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REVIEW

Long-term efficacy and safety of treatment with stimulants and atomoxetine in adult ADHD: A review of controlled and naturalistic studies

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Abstract
Attention-deficit/hyperactivity disorder (ADHD) is a common disorder of childhood that often persists into adulthood. Although stimulant medications are recommended as the first-line treatment for ADHD because of their documented short-term effects in children and adults, less is known about their effects on long-term outcome in adults. Here we review the long-term efficacy and safety of the stimulant drugs methylphenidate and amphetamine, as well as the related compound atomoxetine. We performed a systematic review to identify direct and indirect effects of stimulant therapy on long-term outcome in adults. Five randomized controlled trials (RCTs), and 10 open-label extension studies of initial short-term RCTs, with total follow-up of at least 24 weeks, were identified. All these RCTs found that medication was significantly more efficacious than placebo in treating ADHD in adults, and the extension studies showed that this favorable effect of medication was maintained during the open-label follow-up period. However, since the maximum duration of these pharmacological trials was 4 years, we also reviewed 18 defined naturalistic longitudinal and cross-sectional studies, to provide more information about longer term functional outcomes, side effects and complications. These observational studies also showed positive correlations between early recognition of the disorder, stimulant treatment during childhood and favorable long-term outcome in adult ADHD patients. In conclusion, stimulant therapy of ADHD has long-term beneficial effects and is well tolerated. However, more longitudinal studies of long duration should be performed. In addition, the ethical issues involved in performing double blind RCTs of many years duration should be further explored.

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Contents

1. Introduction

Although attention-deficit hyperactivity disorder (ADHD) for some time was considered a childhood condition, evidence accumulated during the past decades has shown that this disorder often persists into adulthood and is associated with long-term impairments and suffering (Kooij et al., 2010). The estimated prevalence of ADHD in adults is around 3–5% (De Graaf et al., 2008; Fayyad et al., 2007; Kessler et al., 2006; Kooij et al., 2005). Although stimulant medications are recommended as the first-line treatment in ADHD (Seixas et al., 2012), little is known about their effects on long-term outcome, including mortality, symptom levels, occupational performance or quality of life. Until recently, most treatment studies had examined children and adolescents, and had typically been of a few weeks duration. However, study designs in this field are gradually changing, with more studies reporting long-term outcomes, evaluating the effects of comorbidity and using a wider spectrum of outcome measures (Hodgkins et al., 2011). Ultimately, the treatment goal for ADHD, whether initiated during childhood or adulthood should be, not only temporary symptom relief, but also the establishment of a more favorable long-term developmental trajectory.

The primary objective of our study was to perform a systematic review of published long-term treatment trials of adult ADHD patients with either stimulant medications or atomoxetine. We included studies of at least 24 weeks duration, using either prospective or retrospective designs. In addition, we discuss some general methodological challenges encountered in pharmacologic studies of ADHD (Hazell, 2011), identify some important knowledge gaps, and list recommendations for future investigations.

2. Experimental procedures

We performed a systematic search using the following electronic databases: National Library of Medicine Pubmed site, EMBASE and PsycINFO of articles published prior to the 31 January 2012. Citations from identified articles were searched for relevant studies.

We retrieved a total of 3127 articles using multiple combinations of the search terms: ADHD (attention-deficit hyperactivity disorder), trial, clinical trial, long-term, effectiveness, effect, efficacy, outcome, outcomes, occupational outcome, work status, functional, functions, medications, treatment, stimulants, psychostimulants, methylphenidate, (dex)amphetamine, and atomoxetine. By restricting the search to papers published in English on human subjects aged 18 years or older at the time of evaluation and excluding reviews, the number of hits was reduced to 533. Based on the information provided in the abstracts of these articles, we selected only studies with a childhood onset of ADHD or hyperkinetic disorder. For ADHD diagnoses, we required use of DSM-IV, DSM-IV-R, (American Psychiatric Association, 1994, 2000), DSM-III, DSM-III-R (American Psychiatric Association, 1980, 1987; Hechtman et al., 1984), or Utah Criteria (Wender et al., 2011). For hyperkinetic disorder diagnoses we required ICD-10 criteria (World Health Organization, 1993).

Only studies performed on a primary patient sample with a sufficiently large sample size (≥30 subjects) were included. The reviewed studies comprise five randomized controlled trials (RCTs) with durations of 24 weeks or longer (Table 1), and 10 open-label extensions of initial RCTs of a shorter duration (Table 2). There are few RCTs with durations more than 12 weeks (Faraone and Glatt, 2010; Torgersen et al., 2008), and the usual definition of ''intermediate to long-term treatment'' comprises studies of 24 weeks or more (Rosler et al., 2010). Due to the limited information available from published RCTs (few patients, few outcome measures and limited study durations) we also included open-label studies with a prospective follow-up methodology and with a defined medication titration schedule (Table 2). Additional studies of medication treatment with a naturalistic or retrospective design were included if they expanded the duration of treatment or the outcome measures relevant to be evaluated (18 studies, see Supplementary Table 1). We required the outcome measures to be clinically relevant, such as ADHD symptoms, features of mental health or comorbidity, measures of social functions or occupational status and tolerability. Some studies of growth, substance use and cardiovascular risk outcomes were not captured by our review strategy because many of these relied on child, rather than adult samples. We decided to supplement our review with a non-systematic discussion of these studies because these issues are of much interest to clinicians. For these areas, we relied on recent systematic reviews of growth and substance use outcomes and on recent pivotal studies of cardiovascular risk. Studies focusing on specific features such as driving skills, neurocognitive measures, or neuroimaging were not included. A limited number of reviews concerning general topics, such as childhood ADHD, basic pharmacology and methodology are also cited.

3. Results

3.1. Study design

We found five double blind randomized controlled studies (RCTs) treating ADHD adults with stimulants or atomoxetine for 24 weeks or more (Table 1). Additionally, 10 studies reported initial short-term randomized RCTs, followed by an open-label extension for a total duration of 24 weeks or longer (Table 2). We also found 18 treatment studies with naturalistic longitudinal or cross-sectional designs that met our inclusion criteria (Supplementary Table 1). Most of the articles found were open-label treatment studies of adults, but some studies followed adolescents into young adulthood (Biederman et al., 2006; Hechtman, 1985; Powers et al., 2008). Only a few extension studies from initial RCTs provided data for treatment- periods longer than 2 years duration (Adler et al., 2008; Marchant et al., 2011). Some follow-up and retrospectively designed studies assessed patients after 2–13 years of treatment (Barkley et al., 2003; Biederman et al., 2008; Gjervan et al., 2011; Halmoy et al., 2009; Powers et al., 2008). However, due to limitations in study designs, data from such studies should be interpreted cautiously.

3.2. Location of studies and sample size

Ten of 15 (67%) of the RCTs and open-label extension studies and 13 of 18 (72%) of the naturalistic and other studies were performed in the United States of America (USA). The other studies were conducted in Canada (Weiss et al., 2010) and European countries, i.e. Germany (Rosler et al., 2009, 2010), Denmark (Powell et al., 2011), The Netherlands (Buitelaar et al., 2011), Sweden (Bejerot et al., 2010; Ginsberg and Lindefors, 2012) and Norway (Gjervan et al., 2011; Halmoy et al., 2009). The numbers of subjects enrolled in these studies varied between 30 (Ginsberg and Lindefors, 2012) and 725 (Weiss et al., 2010), except for three recent large retrospective cohort studies on the cardiovascular safety of treatment with stimulants, which included hundreds of thousands of person years of children and adults using ADHD drugs (Cooper et al., 2011; Schelleman et al., 2012; Habel et. al., 2011).

3.3. Efficacy measures

All randomized controlled trials (RCTs) and extensions of RCTs used an investigator-rated and/or patient-rated ADHD symptom rating scale and most studies used additional scales. The following investigator-rated ADHD symptom scales were used: the Adult ADHD Investigator Symptom Rating Scale (AISRS) (18 items) (Adler et al., 2009a; Biederman et al., 2010a), the Wender–Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) (Rosler et al., 2009, 2010), the Conners Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv: SV) (Adler et al., 2009a; Young et al., 2011), and the ADHD-Rating Scale IV (ADHD-RS-IV) (Ginsberg et al., 2011). The following self-rating ADHD symptom scales were used: the Conners Adult ADHD rating scale self-report long form CAARS-S:L (Rosler et al., 2009, 2010), and the Adult ADHD Self-Report Scale, 18 items (ASRSv1.1) (Adler et al., 2009b).

The most widely used investigator rated assessment for overall severity and improvement was one of three clinician-rated Clinical Global Impression scales (CGIs): CGI-Severity, CGI-Improvement, and the Clinical Global Impressions-ADHD-Severity of Illness (CGI-ADHD-S) (Adler et al., 2009a). Physician ratings on the Global Assessment of Symptoms and Functioning (GAS and GAF), the Sheehan Disability Scale (SDS) and self-ratings on the Social Adjustment Scale–Self-Report (SAS-SR) were used to evaluate functional outcomes (Adler et al., 2008; Buitelaar et al., 2012; Marchant et al., 2010). Health Related Quality of Life (HRQL) measures in use were the Adult ADHD Quality of Life Measure (AAQoL) (Adler et al., 2009a, 2011) and the Short Form-36 Health Survey version 2 (SF-36v.2) (Ware, 2007; Weiss et al., 2010). Non-ADHD psychopathology was assessed with several scales including the clinician-rated Hamilton depression Scales (17 items) for depression and anxiety (Biederman et al., 2010a; Hamilton, 1959; 1960) and self-ratings on the Symptom Checklist-90-Revised (SCL-90-R) (Biederman et al., 2010b; Derogatis and Cleary, 1977; Rosler et al., 2010).

3.4. Efficacy in long-term studies

3.4.1. Methylphenidate

We found eight long-term RCT and RCT-extension studies of methylphenidate (MPH) (Adler et al., 2009b; Biederman et al., 2010a; Buitelaar et al., 2011; Ginsberg and Lindefors, 2012; Marchant et al., 2010; Rosler et al., 2009, 2010; Wender et al., 2011). Most of the RCT and RCT-extension studies examined

Table 1 Randomized double blinded placebo-controlled trials with at least 24 weeks duration.

Author	Sample	Medication/dose	Duration of study	Measures	Results[a]
Rosler et al. (2009)	*N*=363, MPH ER *n*=241 Placebo *n*=118 (parallel group design) Male 50% ADHD (DSM-IV). (38% previous stimulant treatment) Adults[b]; mean age 35.2±10.1 (MPH ER group)	MPH ER (methylphenidate extended release) (50% MPH IR and 50% MPH ER) Titrated b.i.d. (interval 6–8 h.) first 5 weeks to max. 60 mg/d. Mean daily dose 41.2±18.2 mg at week 24 (0.55 ±0.27 mg/kg body weight)	24 weeks (titration periods 5 weeks and maintenance—phase of 19 weeks)	*Primary outcome*: response-definition: 30% reduction WRAADDS score *Secondary outcome*: CAARS-S:L (DATS) (DSM-IV ADHD symptoms total subscale) (self-report) Overall severity: CGI	61% responders receiving MPH ER, 42% responder in the Placebo group (p=0.001) CAARS-DATS: symptom decrease superior for MPH ER vs. placebo group (p=0.016) Much or very much improved on CGI (CGI <=2); 55% MPH ER vs. 37% in placebo ($p<0.05$) Completers (69%). Premature termination *n*=110 of 359 (31%); 24% MPH ER vs. 43% placebo ($p<0.001$) Adverse events: 13% MPH ER vs. 8% placebo
Rosler et al. (2010)	Secondary analysis of trial described above	Same as above	Same as above	*Primary outcome*: WRAADDS; reduction EDS (Emotional Dysregulation Scale, observer rated, 10 items from) CAARS-S:L; reduction ELS (self-rated six items construct of Emotional Dysregulation Scale) SCL-90-R assessing comorbid psychopathology	MPH-ER superior to placebo reducing emotional symptoms on EDS and ELS, significant from week 5, Cohen's *d* effect size 0.3 (p=0.006) CAARS-S:L ELS: significant reduction, effect size 0.29 (Cohen's *d*) superior to placebo SCL-90-R; OCD-symptoms and self-concept problems declined more in the MPH-ER group (effect size 0.3, p=0.01). Anxiety, depression, anger and hostility, phobia, paranoid ideations and psychoticism were not improved
Biederman et al. (2010a)	Phase 1, *N*=227 randomized OROS MPH *n*=109 (placebo *n*=114) and phase 2, *n*=96; phase 3, *n*=23 Parallel group three phases design ADHD	OROS MPH Mean dosage MPH at phase 1, 78.4±31.7 mg/d (0.97±0.32 mg/kg body weight)	34 weeks study Phase 1; 6-week efficacy trial (*n*=223). Phase 2; 24-week double-blind continuation by responders randomized to OROS MPH (*n*=62) and placebo (*n*=34)	*Primary outcome*: CGI-improvement scale (CGI-I): much or very much approved (CGI-I≤2), and AISRS reduction of larger than 30% Hamilton Depression Scale (17 items) Relapse definition: worsening	Phase 1; OROS MPH group 62% (*n*=67) responders vs. placebo responders 37% (*n*=41) ($p<0.001$) Phase 2; rate of completers did not differ, but OROS MPH responders were more likely to drop because

Table 1 (*continued*)

Author	Sample	Medication/dose	Duration of study	Measures	Results[a]
	(DSM-IV-TR) Male 40 % (OROS MPH group) Adults mean age 34.7±9.25 years (in OROS MPH group)		Phase 3; 4-week double-blind placebo-controlled discontinuation study for MPH responders in phase 2 (OROS MPH *n*=12, placebo *n*=11)	of the phase 1 endpoint CGI-I score of 2 or higher, or improvement from baseline fell below 15% on AISRS score for two consecutive visits	of the adverse effects, and placebo responders because of loss of effect. Phase 3; OROS MPH responders who completed phase 2, randomized for a 4-week, placebo controlled discontinuation. The time by treatment interaction for AISRS was statistically significant (p= 0.009), but not any difference in relapse-rate. Relapse-rate did not differ (18% in both groups). Maintenance of response did not differ. Completers phase 1; no difference between groups, MPH *n*=86, 79% and placebo *n*= 98, 86%. Premature termination by adverse events: *n*=13, 11% MPH ER vs. 3% placebo ($p<0.01$).
Adler et al. (2009a)	*N*=501 randomized to ATX *n*=250 and placebo *n*=251 ADHD (DSM-IV) 72% combined subtype Male 50% adult; mean age 37.6 years	ATX once-daily, morning-dosed Titration steps minimum 7 days, 25 mg–40 mg–80 mg–100 mg/d	6 months	*Primary outcome*: AISRS reduction from baseline *Secondary outcome*: CAARS-Inv:SV CGI scale of ADHD severity ASRSv1.1 (18 items) Adult ADHD Quality of Life Scale (AAQoL) Safety and tolerability; vital signs and adverse events	Mean AISRS total scores for ATX decreased from 38.2 (7.5) at baseline to 21.4 (12.3) at the 6-month end point Placebo from 38.6 (7.0) to 25.8 (13.2) (p = 0.035). AISRS total score, CAARS-Inv:SV index total score, CGI-ADHD-S, and AAQoL, ATX was statistically superior to placebo at the 10-week and 6-month time points Completers: *n*=94 (38%) patients of 250 randomized to ATX *n*=112 (45%) of 250 patients randomized to placebo completed the study

Table 1 (*continued*)

Author	Sample	Medication/dose	Duration of study	Measures	Results[a]
Young et al. (2011)	*N*=502, ATX *n*=268 Placebo *n*=234 Male 51% (ADHD) DSM-IV-TR 67% combined subtype, 33% inattentive adult; mean age 41.2±6.9 years ATX group	ATX (atomoxetine) once-daily (QD), morning-dosed (2-week: on-label titration; 40 mg for 3 days, then 80 mg, or slow titration; 40 mg for 7 days then 80 mg titration). After 24 weeks, PBO patients were rerandomized to either ATX titration strategy	24 weeks	*Primary outcome:* CAARS-Inv:SV Response-definition: 25% decrease on CAARS-Inv:SV *Secondary outcome:* CGI-ADHD-S MADRS State-Trait Anxiety Inventory General and titration safety measures and tolerability	CAARS-Inv:SV total score reduction was greater with ATX over PBO at 12 weeks (−14.33 vs. −10.05; $p < 0.001$) and 24 weeks (−16.43 vs. −8.65; $p < 0.001$; effect size, 0.57) Response: greater for ATX (68%) than PBO (42%; $p < 0.001$) at 24 weeks CGI-ADHD-S improvement for ATX over PBO at 8- and 24-weeks ($p < 0.001$; effect sizes, 0.45 and 0.46, respectively) No significant changes in depressive or anxiety measures Discontinuation due to an adverse event was greater for on-label vs. slow titration, rate of patients experiencing adverse events were similar. Common adverse events included dry mouth, nausea, and decreased appetite (Supplementary Table 2)

ADHD, attention deficit/hyperactivity disorder; AE, adverse events; ATX, atomoxetine; AAQoL, Adult ADHD Quality Of Life Scale; AISRS, The Adult ADHD Investigator Symptom Rating Scale; ASRSv1.1, The Adult ADHD Self-Report Scale version 1.1; CAARS, The Conners' Adult ADHD Rating Scale-Self-Report; -S:L, long; version; -Inv:SV, investigator rated: screening version; DATS, DSM-IV ADHD symptoms total subscale; EDS, Emotional Dysregulation Scale; ELS, Emotional Lability Scale; CGI, The Clinical Global Impression Scale; I, investigator rated; CGI-ADHD-S, CGI scale of ADHD severity; DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders-version IV; TR, text revised; MADRS, Montgomery-Aasberg Depression Rating Scale; MPH, methylphenidate; IR, immediate release; ER, extended release; OROS, osmotic release oral system; OCD, obsessive compulsive disorder; PBO, placebo; SCL-90-R, The Symptom Checklist-90-Revised; WRAADDS, The Wender-Reimherr Adult Attention Deficit Disorder Scale; EDS, Emotional Dysregulation Scale; ELS, Emotional Lability Scale

[a]Side effects are specified in the Supplementary Table 2.

[b]Adults: age ≥ 18 years.

slow release formulations: MPH extended release (MPH ER) or the osmotic release oral system (OROS MPH). Except for a single study using the dextrorotatory enantiomer of MPH, dexmethylphenidate (d-MPH) (Adler et al., 2009b), a mixture of L- and D-threo MPH was used in all studies, including one study of immediate release MPH (MPH IR) (Wender et al., 2011). Details about the samples, study design, measures and outcomes are presented in Tables 1 and 2 and Supplementary Tables 1 and 2.

All the reviewed RCTs found beneficial effects of the active compounds, with statistically significant reductions in both ADHD symptoms and overall clinician rated severity (CGI). In one study, improvements in emotional dysregulation and comorbid psychopathology were statistically

Table 2 Studies with randomized double blinded placebo-controlled start and open-label extension.

Study objective	Sample	Medication	Measures	Duration of treatment	Results	Side effects and safety
Methylphenidate						
Ginsberg and Lindefors (2012) Evaluate OROS MPH in adult male prison inmates	*N*=30 male long-term prison inmates with ADHD (DSM-IV-TR) in open-label phase Adults[a], mean age 33.5 years (95% CI, 26.7–40.2 years)	OROS MPH Titrated up to 72 mg/d during first 5 weeks, flexible dose open label extension; not exceeding 1.3 mg/kg body weight Mean dosage at the end of week 52; 105 mg/d (1.2 mg/kg)	Change in CAARS-O:SV ASRS-CGI-S Global assessment of functioning (GAF)	52-weeks (including 5-weeks RCT, and 47-weeks open-label extension)	Improved ADHD symptoms ($p<0.001$; Cohen's *d* effect size, 2.17) Response (30% decrease of CAARS-O:SV at week 5); 87% responded to OROS MPH compared with 0% for placebo; Number needed to treat (NNT) was 1.1 (95% CI: 1–2). ASRS, CGI and GAF improved during open-label extension. All completed open-label phase.	Adverse effects n.s. No significant changes in systolic or diastolic blood pressure (BP), heart rate or body weight initial 5 weeks 52-weeks study, systolic BP in the MPH group increased by 21.5 mm Hg (95% confidence interval (CI): 8.9–34.0) and diastolic BP by 11.0 mm Hg (95% CI: 4.9–17.1) Heart rate increased by 13.2 beats/min (95% CI: 7.0–19.4) from baseline in the group initially placebo
Buitelaar et al. (2011) Evaluate long-term treatment and maintenance of effect of OROS MPH after withdrawal	*N*=156 open phase, withdrawal phase *n*=45 ADHD (DSM-IV) Male 54% adults, mean age 35.0±10.6 (SD) years; range 18–64 years	OROS MPH Mean dose 64.0±23.3 mg/d (0.75 mg/kg body weight)	CAARS:O-SV and CGI-S CAARS-S SDS (Sheehan Disability Scale)	52 weeks and 4-week withdrawal phase after 52 weeks treatment (initial 5 week RCT, *n*=401)	Open-label phase (*n*=156), mean CAARS:O-SV score decreased 1.9±7.8 ($p<0.01$) from baseline, small statistically significant improvements observed for CAARS-S, CGI-S and SDS In the double-blind withdrawal phase: OROS-MPH (*n*=23), placebo (*n*=22), CAARS:O-SV increased from double-blind baseline in the OROS MPH and placebo arms (4.0±7.6 vs. 6.5±7.8, NS) Completers : 63% (*n*=99) Short-term effects of OROS-MPH continued during long-term treatment	Long-term OROS-MPH treatment was well tolerated No evidence of withdrawal or rebound after discontinuation Vital signs and ECG did not differ from baseline. *n*=2 cases of hypertension in treatment with DBP>90 mm Hg

Marchant et al., 2010 Reexamine findings from RCT for long-term significance	*N*=34 (of 41 in RCT, 47 baseline) ADHD (DSM-IV-TR) Male 65% Adults, mean age 31.5±11.6 years	OROS-MPH, dosage (65% of responders ≤54 mg/d)	WRAADDS Defined sub-groups; (ADHD) alone, emotional dys-regulation (ADHD+ED), and plus oppositional defiant disorder (ODD). ADHD-Rating Scale (ADHD-RS). Personality disorder (PD)	6-months follow-up	Maintained improvement on all three WRAADDS-defined dimensions; attention+ disorganization by 61%, hyperactivity-+impulsivity by 60%, emotional dysregulation 66% for all subgroups ADHD+ED+ODD group showed most long-term improvement on social mal adjustment PD patients were less likely to complete or show improvement Responders in cross-over double-blind phase: 56% Completers of open-label phase: 44% (*n*=18)	No significant differences between baseline and long-term evaluation of vital signs as blood pressure and heart rate and QTc intervals in the electrocardiogram (ECG) Most occurring AE: insomnia, decreased appetite, and anxiety; but no patients discontinued as result
Wender et al. (2011) Determine effects of long-term MPH treatment on symptom severity and social adjustment	*N*=116 ADHD "Utah Criteria" Male72% Adults, mean age 36.9±8.5 years	Immediate release MPH (IR MPH) vs. placebo	Response: 50% reduction of observer rated WRAADDS Clinical Global Impression of Improvement (CGI-I), GAF, the Work and Social Adjustment Scale (WSAS)	Initial RCT, followed by 12-month open-label extension for responders	In the double blind trial more subjects in IR-MPH group responded (74%) vs. placebo (21%) (p=0.01) During open-label trial, symptom severity decreased 80% from baseline WSAS decreased >50% in all subscales indicating improvement Average GAF improved significantly (p<0.0001) Completers: 73% (*n*=57) Adults who responded, improved markedly in long-term treatment in ADHD symptoms and psychosocial functioning	No serious AE
Adler et al. (2009a) Evaluate long-term efficacy and safety of d-MPH-ER	*N*=170 ADHD (DSM-IV), baseline score ADHD-RS≥18 and GAF≤60 Male 61.8% Adults, mean age 39.0±10.8 years; range 18–59 years	Dex-MPH extended release (d-MPH ER) RCT phase with fixed-dose 20–40 mg/d, open label extension phase with flexible dosing	ADHD-RS Proportion of responders on CGI-IA dverse events (AE)	7 months treatment; 5-week RCT followed by 6-month open-label extension (OLE)	60% completed (*N*=103) OLE (102 evaluable) Mean improvement on ADHD-RS (−10.2) switching from placebo to d-MPH-ER (*n*=20), and (−8.4) for they who maintained on d-MPH-ER (*N*=82) Respective CGI-I responder rates were 95.0% and 95.1% Once-daily d-MPH-ER evaluated safe and effective for long-term treatment	Most common AE (>15%): headache, insomnia, decreased appetiteNo serious AE

Table 2 (*continued*)

Study objective	Sample	Medication	Measures	Duration of treatment	Results	Side effects and safety
Amphetamine						
Biederman et al. (2005) Assess the long-term safety and effectiveness of MAS XR	*N*=223 ADHD combined subtype (DSM-IV-TR) Male 59.3% Adults, mean age 39.8±11.5 years	MAS XR Forced-dose-escalation study Start 20 mg/d for week 1, subsequent titration up to 60 mg/d optimum effect	Safety assessments included reported adverse events, laboratory assessments, and monitoring of vital signs ADHD-RS-IV	24-months Extension of a 4-week, multicenter RCT with parallel-group design	ADHD symptoms significantly improved for all subjects as measured by change from baseline in mean ADHD-RS-IV total scores (−7.2±13.04 unit points; $p<0.001$); this was sustained for up to 24 months Treatment with MAS XR 20–60 mg/day for adult ADHD was generally well tolerated and was associated with sustained symptomatic improvement for up to 24 months	Most AEs were of mild to moderate intensity Most common treatment-related AEs (reported at least one occurrence) were dry mouth (43%), infection (33%), insomnia (32%), anorexia/decreased appetite (32%), headache (30%), and nervousness (26%)
Weisler et al. (2005) Assess long-term cardiovascular effects MAS XR	Same sample as cited above	MAS XR Start 20 mg/d for week 1, subsequent titration up to 60 mg/d optimum effect	Resting DBP and systolic BP, and pulse at baseline, and weekly, then monthly ECG, weekly, at 3-, 6- and 12-months	Up to 24 months duration	Mean change in diastolic BP (1.3±9.2 mm Hg; $p=0.042$) , systolic BP (2.3±12.5 mm Hg; $p=0.006$) and pulse (2.1±13.4 bpm; $p=0.019$) were smallOn ECG, QTc (corrected by Bazett's formula) increased 7.2 ms ($p<0.001$) observed at 24 months. No subjects exhibit QTc interval above 480 ms. Cardiovascular effects were minimal in otherwise healthy adults with ADHD Vital signs should be monitored prior to and during treatment	*n*=7 discontinued due to a cardiovascular adverse event; hypertension *n*=5, palpitation/tachycardia *n*=2 Borderline baseline values of vital signs exhibit shift to abnormal values during therapy
Ginsberg et al. (2011) Examine impact of baseline severity on LDX efficacy	*N*=345 ADHD (DSM-IV-TR) Male 54% Adults; range 18–55 years, 10.6% >50 years	Lisdexamphetamine dimesylate (LDX) Dosage 30–70 mg/day; dose-optimization study; mean dose 56.1 mg/d (moderately severity group), (57.1 mg/d in CGI-*S*=6 group)	*Response:* ADHD Rating Scale IV (ADHD-RS-IV) decrease 30% from baseline *Remission:* ADHD-RS-IV score≤18 CGI-S; post hoc stratification of severity (CGI-S) in analysis; moderately (4), markedly or (5) severely (6)	13 months including 4-week RCT and 12-month open-label extension	Clinical response according to stratification of severity (CGI-S = 4, 5, and ≥6, respectively): 79%, 84%, and 88% Symptomatic remission criteria by 64%, 65%, and 72% Increased mean change of ADHD symptoms with greater baseline symptom severity (5,6) ($p<0.0001$), rate of response and met remission criteria by larger proportion Completers: 55% (*n*=158 discontinued).	AE : upper respiratory tract infection (21.8%), insomnia (19.5%), headache (17.2%). dry mouth (16.6%), decreased appetite (14.3%), irritability (11.2%) No serious AE

Atomoxetine						
Adler et al. (2005) Interim report on study of ATX, effectiveness	*N*=384 ADHD (DSM-IV) Male 64% Adult, mean age 42.4±11.2 years Prior stimulant exposure: 47%	Atomoxetine (ATX) Individual flexible dose (50–160 mg/d)	The primary efficacy measure: CAARS-Inv:SV total ADHD symptom score In addition, safety, adverse events, and vital sign assessed	3 years up to 97 weeks	Significant improvement on ATX, mean CAARS-Inv:SV total ADHD symptom scores decreasing 33.2% from 29.2 (baseline of open-label therapy) to 19.5 (endpoint of open-label therapy) ($p < 0.001$) Significant decreases were noted for the secondary efficacy measures The results support the long-term efficacy, safety, and tolerability of ATX for the treatment of adult ADHD	AEs primarily of pharmacologically (noradrenergic) expected effects, increases in heart rate and blood pressure, a slight decrease in weight
Adler et al. (2008) Long-term efficacy and safety of treatment on atomoxetine	*N*=125 ADHD (DSM-IV) Sample derived from the study of 384 patients cited above Male 64% Adult, mean age 42.4±11.2 years	ATX Individual flexible dose (stepwise titrated); range 50–160 mg/d	Change of CAARS-Inv:SV Total ADHD Symptom scores Sheehan Disability Scale	4 years follow up Results from 125 patients remaining in the open-label trial since the interim report at 97 weeks up to 221 weeks of treatment	CAARS-Inv: SV Total ADHD Symptom scores decreased 30.2% (− 8.8, $p < 0.001$) during treatment Significant decreases for the secondary efficacy measures, including the Sheehan Disability ScaleTotal score, improved 25.3% ($p < 0.001$) Completers: 18% (*N*=69)	AEs consisted primarily of pharmacologically (noradrenergic) expected effects Cardiovascular measures not clinically significant Discontinuation rate due to adverse events at week 97 (from baseline): 10.9%, and at 221 weeks 12.2%

AAQoL, Adult ADHD Quality Of Life Scale; ADHD, attention deficit/hyperactivity disorder; AE, adverse events; AISRS, The Adult ADHD Investigator Symptom Rating Scale; ASRS, The Adult ADHD Self-Report Scale; v1.1, version 1.1; ATX, atomoxetine; Bpm, beats pr minute; BP, blood pressure; DBP, diastolic blood pressure, SBP, systolic blood pressure; CAARS, The Conners' Adult ADHD Rating Scale-Self-Report; -O:SV, Observer: Short Version; -S, self-report; -Inv:SV, investigator rated: screening version; -S:L, long. version; -Inv:SV, ; DATS, DSM-IV ADHD symptoms total subscale; EDS, Emotional Dysregulation Scale; ELS, Emotional Lability Scale; CGI, The Clinical Global Impression Scale; I, investigator rated; CGI-ADHD-S, CGI scale of ADHD severity; DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders—version IV; TR, text revised; ECG, electrocardiogram; ED, emotional dysregulation; GAF, global assessment of functioning; HR, heart rate; LDX, lisdexamphetamine dimesylate; MADRS, Montgomery-Aasberg Depression Rating Scale; MAS XR, mixed amphetamine salts extended release; MPH, methylphenidate; IR, immediate release; ER, extended release; OROS, osmotic release oral system; d-MPH, dex-methylphenidate; n.s., non-significant; ODD, oppositional defiant disorder; OLE, open label extension; PBO, placebo; PD, personality disorder; RCT, randomized double blinded placebo-controlled trial; SCL-90-R, The Symptom Checklist-90-Revised; SD, standard deviation; SDS, Sheehan Disability Scale; WRAADDS, The Wender-Reimherr Adult Attention Deficit Disorder Scale; WSAS, The Work and Social Adjustment Scale

[a]Adults: age ≥18 years.

superior to placebo (Rosler et al., 2010); significant improvements in HRQL-measures were also reported in one study (Adler et al., 2009b).

A 24-week RCT of low-dose MPH ER included 363 ADHD adults (Rosler et al., 2009). After titration to a mean daily dose of 41 mg, the response rate was 61%, compared to 42% in the placebo group ($p<0.001$). This yields a number needed to treat (NNT) statistic of 6, which indicates that six patients need to be treated to achieve one medication associated positive response. In a secondary analysis of the same trial, MPH ER was significantly superior to placebo in reducing associated emotional symptoms (Rosler et al., 2010).

Another large RCT of OROS MPH used a three-stage design, where medication was first titrated to optimal response (mean dosage MPH 78 mg/d), and only responders from the placebo and treatment groups continued on their placebo or medication through the 24-week continuation phase (Biederman et al., 2010a). The rates of completion through phase 1 were similar for MPH (79%) and placebo (86%), but the termination by adverse events was higher for the treatment (11%) vs. placebo group (3%; $p<0.01$). In phase 2, while OROS MPH responders were more likely to drop out of the study due to adverse effects, the placebo responders were more likely to drop out due to loss of efficacy. Finally, OROS MPH responders who completed phase 2 were randomized to a 4-week RCT discontinuation of medication. Although there was no difference in relapse rate (18% in both groups), the placebo group showed a statistically significant worsening of symptoms on the AISRS ($p=0.009$).

Efficacy studies have mainly been performed in Psychiatric Outpatient Departments, but a recent 52-week combined RCT and open-label extension study (Ginsberg and Lindefors, 2012) evaluated the efficacy of OROS MPH in a sample of 30 adult male long-term prison inmates (mean dosage MPH 105 mg/d). It defined response as a 30% decrease of assessor rated ADHD symptoms at the end of the RCT phase (week 5). The authors reported a markedly higher response rate in the MPH group (87%) compared with placebo (0%), corresponding to an NNT of 1.1. The other ADHD symptom and functional outcome measures (ASRS, CGI-S ADHD and GAF) also improved significantly during the open-label extension with large effect sizes (Cohen's *d* 1.67, 2.36 and 1.62, respectively). The unusually low placebo response rate may have been due to the use of a prisoner sample.

A multiple phase study of OROS MPH (Buitelaar et al., 2011) started with a 5-week RCT phase ($N=401$) (Medori et al., 2008), followed by an open-label study of 52 weeks ($N=156$), and a 4-week withdrawal phase. Using a mean dosage of 64 mg/d, small but statistically significant reductions in ADHD symptoms and functional impairments were observed using both investigator-rated and self-rated CAARS scales, the CGI-S and the SDS. During the double-blind, 4-week withdrawal phase after the 52-week open treatment phase, investigator rated ADHD symptoms increased from baseline in both the OROS MPH and placebo arms, and the group difference was not statistically significant. However, the short-term effects of OROS-MPH continued during long-term open-label treatment, and the medication was well tolerated.

An open-label extension study of OROS MPH (Marchant et al., 2010) reexamined findings from a previously reported RCT (Reimherr et al., 2007) for long-term significance ($N=34$ of 41 completing the RCT, $N=47$ baseline). Over 80% of the patients in the sample had ADHD with emotional dysregulation or oppositional defiant symptoms. Patients with the highest level of social maladjustment at baseline demonstrated the best long-term improvement on three WRAADDS defined dimensions of attention and disorganization, hyperactivity and impulsivity, and emotional dysregulation. About 64% of responders were on moderate doses of OROS MPH (mean dosage 60 mg/d).

Wender et al. (2011) published a 12-month open-label extension of an initial RCT of immediate release MPH ($N=116$). In the RCT phase of the trial more subjects responded in the MPH group than in the placebo group (74% vs. 21%, $p=0.01$). Only participants who showed a reduction of 50% or more on the WRAADDS in the initial RCT were enrolled in the open-label extension. At the end of the open-label phase, ADHD symptom severity decreased by 80%, the score on the Weissman Social Adjustment Scale decreased $>50\%$ from baseline, and the average GAF score improved significantly ($p<0.0001$). Those who responded in the short term to MPH IR also reported significant long-term improvements in ADHD symptoms and psychosocial functioning.

Adler et al. (2009b) studied an extended release formulation of dexmethylphenidate (d-MPH-ER) in 170 adults with ADHD. A 5-week RCT phase of fixed dose d-MPH-ER (20-40 mg/d) was followed by a 6-month open-label extension with a flexible dose regime to assess long-term efficacy and safety. The CGI-I defined responder rate was high: 95% for those switching from placebo to d-MPH-ER and 95% for those maintained on d-MPH-ER. However, the drop-out rate was also high.

3.4.2. Amphetamine

We found no RCTs with amphetamine meeting our long-term criteria (duration 24 weeks or more). A few long-term RCT-extension studies have been published using lisdexamphetamine (LDX) (Ginsberg et al., 2011) and mixed amphetamine salts extended release (MAS XR) (Biederman et al. 2005; Weisler et al. 2005). We also found one naturalistic study of dexamphetamine (DEX) (Bejerot et al. 2010) (Table 2 and Supplementary Table 1). Several naturalistic studies included amphetamines in the broader group of central stimulants (Supplementary Table 1). The small number of amphetamine studies and the use of different formulations make it difficult to generalize from the findings. With that caveat in mind, all the reviewed studies noted beneficial effects of amphetamine, which was well tolerated and associated with sustained symptomatic improvement for up to 24 months, with statistically significant changes in outcome measures.

A 12-month open-label extension of a 4-week RCT study (Ginsberg et al., 2011) examined the impact of baseline severity on the efficacy of lisdexamphetamine dimesylate (LDX) ($N=345$). Response was defined as an ADHD-RS-IV decrease of at least 30% from baseline, and remission as an ADHD-RS-IV score less than 18. Analyses based on a post hoc stratification of investigator rated overall severity

(CGI-S) demonstrated increased symptom improvement (clinical response-criteria met ranging from 79%–88%), and symptomatic remission (64%–72%) with greater baseline symptom severity.

In a naturalistic study, Weiss et al. (2010) evaluated the effectiveness of MAS XR in adult ADHD patients (N=725) by examining moderators and mediators of symptoms and quality of life outcomes (Supplementary Table 1). After 8 months of treatment, patients reported robust and enduring symptom relief (ADHD-RS-IV change, Cohen's d effect size varying between 1.5 and 2.3). Characteristics such as young age, female gender, more severe illness, and treatment-naive status predicted a greater improvement in ADHD-RS-IV scores. Symptom change and satisfaction with medication independently mediated changes in mental but not physical quality of life outcomes. There was no time lag between changes in symptoms and improved quality of life. Self-reported attention problems were a stronger mediator of ADHD-specific quality of life outcomes than disruptive behavior.

Biederman et al. (2005) studied the long-term effects of MAS XR in a sample of adults with the combined subtype of ADHD (N=223) (Table 2). At the end of a 24-week open-label extension of an initial 4-week double-blind, forced-dose-escalation (with titration up to 60 mg/d) placebo-controlled phase, ADHD symptoms improved significantly for all subjects and this improvement was sustained for 24 months.

3.4.3. Atomoxetine

We found five studies of atomoxetine treatment for adults with ADHD: two intermediate- to long-term RCTs (Adler et al., 2009a; Young et al., 2011) (Table 1), and three long-term open-label RCT extension studies (Adler et al., 2005; Adler et al., 2008; Marchant et al., 2011) (Table 2). The two RCTs used large samples: N=501 (Adler et al., 2009a) and N=502 (Young et al., 2011). Both demonstrated superior efficacy on the primary outcome measures for their treatment groups compared to their placebo groups.

Adler et al. (2009a) started dose-titration at 25 mg/d and proceeded up to 100 mg/d if tolerated. All the outcome measures (the AISRS total score, CAARS-Inv: SV evening index total score, CGI ADHD-S, and AAQoL total score) demonstrated changes in favor of the atomoxetine group at the 10-week and 6-month evaluations. At the 6-month end point, the mean AISRS total scores for the atomoxetine group decreased more (−16.8) than for the placebo group (−12.8; Cohen's d effect size, 0.31, p=0.035). They found rates of completion of 38% for atomoxetine and 45% for placebo. Although not statistically significant different, the low rate of completion in the atomoxetine group may have been related to the higher rate of adverse effects in that group. The authors suggested that the large placebo-effect in this trial could be related to sample bias, where motivated patients were willing to be treated with placebo for an extended period.

The other long-term RCT of atomoxetine treatment (N=234) also used once daily medication, but compared the tolerability of initiating treatment with atomoxetine as a standard titration (on-label) vs. using a slower titration strategy (Young et al., 2011). Improvement as measured by the CAARS-Inv: SV total score was greater for atomoxetine compared with placebo at 12 weeks and 24 weeks (Cohen's d effect size, 0.57, $p<0.001$, see Table 1). At 24 weeks, the response rate was greater for atomoxetine (68%) compared with placebo (42%; $p<0.001$). This yields an NNT of 4. On the CGI-ADHD-S, improvement was greater for atomoxetine over placebo at 8 and 24 weeks (Cohen's d effect sizes, 0.45 and 0.46, respectively). There were no significant changes in depressive or anxiety measures. Discontinuation was more frequent for on-label vs. slow titration due to adverse events, although the rates of patients experiencing adverse events were comparable.

In a 4-year follow-up study (Adler et al., 2008) of an initial larger RCT of 536 patients randomly assigned to treatment with atomoxetine or placebo (Michelson et al., 2003), a subsample of patients were enrolled in an open-label extension treatment study (N=384). At 97 weeks, 259 patients (67%) had discontinued (Adler et al., 2005). At the endpoint of up to 221 weeks of treatment 125 patients remained in study; 82% had discontinued. For those who remained, the CAARS-Inv: SV Total ADHD symptom score decreased by 30% from baseline during treatment. Significant decreases were also observed for the secondary efficacy measures; CAARS-Inv: SV subscales, CAARSA-Self: SF, CGI-ADHD-S, WRAADDS and the Sheehan Disability Scale Total score, which improved by 25% ($p<.001$).

A more recent long-term study of the efficacy of atomoxetine (N=384 of 536 from the prior RCT) used individualized flexible dosing (50–160 mg/d) (Marchant et al., 2011). After 6 months, 61% attained an average dose of 100 mg/day. Responders from the previous double-blind phase achieved a maximum response after 8 weeks of open-label medication, but others continued to improve up to 36 weeks. Women improved more than men on the WRAADDS (p=0.007) and the CAARS (p=0.03). Responders improved 60% in attentional, hyperactive/impulsive, and emotional symptoms. Among atomoxetine non-responders in the double-blind phase 39% became responders during open-label atomoxetine treatment, indicating a later onset of effect for these subjects.

3.5. Long-term studies of functional outcomes

Assessment of functional outcomes in RCT studies is based mainly on patient or clinician rated measures of functioning according to standardized scales. The natural course of ADHD is associated with unfavorable educational and occupational outcomes and increased risk of developing secondary problems, including substance abuse, psychiatric comorbidity and legal/criminal problems. Such indirect outcomes typically evolve gradually over years, making them less easily quantifiable at specific time points, and more challenging to include as variables even in long-term RCTs. Other study designs are thus useful to inform us about the potential outcome of treatment on important functional areas across the life-span (see Supplementary Table 1 for a summary of naturalistic and observational studies).

In their prospective follow-up from 1984, Hechtman et al. found that young hyperactive boys treated with stimulants (for at least 3 years) showed a better outcome in several areas of life (better self-esteem, less accidents and delinquency) than hyperactive youths with ADHD who did not

receive sustained treatment with stimulants. In contrast, no differences were found in educational or occupational achievement (Hechtman et al., 1984). Two other follow-up studies with comparable designs found that treated children with ADHD had better academic achievement (Powers et al., 2008) and were less likely to have repeated a grade compared to their counterparts who had not received treatment with stimulants (Biederman et al., 2009).

Occupational outcome has been less studied than education and school-performance, since studies of ADHD in adulthood have appeared more recently in the literature than studies of ADHD in childhood and adolescence. The effect of treatment on occupational functioning has, however, been the focus of some cross-sectional/retrospective studies of clinically diagnosed adults with ADHD (Gjervan et al., 2011; Halmoy et al., 2009). These studies report a positive correlation between employment status and treatment with stimulants, both current and past. Interestingly, treatment with stimulants in childhood was the strongest predictor for being employed as an adult (OR=3.2, p=0.014) (Halmoy et al., 2009) and older age of treatment initiation was associated with poorer occupational outcomes (Gjervan et al., 2011) even after adjusting for ADHD symptom severity and psychiatric comorbidity. The authors noted that the observed correlation also could reflect a more general beneficial effect of early recognition and intervention. However, their cross-sectional/retrospective design makes it difficult to infer causal relationships between treatment and outcome.

The risk of criminality is increased in children with ADHD growing up, independent of comorbid conduct disorder in childhood. Hechtman et al. (1984) found a reduced risk of later delinquency among treated compared to non-treated children with ADHD followed to young adulthood (see above, Supplementary Table 1). Ginsberg and Lindefors (2012) recently showed that stimulant treatment was as effective in reducing ADHD symptoms among prison inmates with ADHD as for adults with ADHD in general. There is, however, still a need for follow-up studies of this population to assess whether ADHD symptom reduction reduces the risk of later criminal behavior.

3.6. Tolerability, adverse effects and safety

3.6.1. Methylphenidate

The basic pharmacology of psychostimulants and atomoxetine is well established, and the adverse effects reported during systematic trials of these drugs can largely be predicted from their effect on central and peripheral catecholaminergic neurotransmitter systems (Kuczenski and Segal, 1975). Side effects seen in the RCTs are summarized in Supplementary Table 2. All included MPH trials reported a higher prevalence of decreased appetite and mucosal dryness in groups receiving active treatment compared to placebo. Most studies also found changes in cardiovascular parameters associated with receiving active treatment.

In a 24-week RCT study of MPH ER (Rosler et al., 2009), tolerability and safety were assessed both by spontaneously reported adverse events and by use of a manual for the assessment and documentation of psychopathology, the 40 item AMDP-system (Guy and Ban, 1982). This study reported a transient increase in heart rate at 4 weeks that was not significant at 24 weeks. It found no change in mean body weight between the groups. Most adverse events were reported during the titration phase, by week 4, and a global assessment of tolerability at week 24 noted ''good'' and ''very good'' tolerability, with small differences between the MPH-ER group (n=241) and the placebo group (n=118) (79.3% vs. 89.7%).

In another long-term RCT (Biederman et al., 2010a), discontinuation due to adverse events was higher for the OROS MPH group (11% vs. 3%; $p<0.01$) during the 24-week continuation phase. During that phase, OROS MPH responders were more likely to drop out of the study due to adverse effects. Decreased appetite, insomnia, being tense/jittery, mucosal dryness, and some neurological symptoms were statistically significantly more frequent in the OROS-MPH treatment group, and decreased appetite, insomnia, and mucosal dryness were associated with OROS-MPH treatment during phase 2 (Supplementary Table 2), but not during phase 3 (small sample). Like the aforementioned study, there were no reports of death or serious adverse effects in this study.

In a large (N=550), 1 year, prospective open-label study of OROS MPH (Adler et al., 2011), only 44% completed 12 months of treatment, with the most common adverse events being a mean weight decrease, decreased appetite, headache, and insomnia. There were small mean increases in several cardiovascular parameters, but no serious adverse events or clinically significant changes in electrocardiogram (ECG) or laboratory values. Similarly, in a long-term study of treatment with d-MPH-ER the most common adverse events were headache, insomnia, and decreased appetite (Adler et al., 2009b).

In a recent 52-week combined RCT and open-label extension study of OROS MPH in prison inmates (Ginsberg and Lindefors, 2012), the authors found no statistically significant drug-placebo differences in the proportions of adverse effects during the initial 5-week RCT, including changes in systolic blood pressure, diastolic blood pressure, heart rate and body weight. However, at the end of the 47-week open-label MPH treatment period, they reported increases in the following cardiovascular parameters: systolic blood pressure of 21.5 mm Hg in the OROS MPH group, vs. 6.3 mm Hg in the placebo group, diastolic blood pressure of 11.0 mm Hg vs. 0.5 mm Hg, and heart rate of 4.6 beats/min vs. 13.2 in the placebo group.

In their naturalistic follow-up study of 86 MPH treated patients and 47 DEX treated patients, Bejerot et al. (2010) reported an increased heart rate from 70 to 80 beats/min (p=0.00003) while blood pressure remained unchanged at the $\geq$2-year follow-up. No severe side effects or drug abuse was detected.

3.6.2. Amphetamines

Long-term use of amphetamines reveals similar side effects as with MPH. Two treatment studies mainly focused on the long-term safety and tolerability of amphetamines (Biederman et al., 2005; Weisler et al., 2005) (Table 2). The first study addressed the long-term cardiovascular effects of MAS XR (n=223) (Weisler et al., 2005). Patients with ADHD

were titrated with MAS XR from 20 mg/d for 1 week, with subsequent steps up to 60 mg/d to obtain an optimal effect. Safety assessments included spontaneously reported adverse events, laboratory assessments, and monitoring of vital signs. After 24 months, small, but significant changes in cardiovascular parameters were observed. The most common treatment-related adverse events were dry mouth, infection, insomnia, anorexia/decreased appetite, headache, and nervousness (Biederman et al., 2005).

Similar findings were reported from a 12-month open-label extension of a 4-week RCT study of LDX efficacy (Ginsberg et al., 2011) (N=345 adults) (Table 2). They found LDX to be associated with insomnia, headaches, dry mouth, decreased appetite, and irritability, and also with more frequent upper respiratory tract infections (21.8%) which have not been reported in other stimulant or atomoxetine studies.

Another potential adverse effect of stimulant medication could be the exacerbation or emergence of psychopathology. In contrast to this prediction, one RCT reported greater reductions of obsessive-compulsive symptoms and self-concept problems in the MPH group compared to placebo, but no changes in anxiety, depression, anger and hostility, phobia, paranoid ideations and psychoticism (Rosler et al., 2010). Similarly, another study found no significant difference at endpoint between MPH and placebo for anxiety and depression scores (Biederman et al., 2010a) (Table 1). Some studies have reported increased nervousness, irritability and sleep disturbances as adverse events of stimulants (Adler et al., 2011; Biederman et al., 2005; Ginsberg et al., 2011) (Table 2 and Supplementary Table 1).

A naturalistic study assessed psychopathology over a 10-year follow-up (n=112) (Biederman et al., 2009) (Supplementary Table 1). It found no increased risk for depression or anxiety disorders due to the pharmacologic treatment of ADHD, but those previously treated with stimulants, were significantly less likely to develop depressive, anxiety and disruptive behavior disorders compared with subjects with ADHD not treated.

Few studies have examined the impact of stimulant pharmacotherapy for ADHD on sleep and sleep-disturbances in adults. In a 24-week RCT of OROS MPH Biederman et al. (2010a) reported a higher rate of insomnia in the treated group than the placebo group (19% vs. 3%). Young et al. (2011) found similar rates of insomnia (13% vs. 6%) at the 24-week end point of their RCT of atomoxetine (Supplementary Table 2). In contrast Rosler et al. (2009) and Adler et al. (2009a, 2009b) did not find any significant effects on sleep for MPH ER and atomoxetine, respectively. No long-term data were found for amphetamine products.

3.6.3. Atomoxetine

Although atomoxetine is not considered a stimulant, the drug has many similar side effects (Supplementary Table 2). Two long-term RCTs found a slight increase in blood pressure and heart rate during treatment with atomoxetine (Adler et al., 2009a; Young et al., 2011). At the 10-week time point in the study Adler et al. (2009a), diastolic blood pressure increased by 1.7 mm Hg for atomoxetine vs. 0.2 mm Hg for placebo, but the difference was not statistically significant at 6 months. However, heart rate increased by 3.8 beats/min for atomoxetine vs. 1.5 beats/min for placebo and was statistically significant at the 6-month end point. Dose titration started at 25 mg/d with titration up to 100 mg/d if tolerated. The rate of completion was 38% for the atomoxetine group and 45% for placebo. Discontinuations due to adverse events were 17.2% and 5.6% for atomoxetine and placebo, respectively (p=0.001). The following treatment-emergent adverse events (reported by at least 5% of patients) were significantly more common in the atomoxetine group at the 10-week time point: nausea, dry mouth, fatigue, decreased appetite, urinary hesitation, and erectile dysfunction. At the 6-month evaluation, these adverse events and dizziness were more frequent in the atomoxetine group (Adler et al., 2009a).

Young et al. (2011) found statistically significant increases of systolic blood pressure (supine positions; 2.6 for atomoxetine vs. 0.1 mm Hg for placebo, p=0.009), diastolic blood pressure (2.6 vs. 0.03 mm Hg; $p<0.001$), and heart rate (4.4 vs. −0.6 beats/min; $p<0.001$) at 24 weeks of treatment. This study also reported changes in ECG parameters (reduced PR interval; −3.7 vs. 1.4 ms, and elongated QTCB interval; 6.6 vs. 0.4 ms). One serious adverse event of atrial fibrillation and one of supraventricular tachycardia was reported in the sample of 266 patients. In this study of once daily medication, tolerability of two different dose-titration regimes was compared: the standard titration (on-label) vs. a slower titration strategy. They found no significant changes in depressive or anxiety measures, but discontinuation was more frequent for on-label vs. slow titration due to adverse events, although the rates of patients experiencing adverse events were similar. The most common adverse events were dry mouth, nausea, and decreased appetite (Young et al., 2011) (Supplementary Table 2).

In a 4-year follow-up study (Adler et al., 2008) of patients from an initial larger RCT, 125 patients remained in a subsequent open-label trial with up to 221 weeks of treatment. Heart rate slightly increased from baseline by 4.4 beats/min ($p>.001$), diastolic blood pressure increased 1.6 mm Hg (p=0.001), and systolic blood pressure increased 2.0 mm Hg (p=0.002). There were no clinically significant changes in QTcF (corrected QT interval by Fridericia's formulae) reported at the end-point time. Weight loss was statistically significant (mean change −0.94 kg, $p<0.001$).

3.7. Naturalistic studies of adverse effects

The present review also includes naturalistic studies addressing long-term effects of stimulant drug therapy that have not been investigated in the RCTs or RCT extension studies (Supplementary Table 1). A longstanding concern about stimulants' potential effects on growth in children and adolescents arose from their known anorexic effects. Consistent with this, all long-term RCTs found in our search reported decreased appetite in the treatment group (Table 1 and Supplementary Table 2).

Perhaps the most important clinical question about stimulants and growth is their effect on ultimate growth attained in adulthood. Klein and Mannuzza (1988) and Hechtman et al. (1984) found that individuals with ADHD who showed growth deficits while treated with stimulants as

children no longer showed such deficits as adults (Supplementary Table 1). Kramer et al. (2000) reported a prospective, long-term follow-up study of 97 adults between the ages of 21 and 23 years who had been treated clinically with MPH for an average of 36 months in childhood. Because these subjects did not differ in average height or weight from family, community, or un-medicated control, it seems reasonable to conclude that their MPH treatment in childhood did not lead to growth deficits in adulthood. Biederman et al. (2010b) reported naturalistic longitudinal data from 124 ADHD patients that had been followed from 10 to 11 years into adulthood. They found no differences in final adult height between ADHD patients who had and had not been treated with stimulants in childhood.

Several authors have found an increased proportion of substance use disorder co-morbid with ADHD in adults (Biederman et al., 2006; Gjervan et al., 2011; Halmoy et al., 2009). In a prospective follow-up study Biederman et al. (2008) reported no significant relation between stimulant treatment and alcohol, drug, or nicotine use disorders (Supplementary Table 1), even when the analyses adjusted for conduct disorder. Similar findings were reported in a retrospective study of 206 ADHD adults (Faraone et al., 2007a). This study showed a high degree of consistency across substances of abuse in finding no link between prior pharmacotherapy for ADHD and subsequent substance use disorders.

Two articles from one large epidemiological cohort study in the USA recently explored whether current use of stimulants and atomoxetine is associated with increased risk of serious cardiovascular events. One study of children and young adults (n=1,200,438 subjects, ages of 2–24 years) (Cooper et al., 2011), and another of young and middle-aged adult medication users (n=150,359, aged 25–64 years) (Habel et al., 2011) identified serious cardiovascular events (sudden cardiac death, acute myocardial infarction, and stroke) from health-plan data and vital records. End points were validated by medical record review. The child and young adult study evaluated 2,579,104 person-years of follow-up, including 373,667 person-years of current use of ADHD drugs. The adult study included 806,182 person-years of follow-up (median, 1.3 years per person).

In the 25–64 age group, the multivariate-adjusted rate ratio of serious cardiovascular events for current use vs. non-use of ADHD medications was lower than 1, possibly due to healthy-user bias (Habel et al., 2011). The adjusted risk ratio was lower (0.77) among new users of ADHD medications, which also can be attributed to healthy-user bias. Importantly, the risk of serious cardiovascular events was similar among patients receiving ADHD medications and controls not using these drugs. The adjusted risk ratio for current use vs. remote use was 1.03 (95% CI, 0.86–1.24); and for new use vs. remote use, 1.02 (95% CI, 0.82–1.28). These results suggest that ADHD medications are not associated with an increased risk for serious cardiovascular events.

Another large cohort study evaluated 43,999 new users of methylphenidate (MPH) based on administrative data from a five-state Medicaid database and a US 14-state commercial insurance database (Schelleman et al., 2012). The authors sought to determine whether the use of MPH in adults is associated with elevated rates of serious cardiovascular events compared with rates in 175,955 non-users. MPH users were matched on state, sex, and age to as many as four comparison non-user subjects. Events recorded were (1) sudden death or ventricular arrhythmia, (2) stroke, (3) myocardial infarction, and (4) a composite end point of stroke or myocardial infarction. The age-standardized incidence rate per 1000 person-years of sudden death or ventricular arrhythmia was 2.17 in MPH users and 0.98 in non-users, which yielded an adjusted hazard ratio of 1.84 (95% CI=1.33–2.55). Although these data suggest that MPH use increased the risk for sudden death or ventricular arrhythmia, the risk decreased with increasing dose, which weakened the inference that the observed association with stimulant medication was causal. There were no differences between MPH users and non-users for stroke, myocardial infarction, and the composite endpoint of stroke or myocardial infarction.

4. Discussion

4.1. Long-term treatment outcomes

Our review of long-term, follow-up studies of the pharmacologic treatment of ADHD adults presents an emerging literature that documents the long-term efficacy of ADHD medications in several ways. All the RCTs found that ADHD medications were significantly more efficacious than placebo. These significant differences favoring medication were maintained through the end of the follow-up period. Likewise, all the open label extension studies showed that the efficacy demonstrated during the acute placebo controlled phase was either maintained or improved during the follow-up period. Finally, some naturalistic studies suggest that the pharmacological treatment of ADHD youth does not exacerbate comorbid psychopathology and may reduce their subsequent risk for depression and substance use disorders.

Although these efficacy findings are reassuring, they are limited in several ways. Most notably, the evidence base is sparse, with only five RCTs, 11 open label extension studies and 15 naturalistic studies, and this small number of studies and diversity of study designs does not allow for a meta-analytic approach.

The long-term studies also show high rates of non-adherence to ADHD medications (Tables 1 and 2). If non-adherence is associated with poor efficacy, then long-term studies might overestimate the magnitude of long-term efficacy. For example, Bejerot et al. (2010) found that only 50% remained in treatment after 2 years; 15% dropped out because of lack of efficacy and the amount of clinical response over the first 6–9 months predicted adherence to treatment at the 2 year follow-up. This suggests that more work is needed to understand the implications of non-adherence in long-term studies of efficacy and to improve adherence among adults with ADHD.

Another concern is that placebo effects were fairly large with RCTs suggesting placebo response rates as high as 42%. Although high placebo response rates do not challenge the statistical significance of efficacy effects, they do limit the relative clinical efficacy as indicated in the NNT statistics, which suggest that between four and six patients need to be treated to achieve a good, medication-related, long-term treatment response. It is also notable that the long-term placebo response rates are much higher than short-term

placebo response rates. For example, in the studies reviewed by Faraone and Glatt (2010), short-term placebo response rates from stimulant studies of adult ADHD range from 7% to 39% with a mean of 24.7%. This suggests that there may be an incremental placebo effect with time, although more work is needed to evaluate this idea. Furthermore, although we have not performed any systematic analysis to search for possible publication bias, this cannot be excluded.

4.2. Side-effects and special concerns

Regarding adverse events, it is reassuring to know that the adverse events most commonly reported with long-term ADHD medication treatments are relatively minor (see Supplementary Table 2). It is also reassuring to know that long-term treatment does not markedly exacerbate or cause psychopathology, although there is some risk for increases in nervousness, irritability and sleep disturbance. A guideline group of the European Network for Hyperkinetic Disorders (EUNETHYDIS) have reviewed the literature on children and given guidelines on managing adverse effects of medication for ADHD that provides useful information on the long-term side effects in treated children and adolescents (Graham et al., 2011). Although the mechanism of action of stimulants has raised concerns about effects on growth, the cardiovascular system and substance abuse risk, these concerns have been mostly allayed by long term studies.

4.3. Effect on growth

Regarding growth, it is clear that stimulants given to growing children lead to delays in normal gains in height and weights, which either attenuates over time or reverse after discontinuation. A quantitative review by Faraone et al. (2008) showed that growth deficits are relatively larger in children compared with adolescents and that treatment cessation typically leads to a normalization of growth trajectories . Deficits in height and weight were also correlated, suggesting that failure to make expected height gains could be attributed to the lack of interest in eating and inadequate nutrition that contributes to weight loss (Faraone et al., 2008). If that is true, then it is possible that clinical strategies used to improve nutrition and encourage weight gain would reduce deficits in expected height, but no study directly examined this hypothesis. Thus, although the attainment of normal adult height is not compromised in naturalistic studies, physicians still need to monitor the growth of stimulant treated ADHD youth. In contrast, growth deficits have not been observed in studies of atomoxetine that prospectively followed children for up to 5 years (Donnelly et al., 2009; Spencer et al., 2007; Wilens et al., 2006).

4.4. Cardiac risk

Data from large population based studies (Cooper et al., 2011; Habel et al., 2011) could not demonstrate any increased risk for sudden death or ventricular arrhythmia with use of central stimulants. Schelleman et al. (2012) found initiation of MPH associated with a 1.8 fold risk in sudden death or ventricular arrhythmia; however lack of a dose–response relationship suggested this relation was not causal. Even though there is some variability in the reviewed studies, our review suggests that stimulants and atomoxetine are associated, on average, with only small elevations in blood pressure and heart rate. These medications should not be used with patients having pre-existing cardiac abnormalities, and cardiovascular parameters should be monitored in stimulant treated adults with ADHD, especially those with borderline abnormal cardiovascular signs.

4.5. Risk of substance use disorders

One well replicated fact about ADHD is that it predicts substance use disorders. This has been shown conclusively in a meta-analysis of prospective longitudinal studies of ADHD youth (Lee et al., 2011), and confirmed in cross-sectional studies of ADHD adults (Arias et al., 2008; Daigre Blanco et al., 2009; Faraone et al., 2007a, 2007b; Faraone and Wilens, 2007). Because stimulants are potentially abusable one important concern has been if long-term stimulant treatment could lead to substance use disorders. To clarify former contradictory findings from prospective, naturalistic follow-up studies, Wilens et al. (Faraone and Wilens, 2003; Wilens et al., 2003) conducted a meta-analysis and found that stimulant treated ADHD youth were 50% less likely to develop substance use disorders than ADHD youth that had not been treated. The authors concluded that, rather than causing substance use disorders, the evidence suggested that stimulant medications protect ADHD youth from developing substance use disorders. There were, however, differences when the authors stratified studies by those that followed children into adolescence and those that completed follow-up in adulthood. When analyses were limited to studies that followed children into adulthood, stimulant treated ADHD youth were only 1.4 times less likely to develop substance use disorders in adulthood compared with ADHD youth that had not been treated with stimulants. A retrospective study by Faraone demonstrated no link between prior pharmacotherapy for ADHD and subsequent substance use disorders (Faraone et al., 2007a).

We do not know why stimulant therapy protects against substance use disorders in adolescence, or why this protective effect disappears in adulthood. If the effect is mediated by symptom reduction, one possibility may be that the efficacy of stimulants seems to be higher for children than for adults, as seen if one compares medication effect sizes reported from meta-analyses of youth (Faraone and Buitelaar, 2010) and adults (Faraone and Glatt, 2010). Furthermore, due to parental monitoring, treatment compliance and hence efficacy are greater for youth than adults. Although the current literature is reassuring that treating ADHD with stimulants do not increase the risk for substance use disorders, clinicians should be alert to the serious problem of the misuse and diversion among ADHD adults, especially in the college population (Faraone and Wilens, 2007; Kaye and Darke, 2012; Wilens et al., 2008).

4.6. Conclusions and recommendations

The long-term goal of pharmacotherapy is to reduce the functional impairments associated with ADHD. Although the

relevant literature is small and primarily naturalistic, it suggests that the pharmacologic treatment of ADHD leads to higher educational levels and occupational status, better self-esteem, fewer accidents, and less delinquency. Although some studies find no long-term effects of medication on functional impairments, no studies suggest that pharmacologic treatment worsens impairments. Some negative findings are to be expected due to selection biases, the use of small samples and confounding of naturalistic studies. Because more severely affected individuals are overrepresented among treated patients, if appropriate statistical procedures are not implemented, naturalistic studies can erroneously conclude that treatment is ineffective or even worsens outcomes (Faraone et al., 1992; Kessler et al., 2005).

There are two main clinical implications from our review. First, clinicians can be confident in communicating to adult ADHD patients that, if they maintain treatment, their long-term prognosis is good, taking into account how ''long-term'' has been defined in our review. Second, they can be equally confident that the burden of adverse events is modest if subjects have been screened for pre-existing cardiac conditions. If clinicians are not achieving the positive outcome suggested by this review, they should determine if their dosing regimens are not in accord with what has been used in the outcome studies reviewed and also assess adherence to treatment before concluding about the degree of response for the individual patient.

The conclusions of our review should be interpreted in the context of several limitations of the studies we reviewed. Unlike short-term clinical trials, which typically focus on a narrow set of outcomes such as counts of ADHD symptoms, the long-term studies comprise a substantial diversity of outcome measures and study designs. This diversity does not allow for a meta-analytic approach, which would have been preferable. Moreover, several issues require further study. Importantly, no generally accepted definition exists for what is regarded as a long-term study, as this will obviously depend on the condition that is being treated. At a time when ADHD was considered a self-limiting developmental disorder of childhood, the need for studies of many years duration was difficult to imagine or fund. In the Multimodal Treatment of ADHD study, intermediate duration was defined as between 3 and 9 months and long-term effects were measured at 14 months and beyond (Molina et al., 2009; Swanson and Hechtman, 2005). Here, we adopted a practical compromise by including studies down to 24 weeks of duration. Otherwise, we would have been left with very little data. However, as recently accumulated knowledge has transformed our view of ADHD as more of a life-long condition, this knowledge gap has become more obvious. Thus, the time perspective for treatment studies of ADHD should be no different from studies on schizophrenia, diabetes mellitus or hypertension. In all these conditions, treatment effects should be studied for decades rather than months. Still, a recurrent theme in nearly all systematic reviews, within all therapeutic areas, performed by the Cochrane initiative is the shortage of long-term treatment data (www.Cochrane.org).

Optimally, all end points in RCTs of ADHD should be validated. However, at the current state, this appears not to be feasible. Concrete and simple outcome variables on large samples may be preferable to sophisticated psychological measures with unclear ecological validity. Thus, the information from prescription databases, linked to health registries, could give information on a sample size and time scale not feasible for conventional RCTs.

In many areas of medicine, the ethical issues involved in performing long-term RCTs are currently being discussed. Given the established efficacy and safety profile of ADHD medications, it is hard to imagine ethical committees approving the use of placebos for many years. That leaves us with open-label extensions and naturalistic studies, along with their concomitant biases and confounds. The Multimodal Treatment of ADHD study illustrates the difficulties in drawing causal inferences from such research designs. While the RCT period only lasted 14 months, additional outcomes from that study have been measured after 8 and 12 years. This has generated additional insights and, unfortunately, considerable confusion (Molina et al., 2009; Swanson and Hechtman, 2005).

In ADHD treatment, as well as in many other therapeutic areas, health economic perspectives on interventions are increasingly requested and discussed. It is expected that a treatment should contribute to a measurable increase in quality adjusted life years or other measures of long-term benefit. Few of the studies cited here contain such data or are suitable for calculation of such treatment effects. Another limitation of current long-term studies has been the focus on ADHD symptoms as a measure of efficacy. Although such data are essential, clinicians and patients are more concerned about the functional implications of drug treatment. Future work should incorporate more measures of functional impairment. It should also evaluate the degree to which the patient's symptoms and behavior have been optimized, rather than simply evaluating whether they have achieved an arbitrary response criterion. Expectations from both patients and clinicians are that treatment will be beneficial in terms of long-term outcome in important life domains, and that the risks associated with treatment will not exceed these benefits. Thus, the goal of ADHD treatment should be the remission of symptoms and impairments and new research protocols are urgently needed to address these goals (Ramos-Quiroga and Casas, 2011).

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Conflict of interest

Dr. Fredriksen has no financial relationship with any company whose products are mentioned in this paper, and nothing to disclose. In the past year, Dr. Faraone received consulting income and research support from Shire, Otsuka and Alcobra and research support from the National Institutes of Health (NIH). In previous years, he received consulting fees or was on Advisory Boards or participated in continuing medical education programs sponsored by Shire, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. Dr. Faraone receives royalties from books published by Guilford Press: Straight Talk

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Appendix A. Supporting information

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