also instructed to make notes about other data they considered to be of clinical relevance or importance for the evaluation of the quality of the meta-analysis.

Results

We identified 8 studies that fulfilled inclusion criteria (see Tables 1–3 for an overview of the studies).

Three studies computed pooled effect sizes for the comparison of drugs with placebo[32–34] (Table 1), and 4 compared different drugs[35–38] (Table 2). Only 1 study covered psychosocial intervention[39] (Table 3), but this study has methodological problems and should be carefully considered. The main findings for these studies are described in the following sections and in Tables 1–3.

Stimulant medications for the treatment of adults with ADHD

The available meta-analyses consistently showed stimulants to significantly decrease ADHD symptoms on a short-term basis when compared to placebo with a medium to high ES (see Tables 1 and 2). For the direct comparison with placebo, ESs were 0.9 for methylphenidate,[32] 0.73 for mixed amphetamine salts,[36] 0.6 for dexamphetamine,[36] 0.8 for lisdexamphetamine extracted from a single study,[36] and 0.67 when stimulants were considered in general.[37] The use of higher doses was associated with larger effect size.[32] Proportion of respondents was used as an outcome only for one meta-analysis, which showed short-acting stimulants to reach an ES of 4.32, while long-acting stimulants performed significantly lower with an ES of 1.35.[35] This difference regarding ES for long- and short-acting stimulants was also found in another meta-analysis by Faraone and Glatt,[38] which found a nonsignificant statistical difference for the effect of short- versus long-acting stimulants (0.96 versus 0.73, respectively). Only one meta-analysis looked at the issue of adherence. Castells *et al*[36] compared the pooled effect of different amphetamine derivatives and found all of them to significantly decrease ADHD symptoms. However, only mixed amphetamine salts (MAS) increased retention to treatment.

Nonstimulant medications for the treatment of adults with ADHD

Significantly fewer meta-analytic data exist with regarding the effect of nonstimulant drugs (see Table 2 for an overview). Two meta-analyses computed the ES of nonstimulants as a group. One found nonstimulants to have a significant lower ES of 0.39 than that of stimulants (ES for short-acting stimulants was 0.96 and for long-acting stimulants was 0.73[11]). In the other meta-analysis, the ES of nonstimulants was 0.59 versus 0.67 of stimulants, but between-group differences were not tested.[37] Data on the effect of individual drugs are scarce, and pooled estimations are only available for bupropion. Three different studies computed the pooled ES for bupropion. All of them used response rate as the main outcome; 2 of these meta-analyses were based on the same 5 trials, but used different statistical methods and outcomes and found different results. Maneeton *et al*[33] found a pooled relative risk (RR) of 1.67, and Verbeeck *et al*[34] found an odds ratio (OR) of 2.42. In both cases, results favored bupropion over placebo. In Maneeton *et al*'s meta-analysis, the number needed to treat found for bupropion was 4.6, and the discontinuation rate due to adverse events was not higher for bupropion than that of placebo.[33] Peterson *et al*[35] used similar inclusion criteria for a systematic search of clinical trials but found only 3 of the 5 studies identified by the other 2 authors; for this study, pooled ES for bupropion was 1.87 for the comparison with placebo, and a RR of 2.24 was found favoring short-acting stimulants over bupropion. Some data about individual studies for other antidepressants were described in Verbeeck *et al*'s meta-analysis (Table 2),[34] but because only one study per drug was available, pooled estimation was not possible. No pooled estimation was identified for atomoxetine, alpha-2-agonists, modafinil, and other antidepressants.

Psychosocial interventions for the treatment of adults with ADHD

Only one meta-analysis was identified that computed the pooled ES for psychosocial interventions; however, this meta-analysis has important methodological problems.[39] The inclusion criteria for trials of psychosocial interventions are not clearly stated, but apparently noncontrolled trials were included, while for the estimation of the ES for pharmacological treatment, only controlled trials were admitted. The authors found an ES of 0.84 for cognitive behavioral therapy and 0.44 for pharmacotherapy, but the manuscript lacks a clear description about which outcome measures were considered for the ES estimation.

Discussion

We conducted a systematic review to identify meta-analyses about the treatment of adults with ADHD. We identified 8 meta-analyses that computed the ES of pharmacological and psychosocial interventions. Most data available were about stimulants; very little information about nonstimulants or psychosocial treatments was available.

Stimulants were consistently shown to decrease ADHD symptoms, and the ESs found were medium to high, independent of the stimulant drug considered. The highest ES was found for methylphenidate,[32] but no direct comparison between methylphenidate and other drugs is available. Short-acting stimulants were superior to long-acting stimulants.[35,38] Apart from stimulants, the only drug to have a pooled estimation calculated for its ES was bupropion.[33,35] Bupropion was inferior to stimulants. When the ES for all

Table 1. *Meta-analyses of trials testing drugs in comparison to placebo*

First author, year	N of studies included (participants)	Age range (% of boys)	Selection criteria	Intervention	Duration of trials included	Sources of search	Quality of studies included	Pooled effect-size (ES) for ADHD symptoms reduction with respective confidence interval and other relevant results about efficacy
Faraone *et al*, 2004[32]	6 (253)	Mean age varied from 27–40 y (43–100% male)	1) Randomized, double-blind placebo controlled 2) DSM-III, DSM-III-R, or DSM-IV diagnostic criteria 3) Presentation of means and SD for drug and placebo	Methylphenidate vs placebo	Not described	CINAHL, Cochrane Database, E-psyche, ERIC, MEDLINE, PubMed, Ovid, PreMEDLINE, Social Sciences Abstracts. (no limit for the year of publication)	Studies' quality was not systematically assessed.	ES 0.9 ($z = 4.3$, $P < 0.001$, CI not provided) Variability among studies was statistically significant. Larger ES significantly associated with physician ratings of outcome and use of higher doses.
Maneeton *et al*, 2011[33]	5 (349)	Mean age 35.53 y for bupropion and 37.03 for placebo group (61% were male).	1) Randomized, placebo controlled trials of bupropion 2) Adults (18 years old or more) 3) Diagnosis ADHD spectrum any subtype of attention-deficit hyperactivity disorder (attention-deficit disorder, hyperkinetic disorder, minimal brain dysfunction, minimal cerebral dysfunction or minor cerebral dysfunction), but only studies including DSMIV ADHD ended up being included; 4) One of the following outcome measures: ADHD rating scale score, response rate, overall discontinuation rate, or discontinuation rate due to adverse events.	Bupropion vs placebo	6–12 weeks	CINAHL, Cochrane Controlled Trials Register, EMBASE, MEDLINE, PsycINFO. (Until October 2010)	Acceptable. All studies lacked information about randomization and allocation methods.	Response rate for bupropion was significantly greater than that for placebo [RR of 1.67 (1.23–2.26), $I^2 = 17.4\%$)]. The pooled mean changes in ADHD scores were also greater for bupropion than for placebo [5.08 (3.13–7.03), $I^2 = 0\%$]. NNT was 4.6 (3.1–8.8). Discontinuation rate for bupropion was not significantly higher than for placebo [RR of 1.11 (0.71–1.72), $I^2 = 0\%$]. The pooled discontinuation rate due to adverse events was also not significantly higher for bupropion than for placebo [RR 0.87 (0.08–9.79), $I^2 = 48.6\%$].

Table 1. Continued

First author, year	N of studies included (participants)	Age range (% of boys)	Selection criteria	Intervention	Duration of trials included	Sources of search	Quality of studies included	Pooled effect-size (ES) for ADHD symptoms reduction with respective confidence interval and other relevant results about efficacy
Verbeeck *et al*, 2009[34]	5 (349)—only 5 studies with bupropion Those five studies are the same used by Maneeton *et al*[33] for their meta-analysis in 2011 (described in the row above).		1) Controlled trials comparing antidepressants or lithium with placebo* 2) Adults 3) Treatment of ADHD.	Bupropion vs placebo (For the meta-analysis only, bupropion vs placebo was considered, but the other three studies are described involving the use of lithium, paroxetine, and desipramine.)	5–12 weeks	The Cochrane Library (Central), PubMed, PsycINFO. (Until August 2008)	Acceptable. All studies lacked information about randomization and allocation methods.	Meta-analysis of 5 studies: Bupropion superior to placebo according to CGI [OR 2.42 (1.09–5.36)]. In the only one study with desipramine, it was associated with response in 68% of the patients versus 0% with placebo. An 8-week crossover design study comparing 40 mg methylphenidate and 1200 mg of lithium showed no differences between groups (48% for methylphenidate and 37% for lithium in the reduction of irritability, aggressive outbursts, antisocial behavior, anxiety, and depression). A 20-week study showed paroxetine to be as effective as placebo for the treatment of ADHD (response occurred in 64% of patients with dextroamphetamine, 44% with paroxetine+dextroamphetamine, 17% with paroxetine, and 16% with placebo).

*This is stated in the methodologies, but there is no placebo group described in one of the studies described, the one testing lithium.

ADHD = attention-deficit/hyperactivity disorder; CGI = Clinical Global Improvement Scale; DSMII, DSMIII, DMSIIIR, DSMIV = *Diagnostic and Statistical Manual of Mental Disorders*, 2nd, 3rd, 3rd rev., or 4th edition, respectively; ES = effect size; MAS = mixed amphetamine salts; OR = odds ratio; RR = relative risk; vs = versus; SD = standard Deviation; SR = standard release; y = years.

Table 2. *Meta-analyses of trials comparing different drugs for ADHD*

First author, year	N of studies included (participants)	Age range (% of boys)	Selection criteria	Intervention	Duration of trials included	Sources of search	Quality of studies included	Pooled effect-size (ES) for ADHD symptoms reduction with respective confidence interval and other relevant results about efficacy
Castells *et al*, 2011[36]	7 (1091)	Mean age 36.8 (35.1–41.2 y) (55% male)	1) Randomized controlled trials 2) Adults aged over 18 3) ADHD diagnosis by standardized criteria 4) Comparison of amphetamine derivatives against placebo or an active intervention 5) Primary outcome severity of ADHD symptoms 6) Secondary outcome other measures of efficacy and adverse events reports	Lisdexamphetamine vs MAS vs dextroamphetamines	Mean study length of 8.1 weeks (2–20 weeks)	CENTRAL, CINAHL, clinicaltrials.gov, EMBASE, PubMed, PsycINFO, UK Clinical Trials Gateway, and references obtained from articles and experts in the field (no limit for starting date, ending date February or March 2010)	Low to very low.	Amphetamines ES 0.72 (0.57–0.87), but did not improve retention in treatment and were associated with increased dropout due to adverse events (RR 3.03; CI: 1.52–6.05). ES for dexamphetamine 0.6 (0.2–1.0); ES for lisdexamphetamine based on a single study 0.8 (0.53–1.07); ES for MAS 0.73 (0.51–0.96) The three amphetamine derivatives investigated were all efficacious for reducing ADHD symptoms, but MAS also increased retention in treatment. Publication bias may have favored amphetamines ES.
Peterson *et al*, 2008[35]	22 (2203)	Mean age 38 y (95% male)	1) English language 2) Randomized placebo controlled trials 3) Adult population	Short-acting stimulants vs long-acting stimulants vs nonstimulants (atomoxetine, bupropion)	2–13 weeks	Cochrane Central Register Trials (first quarter 2007); Cochrane Database of Systematic Reviews (first quarter 2007), Drug@FDA, EMBASE (second quarter 2004), MEDLINE (1966 to March week 3, 2007), PsycINFO, reference lists.	All but 1 study lacked information about randomization and allocation methods. Reasons for exclusion frequently not reported. All studies double blinded.	ES based on proportion of respondents (defined differently across studies, most commonly ≥30% symptoms improvement). ES for short-acting stimulants 4.32 (3.03–6.16); long-acting 1.35 (1.00–1.84); bupropion 1.87 (1.36–2.58). Data for atomoxetine not available. Significant heterogeneity for long-acting stimulants. Short-acting stimulants superior to bupropion (RR 2.24, CI 2.23–4.08) and long-acting stimulants (RR 3.26, CI 2.03–5.22). No evidence of publication bias.
Mészáros *et al*, 2009[37]	12 (1991)	Mean age 39.3 y for drug and 37.7 y for placebo (drug 58.6%; placebo 57.8%)	1) Double-blind placebo controlled trials (cross-over design data were extracted from the period before the crossover) 2) Short term (≤12 weeks) 3) English language	Stimulants vs nonstimulants (atomoxetine, bupropion, desipramine)	4–10 weeks	MEDLINE, PubMed (1994–2070)	Studies' quality was not systematically assessed.	ES for stimulants 0.67 (0.36–0.97); ES for nonstimulants 0.59 (0.37–0.81). Significance of differences found was not tested. No significant effect of publication bias. No mention is made about tests for heterogeneity.

Table 2. Continued

First author, year	N of studies included (participants)	Age range (% of boys)	Selection criteria	Intervention	Duration of trials included	Sources of search	Quality of studies included	Pooled effect-size (ES) for ADHD symptoms reduction with respective confidence interval and other relevant results about efficacy
Faraone and Glatt, 2010[38]	18 (not described)	Mean age 38 for N-St, 38 for SA-St and 36 for LA-St (proportion of male 63, 55, and 55%)	1) Randomized, double blind, placebo controlled methodology 2) DSM-III, DSM-IIIR, or DSM-IV ADHD 3) 2 weeks or more 4) Presented means and SDs Excluded if: 1) Less than 20 subjects per group 2) Explored appropriate dose for future work 3) Sample recruitment based on comorbid condition	Short-acting stimulants vs long-acting stimulants vs non-stimulants (ABT-418; atomoxetine, modafinil, bupropion, paroxetine)	Not described	CINAHL, Cochrane Database, e-psyche, ERIC, MEDLINE, PreMEDLINE, PubMed, Social Sciences Abstracts, APA, and AACAP meetings. (1979–ending date not provided)	Studies' quality was not systematically assessed, but influence of studies characteristics on ES estimation were estimated.	ES for long-acting stimulants 0.73, no significant heterogeneity; short-acting stimulants 0.96, significant heterogeneity; nonstimulants 0.39, no significant heterogeneity (CIs not provided). No evidence of publication bias for the nonstimulants or long acting stimulants, evidence of publication bias for short-acting stimulants. Corrected ES for short-acting stimulants 0.86. ESs of nonstimulants were significant lower than those for long- and short-acting stimulants. After correction for studies' characteristics that were significantly biasing studies' results, the stimulants continued to be superior to nonstimulants, but differences between short- and long-acting stimulants disappeared.

AACAP = American Academy of Child and Adolescence Psychiatry; ADHD = attention-deficit/hyperactivity disorder; APA = American Psychiatric Association; CI = confidence interval; DSMII, DSMIII, DMSIIIR, DSMIV = *Diagnostic and Statistical Manual of Mental Disorders*, 2nd, 3rd, 3rd rev., or 4th edition, respectively; ES = effect size; LA-St = long-acting stimulants; MAS = mixed amphetamine salts; RR = relative risk; vs = versus; SA-St = short-acting stimulants; SR = standard release; y = years.

Table 3. *Meta-analysis of trials comparing psychosocial interventions and pharmacotherapy for the treatment of ADHD*

First author, year	N of studies included (participants)	Age range (% of boys)	Selection criteria	Intervention	Duration of trials included	Sources of search	Quality of studies included	Pooled effect-size (ES) for ADHD symptoms reduction with respective confidence interval and other relevant results about efficacy
Linderkamp and Lauth, 2011[39]	Psychotherapy: 12 Medication: 43	Mean age 31–46 (for psychotherapy studies, not provided for other studies)	For psychotherapy trials not clearly stated, but noncontrolled trials were included. For pharmacotherapy studies, only controlled trials were included.	Cognitive behavioral therapy Pharmacotherapy (atomoxetine, bupropion, methylphenidate, and mixed amphetamine salts).	4 weeks to 1 year.	Google Scholar literature databases, PsycINFO, Psych Index. (Until first quarter 2011)	Not systematically assessed.	Outcomes for ES estimation are not provided. ES for psychotherapy 0.84 (0.64–1.04) ES for Pharmacotherapy 0.44 (0.37–0.5) Because of a series of methodological problems, the results for this meta-analysis should be parsimoniously considered.

ADHD = attention-deficit/hyperactivity disorder; ES = effect size.

nonstimulants as a group was compared to stimulants, nonstimulants performed significantly lower.[37,38] The only study to compute the pooled ES for psychosocial intervention has limitations, and no definitive conclusion can be drawn from its data.[39]

It must be highlighted that meta-analyses have several limitations. Most importantly, they rely on available clinical trials, and the methodology used by each author may vary markedly. For this reason, the ESs reported in this manuscript should not be interpreted as unequivocal, and, most importantly, they are not comparable between each other. Values of ES should be interpreted under the context of the methodology used in each specific meta-analysis. A good example was described in this review, in which two different meta-analyses computed the ES of bupropion based on the same 5 clinical trials and found different values.[33,34] The quality of studies included and the outcomes measures can also lead to distorted results. If the ES is computed based on a pre–post treatment comparison, it is more likely to overestimate the power of the intervention than ESs that are calculated based on the comparison with a passive control group. ES based in passive control groups, however, is likely to be overestimated when compared to that coming from studies that used active control groups. The dose of medication used in the trials included also has to be considered; when trials using low doses of medication are included, there will be an obvious tendency to report lower ESs.

The results presented here show a concerning lack of meta-analytic data to answer a number of important clinical questions.

First, the mean age range for almost all meta-analyses was between 35 and 45 years, and consequently no conclusions can be drawn with regarding the treatment response of older adults and the elderly population. Although there is limited information on the prevalence of ADHD among the elderly, a recent, well conducted epidemiological study from the Netherlands revealed a prevalence of 2.8% for the full-blown syndrome, but a higher prevalence of 4.2% when symptomatic cases not fulfilling criteria were considered.[40] These data suggest that a large population of sufferers is being disregarded in clinical trials with better methodology. It is important to note that these are the ones included in meta-analyses.

Second, although 2 meta-analyses provide the ES for nonstimulants as a group, pooled estimations of the ES for most drugs individually are not available. It is worth mentioning that there is no pooled estimation for atomoxetine, a drug that is recommended as first-line treatment in different guidelines and with a number of clinical trials already available.[25] It is important to note that the computation of the ES for

nonstimulants as a group is of reduced clinical relevance, since nonstimulants make reference to a very heterogeneous group of drugs without shared pharmacological properties, and consequently have very different effects with no expected similar efficacy.

Third, most meta-analyses have used mean scores from ADHD rating scales for the estimation of ES. The field has progressed in recent years, as researchers have become much more interested in functional outcomes than simply in reduction of symptom scores.[41] It would be interesting to have more information about other important outcomes, such as academic and occupational functioning, interpersonal relationships, and reduction in accidents.

Fourth, most trials included in the meta-analyses were short and lacked information about adherence. Adherence to treatment is a very relevant issue, because naturalistic studies have shown that persistence for drug treatment with stimulants is not the rule. More than 50% of patients quit stimulants after 90 days of treatment, and treatment maintenance for more than 180 days is unusual.[42–44] Of particular interest is the issue of adherence to long- versus short-acting stimulants. Long-acting drugs are more expensive, and different guidelines suggest that their prescription would increase adherence due to their better once-a-day posology. Adherence has only been analyzed as an outcome for the ES estimation in one meta-analysis. This meta-analysis, however, did not compare long- to short-acting drugs, but instead, it compared different amphetamine derivatives (MAS, lisdexamphetamine, and dextroamphetamine).[36] Also of note is the tendency for higher ESs for short- versus long-acting formulations (although this was not statistically significant in one of the meta-analyses). This finding is surprising, since short-acting and long-acting stimulants are pharmacologically identical, with the only difference being pharmacokinetic properties favoring long-acting stimulants. In the meta-analysis Faraone *et al*,[32] however, there is some evidence that the superiority found for short-acting drugs may have been caused by publication bias.[36] After correcting for study characteristics that were significantly biasing the studies' results, differences between short- and long-acting stimulants disappeared.[36]

Finally, of major concern is the lack of meta-analytic data about psychosocial treatments. Psychosocial treatments are routinely prescribed for ADHD patients in an attempt to reduce psychosocial problems related to symptoms. For the pediatric population, there are at least 7 meta-analyses on this topic.[16–22] One natural explanation for the lack of such adequate meta-analysis is the reduced number of trials. Although coming from a single trial, one encouraging finding in the field comes from a randomized clinical trial showing significantly reduced ADHD scores for adults using a combination of medication and CBT.[45] However, it is important to bear in mind that Linderkamp and Lauth[39] included both controlled and uncontrolled trials and identified only 12 studies in their meta-analysis. Nevertheless, the use of meta-analytic methods to evaluate the efficacy of psychosocial interventions is questionable because interventions in this field are markedly heterogeneous, making it difficult to interpret the results of pooled estimations.[20]

Conclusion

Although the literature about child and adolescent ADHD is extensive, less data exist about adult ADHD. Very few meta-analyses have assessed pharmacological interventions for adults with ADHD, and we identified only one meta-analysis that evaluated psychosocial interventions. Results from meta-analyses suggest that stimulants are effective in decreasing ADHD symptoms on a short-term basis with a medium to large ES. Short-acting stimulants might be superior to long-acting stimulants, but no data on difference in adherence are available for the comparison of these two types of formulations. Bupropion is superior to placebo, but is less effective than stimulants. No pooled estimations are available for other drugs. No conclusions about the impact of psychosocial interventions can be drawn based on the meta-analytic data. There are no meta-analysis showing the effectiveness of some intervention whose effectiveness has been clearly demonstrated in clinical trials. This fact is concerning, and should be addressed in future research.

Disclosures

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