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An update on the pharmacotherapy of attention-deficit/hyperactivity disorder in adults

Timothy E Wilens[1,2,†], **Nicholas R Morrison**[1], and **Jefferson Prince**[1,2,3]

[1]Clinical Research Program in Pediatric Psychopharmacology, Child Psychiatry Service, Massachusetts General Hospital, Boston, MA, USA

[2]Harvard Medical School, Cambridge, MA, USA

[3]North Shore Children's Hospital, Salem, MA, USA

Abstract

Adults with attention-deficit/hyperactivity disorder (ADHD) are more frequently presenting for diagnosis and treatment. Medication is considered to be appropriate among available treatments for ADHD; however, the evidence supporting the use of pharmacotherapeutics for adults with ADHD remains less established. In this article, the effectiveness and dosing parameters of the various agents investigated for adult ADHD are reviewed. In adults with ADHD, short-term improvements in symptomatology have been documented through the use of stimulants and antidepressants. Studies suggest that methylphenidate and amphetamine maintained an immediate onset of action, whereas the ADHD response to the nonstimulants appeared to be delayed. At a group level, there appears to be some, albeit not entirely consistent, dose-dependent responses to amphetamine and methylphenidate. Generally speaking, variability in diagnostic criteria, dosing parameters and response rates between the various studies was considerable, and most studies were of a relatively short duration. The aggregate literature shows that the stimulants and catecholaminergic nonstimulants investigated had a clinically significant beneficial effect on treating ADHD in adults.

Keywords

adult; amphetamine; antidepressants; atomoxetine; attention-deficit/hyperactivity disorder; methylphenidate; pharmacotherapy; stimulants

[†]Author for correspondence: Tel.: +1 617 726 1731, Fax: +1 617 724 3742, twilens@partners.org.

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Attention-deficit/hyperactivity disorder (ADHD; use in this article also refers to previous definitions of the disorder) is a prevalent disorder estimated to affect 3–9% of school age children and up to 5% of adults [1,2]. Historically, ADHD was not considered to continue beyond adolescence. However, long-term controlled follow-up studies have demonstrated the persistence of prominent symptoms and/or impairment in approximately 50% of young adults diagnosed with ADHD in childhood [3–7].

Compared to their non-ADHD peers, adults with ADHD have been reported to have more conflicts in social and marital relations, and underachievement in their careers, economic status and academics despite adequate intellectual abilities [3–7]. A bidirectional over-representation of comorbidity within ADHD has been reported, with adults with ADHD manifesting higher rates of anxiety, mood and substance abuse disorders than non-ADHD adults [8,9]. Conversely, adults with depression, bipolar and substance abuse disorders have been characterized as maintaining high rates of ADHD [10,11].

Longitudinally derived data in ADHD youth lifespan connote that whereas symptoms of hyperactivity and impulsivity decay over time, the symptoms of inattention persist [12,13]. In support of this, data derived from a large group of adults with ADHD indicate that whereas approximately 50% of adults display clinically significant levels of hyperactive/impulsive symptomatology, 90% display prominent attentional symptomatology [14,15]. More specifically, adults with ADHD evidence a variety of core attentional ADHD symptoms, including poor attention and concentration, easy distractibility, frequent shifting of activities, day dreaming and forgetfulness; followed more distantly by impulsivity, impatience, boredom, fidgeting and intrusiveness [15]. ADHD adults are considered to experience executive function deficits, such as a reduced ability to attend, encode and manipulate information, and difficulties with organization and time management [16], as well as deficits in emotional regulation [17].

Attention-deficit/hyperactivity disorder can be diagnosed in adults by carefully querying developmentally appropriate criteria from the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM IV) [18], regarding the childhood onset, persistence and current presence of these symptoms [19]. Adult self-report scales, such as the Adult Self-Report Scale, the Wender–Reimherr scale, Brown Attention-Deficit Disorder scale and Conners' rating scale may assist in diagnosing adults with ADHD [19]. It is important to set clear and realistic treatment goals with the adult and identify specific symptoms and problematic areas of functioning as targets of treatment. To aid in the diagnosis of ADHD in adults, clinicians should use the DSM IV Text Revision criteria and apply them in a developmentally appropriate manner. Clinicians may find it useful to employ self-report scales, including the Wender–Reimherr Adult Attention Deficit Disorder Rating Scale [20] and the Brown Adult ADHD Scale. In order to monitor treatment response, investigator scales exist, including the ADHD Rating Scale and the Conners' adult ADHD rating scale [19]. Additional therapies often compliment the effects of medication. As with children, college students and adults returning to school may benefit from additional educational supports. Coaching and organization training appear to be useful, but remain understudied [21]. Whereas traditional insight-oriented psychotherapies do not appear efficacious for ADHD [22], cognitive behavioral therapy that is adapted for adults with ADHD has been developed [23], with recent controlled data suggesting its efficacy in both individual [24] and group settings [25], when used alone or adjunctly with pharmacotherapy.

Over the course of the past two decades, the database on the safety, tolerability and efficacy of medications to treat adults with ADHD has expanded greatly. To date there are three

medication classes specifically US FDA approved for the treatment of ADHD in adults; atomoxetine (ATX), amphetamine (AMP) and methylphenidate (MPH).

Although medication therapy is well studied in treating ADHD in children, the use of pharmacotherapeutic agents for adults with ADHD is evolving [26,27]. In the following sections, we review the literature on the use of medication treatment for ADHD in adults. We focus on the efficacy in shorter-term controlled trials and effectiveness in longer-term trials. We also examine the use of medications in the context of special populations, tolerability, medical screening and monitoring.

Methods

In this article, we conducted a systematic computerized search of all studies available in English relevant to the treatment of ADHD in adults. We selected studies with adequate description of study methodology to permit critical evaluation of findings. We focused on studies with primary measures of ADHD outcome that were clinical in nature. Based on the relatively large literature in some areas, we included only controlled studies of stimulants that were shorter term (<12 weeks) in duration. For shorter-term studies, we included both open and controlled studies of nonstimulants. For stimulant and nonstimulant studies that were at least 12 weeks in duration (longer term), we included both open and controlled stimulant and nonstimulant trials. We did not include studies of pemoline (off market) or briefer studies predominately examining neuromarkers or neuropsychological measures as the primary outcome.

Subject participation reflects all subjects enrolled and entered into the trial (intent to treat) regardless of placebo or active medication assignment or premature drop. Response rate reflects percentage of subjects at the end of the trial reported as having a clinically significant improvement with treatment (by clinical global impression or predefined reduction in symptoms). Weighted means (response rate × number of subjects) were calculated with available data for individual stimulant medications and placebo.

Results

Stimulants

The stimulants are among the most common medications used to treat ADHD across the lifespan. Stimulants have been shown to increase intrasynaptic concentrations of dopamine (DA) and norepinephrine (NE; for a review, see [28,29]). Owing to the methodological limitations in studying NE reuptake (inhibition), more is known about DA. MPH primarily acts by blocking the reuptake of DA by binding to the DA transporter protein on the presynaptic membrane [30], although postsynaptic activation of β-receptors may also be present [28,31]. While AMPs diminish presynaptic reuptake of DA, they also are taken into the DA neuron and facilitate the release of DA from vesicles into the cytoplasm, prevent reuptake from the cytoplasm into the vesicles and are associated with the release of more DA from the presynaptic neuron [28]. In addition, stimulants (AMP > MPH) increase levels of NE and 5-hydroxy-tryptamine (5-HT) in the interneuronal space.

Although it is clear that MPH and AMP have distinct pharmacodynamic properties and that clinically, patients often express a preference for one preparation over another, the reason(s) underlying this preference remain understudied. We understand their preference to be based on a combination of tolerability and efficacy. However, to date, we are not aware of any data that helps clinicians predict whether an individual patient will tolerate or respond to either MPH or AMP preferentially, and the usual clinical practice is to try one or both. Through differences in absorption through transdermal or gastrointestinal (GI) administration,

prodrug metabolism, uptake into the CNS and distribution in the brain, even stimulants within the same class may differ in their effects on neurotransmission and, ultimately, efficacy [32–35].

In comparison to the more than 300 controlled studies of stimulant efficacy in pediatric ADHD (for a review, see [36–39]), there are at least 25 short-term controlled stimulant trials in adults with ADHD including 2804 subjects, and at least 15 longer-term stimulant trials including 1989 subjects (Tables 1 & 2) [32–34,40–79]. The majority of recent larger stimulant studies were undertaken with commercial support.

Although historically children and adolescents in controlled studies demonstrate a consistent response rate to stimulants of approximately 70% [39,80], the response rate of adults with ADHD to stimulants has been variable. While in an open-label trial with dexmethylphenidate (d-MPH), the response rate in adults was reported to be 95% [75], in controlled trials the response rates to stimulants in adults range from 25 [41] to 78% [44], with a short-term controlled weighted mean of 60% response rate and a longer-term weighted mean of 74% response rate. It is important to note that in trials of adults with ADHD, efficacy between AMP (n = 9 studies including 1118 subjects; weighted mean: 61% response rate vs 20% placebo) and MPH (n = 19 controlled short-term studies including 1913 subjects; weighted mean: 60% response rate vs 26% placebo) are similar. Moreover, adults with ADHD overall manifest a 26 and 34% response to placebo in short-term (n = 18) and longer-term (n = 7) controlled trials, respectively. Although the initial trials in adults with ADHD studied the safety, tolerability and efficacy of immediate or intermediate stimulant preparations (including at least 14 studies of the immediate or intermediate [e.g., MPH sustained release] release forms of MPH, and eight studies of immediate or intermediate release AMP [including mixed AMP salts]), recent work has focused on investigating the effects of the extended delivery preparations of MPH or AMP (including 17 trials of osmotic-release oral system [OROS] MPH, d-MPH extended release (ER), MPH ER, mixed amphetamine salts [MAS] ER and d-AMP ER). These recent trials are particularly reassuring as these are the stimulant preparations usually prescribed in clinical practice.

There are several factors that may account for the differences in response rate for these medications, including the criteria used to determine ADHD, varying stimulant doses, inclusion of psychopathology and differing methods of determining overall response. Dosing of AMP and MPH, for example, appears important in outcome: controlled investigations using higher immediate release (IR) MPH dosing (≥1.0 mg/kg/day) resulted in more robust outcomes [44] than those using lower MPH dosing (<0.7 mg/kg/day) [41,81]; likewise, data from studies with AMP suggest higher response rates with higher doses (48% response rate using 0.3 mg/kg/day [48] vs 70% response rate using 0.9 mg/kg/day [47]). Interestingly, an inconsistent dose response has been shown in recent large multisite dose ranging studies. For example, Medori *et al.* failed to show a dose–response relationship when using 18–72 mg/day of OROS MPH [34]. Spencer *et al.* also reported that 20–40 mg/day of d-MPH ER resulted in an inconsistent dose–response relationship [32]. Likewise, Adler *et al.* using 30–70 mg/day of lisdexamfetamine dimesylate (LDX) found a similar response rate of between 57 and 62% across all doses [57]. In applying these data to clinical practice, it is imperative for clinicians to recognize that research data are collected on a selected patient population and at a group level. Within a group, there is a wide range of doses to which individual patients may respond. In fact, some patients may respond to low or intermediate stimulant doses. In our clinical practice, like in a research study, we recommend the initiation of stimulant medication at a low dose and titrating upwards in a reasonable time course, usually at 1-week intervals. These intervals permit the patient and clinicians to gather enough data about the tolerability and effectiveness of the chosen

medication in order to inform clinical decision making. It is equally important to recognize that some patients require a relatively higher dose in order to achieve a clinical response. The most important factor underlying the safe and proper titration of stimulant medications is the ongoing collaborative relationship between the clinician and patient.

There continues to be a paucity of longer-term data related to stimulants for ADHD. To date, there have been eight open (n = 1023 subjects) and seven controlled (n = 1136 subjects) studies of at least 12 weeks in duration (Table 2). The majority of longer-term studies are open studies that follow on to controlled shorter-term studies. Wender *et al.* studied 78 subjects who were part of a controlled trial for 12 months and found that those who responded to MPH in the short term responded to longer-term treatment with improvement in ADHD [64]. Weiss *et al.* demonstrated continued improvement with dextroamphetamine (d-AMP) alone or in combination with paroxetine (64 and 44% response rates vs 16% placebo, respectively) over a 20-week study [70]. Rösler *et al.* showed that MPH ER significantly improved ADHD (61 vs 42% placebo) and related symptoms over the 24 weeks of the study [72]. These limited data seem to suggest that the response to stimulants is sustained at the 24–72 week follow-up end points [79].

Open-label studies have also shown the effectiveness of longer-term stimulants in adults with ADHD. In a 12-month study following a double-blind, placebo-controlled trial of initially 349 subjects receiving 30–70 mg/day of LDX, Weisler *et al.* reported an 84% improvement of the intention to treat population on the Clinical Global Impression Improvement (CGI-I) at end point, and most adverse events were mild-to-moderate in severity [70]. In a similar 6-month, open-label study following a randomized, placebo-controlled trial of OROS MPH, Marchant *et al.* found that 85% of the 34 enrolled subjects demonstrated improvement on the CGI-I [77]. Again in this study, adverse events were generally considered to be minimal [77]. These aggregate data seem to support the longer-term effectiveness and tolerability of stimulants in adults.

Plasma levels of the stimulants [44,82], as well as gender and psychiatric comorbidity [44,45,83], have not been implicated in variable medication response in ADHD adults; however, exclusion criteria and limited sample sizes constrain generalizability of these findings. Similar findings between response rates and adverse effects have been reported between ER and IR stimulants. For instance, Spencer *et al.* reported similar response rates and adverse effects using similar dosing of three-times daily IR MPH and once-daily ER OROS MPH [63].

The side effects of the stimulants in ADHD adults have been reported to be generally mild to moderate, with dry mouth, insomnia, edginess, diminished appetite, weight loss, dysphoria, obsessiveness, tics and headaches observed most frequently. No cases of stimulant-related psychosis at therapeutic doses have been reported in adults during clinical trials.

There has been recent debate about the cardiovascular effects of stimulants across the lifespan [84–87]. As a result of the greater prevalence of ADHD studies in children and adolescents, recent work has focused on cardiovascular trends in these populations [88,89]. Despite the more limited work conducted on adults with ADHD, cardiovascular adverse effects of stimulant use in adults have been documented and are based on trials that indicate a consistent increase in systolic and diastolic blood pressures (3–5 mmHg) and heart rate (5 bpm). These statistically significant increases appear to be correlated to dose; however, the correlations do not appear to be strongly correlated with dose [75,90,91]. Longer-term data on the cardiovascular effects of these medications in both children and adults suggest a lack of tolerance to the pressor and chronotropic effects of these medications [68,92]. Little data

are available outside of blood pressure and pulse effects [68]. Schubiner and colleagues reported abnormalities in the autonomic nervous system in a pilot sample of 61 individuals treated with various forms of MPH and AMP [93]. Although the significance of these findings is unknown, only 4% of the control group manifested abnormalities in the autonomic nervous system compared with 24% in the ADHD group. Hammerness *et al.* recently reported prolonged heart rate recovery at 4 min in a small group of adults, but no other clinically significant changes in cardiac functioning or structure after up to 6 months of treatment with lisdexamfetamine [94]. Wilens *et al.* studied adults with treated hypertension openly treated with MAS ER up to 60 mg/day and found no recurrent hypertension or other cardiovascular adverse outcome during the 6-week study [95].

No laboratory abnormalities have been reported in adults treated with stimulants, including complete blood counts, renal or liver function tests. Given the sympathomimetic properties of stimulants and potential effects on the cardiovascular system, evaluating symptoms referable to cardiovascular dysfunction (e.g., chest pain, palpitations and syncope) [87,96], and the monitoring of blood pressure and pulse at baseline and during treatment are recommended.

Despite the potential abuse of the stimulants, there has been a remarkable lack of reports of stimulant abuse in controlled or retrospective studies of adults with ADHD [97]. Of interest, more recent controlled studies of active substance abusers have failed to show worsening of substance abuse or misuse of the substances during the study [61,71,78,98,99]. Although the subjects' addiction did not improve in these studies, the investigators were able to demonstrate some limited improvement in ADHD symptoms. The long-term effects of stimulant exposure on later substance abuse in adults are inconsistent, with the bulk of studies showing either lower rates or no effects on substance abuse compared with matched groups of adults not treated with stimulants during their youth [100–103]. Interestingly, differences in abuse liability appear to be noted, with ER manifesting lower likeability ratings compared with IR MPH-based stimulants [104], as well as prodrug amphetamines (lisdexamfetamine) similarly having lower likeability than comparable doses of IR AMP [105]. For MPH, it has been speculated that the rate of increase of the MPH levels in the brain and the level of saturation of DA transporter protein is related to the abuse liability of the stimulant [104,106]. While the majority of individuals treated for ADHD use their medications appropriately [107], survey studies have indicated that approximately 5% of college students have misused stimulants [108] and that it is more common in competitive colleges, more often misused for their procognitive effects than euphoria, and more frequently occurs with immediate-compared with ER stimulant preparations.

Noradrenergic agents

Atomoxetine—Atomoxetine (ATX) was the first medication approved by the US FDA for specifically treating ADHD in adults (Table 3) [99,109–157]. Unlike the stimulants, ATX is not a controlled medication. ATX specifically inhibits presynaptic NE reuptake, resulting in increased synaptic NE [158] and DA [158].

Atomoxetine has been studied in at least eight controlled and six open studies constituting 2938 subjects. An initial 10-week study of ATX in 536 subjects resulted in reductions from baseline in Conners' adult ADHD rating scale scores of approximately 30% (vs 20% for placebo), with similar reductions in symptoms of inattention and hyperactivity/impulsivity [135]. A re-examination of this data set emphasized that symptoms of emotional dysregulation showed a treatment response similar to other ADHD symptoms [17]. More recently, ATX has been studied in another multisite, large, longer-term trial demonstrating continued efficacy for ADHD in adults [157].

Longer-term data also suggests an ongoing effectiveness of ATX in adults. In a large controlled 6-month study of ATX, significant findings compared with placebo were noted acutely at 10 weeks and at the 6-month end point [151]. In an earlier follow-up study and final report, Adler *et al.* demonstrated improved outcome in ADHD, with >30% of symptoms reduced compared with baseline at up to 221 weeks [138]. In this study of originally 384 adults, there were no new long-term adverse effects that emerged owing to the drug. Similarly, Marchant *et al.* reported on this population of 384 adults treated openly for up to 156 weeks following two multicenter, double-blind trials in which responders had significant improvement in ADHD and emotionality [139]. Interestingly, 39% of ATX subjects enrolled in the double-blind studies who were ADHD nonresponders converted to responders during the open-label treatment [139].

Atomoxetine is rapidly absorbed following oral administration and food does not appear to affect absorption. ATX is primarily metabolized via the hepatic cytochrome P450 system, through the 2D6 enzyme into 4-hydroxyatomoxetine [159]. In addition to the treatment of both inattention and hyperactivity/impulsivity in adults with ADHD, ATX may be particularly useful when anxiety, mood or tics co-occur with ADHD. For example, Adler *et al.* in a large, 14-week multisite study of ATX in adults with ADHD and social anxiety disorder reported clinically significant effects on both ADHD and on anxiety [150]. Owing to its lack of abuse liability [160], ATX may be particularly of use in adults with current substance use issues. Wilens and associates demonstrated in a 12-week controlled trial that treatment with ATX in recently abstinent alcoholics was associated with improved ADHD and reduced drinking, although absolute abstinent rates were unaffected [147]. Similarly, McRae-Clark *et al.* that ATX generated greater improvement for those receiving ATX than those being treated with placebo demonstrated in a 12-week controlled trial, although no differences in marijuana use outcomes were noted [155]. Moreover, ATX has not been reported to have serious drug interactions with alcohol or marijuana, although increased sedation is reported in the context of heavy alcohol use [161].

The most common side effects observed with ATX appear reflective of increased noradrenergic tone and include dry mouth, insomnia, nausea, decreased appetite, constipation, decreased libido, dizziness and sweating [135]. There have been reports of hepatoxicity in two patients taking ATX, with both patients recovering upon discontinuation. ATX has similar cardiovascular effects to stimulants; therefore, ATX should be used cautiously in adults with hypertension or other cardiovascular risk factors. Unlike the ‘black box’ in children, no increased suicidality has been reported in studies of adults with ADHD receiving ATX.

α-agonists—The FDA-approved α-adrenergic agonists clonidine and guanfacine have been used in childhood ADHD, particularly in those cases with a marked hyperactive or aggressive component [162]. Although forms of both clonidine (Kapvay) and guanfacine ER (Intuniv) are now FDA approved for the treatment of children with ADHD, they are not approved in the treatment of adults with ADHD and, in fact, there is a dearth of data on the safety, tolerability and efficacy on the α-agonists in adults with ADHD. Taylor and Russo reported results from 17 adults treated with either d-AMP or guanfacine IR and found similar reductions in ADHD symptoms compared with placebo, with a similar response between active treatments [128]. To date, no studies of clonidine for ADHD have been completed in adults. Although unstudied under controlled conditions, β-blockers may be useful in the treatment of adult ADHD [113,163]. Propanalol, for example, has demonstrated improvement in symptoms of adults with ADHD and temper outbursts [113]. It has also been reported that β-blockers, when used in conjunction with stimulants, may mediate ADHD in adults [163]; however, it may be that the combined pharmacotherapy was beneficial, in that it reduced stimulant-induced adverse events, including headaches and

feelings of edginess and anxiety [39]. Clearly more efficacy and tolerability investigation with antihypertensives is necessary prior to any recommendations on their use in adults with ADHD.

Antidepressants

Bupropion—Bupropion, an antidepressant with mixed catecholaminergic effects, has been reported to be moderately helpful in reducing ADHD symptoms in children [164]. There have been at least four open and six controlled trials involving 507 subjects using bupropion in adults with ADHD. In a 6-week, double-blind placebo-controlled trial [132], bupropion at 200 mg sustained release (SR) twice-daily (final mean dose: 362 mg/day) resulted in a 42% reduction in the ADHD rating scale, with 52% of subjects treated with bupropion considered responders. Similar results were found by Reimherr *et al.* [142] and when using an alternative once-daily preparation [140]. Dosing of 400–450 mg (SR or ER preparations) is usually necessary for best efficacy and there appears to be a delayed onset of action. Side effects include insomnia, edginess and a low risk for seizures. Despite the small numbers of adults studied, bupropion may be helpful in ADHD, particularly when associated with comorbid depression [165], substance abuse [133,152] or bipolar disorder [134].

Tricyclic antidepressants—Despite their broad array of use in children and adolescents, there are only two studies of tricyclic antidepressants (TCAs) in adult ADHD. Compared to the stimulants, TCAs have negligible abuse liability, single daily dosing and efficacy for anxiety and depression. A controlled trial of desipramine with a target dose of 200 mg daily resulted in significant reductions in ADHD symptoms in adults [122]. In this study, although response was noted during the initial 2-week titration, progressive response was noted at weeks 4 and 6. Whereas a minority of subjects responded to <100 mg daily, the majority required higher dosing for efficacy.

Monoamine oxidase inhibitor—The monoamine oxidase inhibitor (MAOI) antidepressants have been studied for the treatment of ADHD. Given the impulsivity and inattention seen in adults with ADHD, the use of MAOIs in these patients should be limited owing to potential serious adverse events. While open studies with pargyline and deprenyl in adult ADHD demonstrated modest improvements [110,111], a controlled trial of selegeline (L-deprenyl) yielded less enthusiastic findings [123]. Despite Ernst *et al.*'s report on dose-dependent improvements with oral selegeline in ADHD symptoms, these findings were not significant when compared with a high placebo response [123]. Moclobemide, a reversible MAOI, has not yet been shown to be effective in the treatment of adult ADHD. Of important note, selective serotonin-reuptake inhibitors have not proven themselves to be effective in ADHD treatment [70], although venlafaxine, which maintains noradrenergic and serotonergic properties, appears to be mildly efficacious in moderating ADHD symptoms. Three open studies involving 41 adults support this postulation. In these studies, 75% of adults who tolerated venlafaxine had a measurable reduction in their ADHD symptomatology at doses of 75–150 mg daily [119,121,166]. In summary, antidepressants with documented efficacy in ADHD share a catecholaminergic (particularly noradrenergic or dopaminergic) mechanism of action.

Wake-promoting agents

Medications used to promote wakefulness have also been evaluated for the treatment of ADHD, in part, based on their non-specific effects on CNS arousal functioning. Moreover, from a historical point of view, stimulant agents sometimes used in ADHD have also been used in the treatment of sleep disorders [167]. Despite modafinil's purported efficacy in one single-site controlled trial, with 48% of adult participants responding to the antinarcoleptic,

results from multisite controlled studies have failed to demonstrate the agent's superiority over placebo [127], highlighting the ongoing discrepancies in the effectiveness of wake-promoting agents.

Experimental agents

Amino acids—Under the assumption that ADHD may be correlated with a deficiency in the catecholaminergic system, Wender and colleagues initiated trials with the amino acids [109,112,114]. These researchers were of the opinion that the administration of precursors of these systems could reverse the deficits. Open studies involving L-DOPA and tyrosine in adults with ADHD have yielded unfortunate results despite robust dosing and sufficient trial duration (Table 3) [109,112,114]. Controlled studies of phenylalanine in adults with ADHD have produced similar results. Side effects were particularly evident, and initial improvements in ADHD symptomatology typically subsided after 2 weeks of treatment.

The intersection of nicotine use and ADHD has generated considerable interest recently. Findings include higher than expected overlap of cigarette smoking in adults diagnosed with ADHD [168] and a substantial literature attesting to the positive effect of nicotine on improving cognitive ability [169,170]. Whereas smaller crossover studies of nicotinic analogs with either full or partial agonistic properties demonstrated efficacy in adults with ADHD [125,144], more recent larger multisite parallel-design studies failed to show a significant effect of this compound reducing ADHD symptomatology [171]. Side effects included nausea, GI activation and dizziness. Although these agents have demonstrated efficacy in Alzheimer's disease, there are currently no published studies demonstrating a positive effect of cholinesterase inhibitors in adults with ADHD.

The antidepressant nomifensine has been shown in an open study to be useful in ADHD [115]; however, safety issues have limited its availability. *S*-adenosylmethionine (SAMe), an anti-depressant available over-the-counter, has also been reported in one open study to be effective for ADHD [116]. Histamine appears to be important in the arousal system and may impact attention. Histaminergic agents have been examined in adults with ADHD: a recent controlled pilot study with a histamine agonist did not demonstrate significance compared with placebo [172].

Combined pharmacotherapy

Despite a paucity of controlled data investigating and assessing the efficacy, tolerability and safety of combining multiple agents for the treatment of ADHD in adults, combination treatment may be necessary, particularly for those exhibiting residual symptomatology with single agents or psychiatric comorbidity. For example, in a naturalistic report of TCAs for adults with ADHD, 59% received adjunctive stimulants [118]. Weiss *et al.* prospectively studied the use of stimulants alone or in combination with paroxetine for ADHD in adults and did not show improvement in ADHD outcome associated with paroxetine [70]. Improvement in anxiety symptoms was shown in those adults receiving paroxetine as part of their regimen [70]. In cases of partial response or adverse effects with stimulants, the addition of α-agonists, ATX or TCAs have been reported in pediatric studies to be helpful and well tolerated [173–176], although these remain unstudied in adults.

Expert commentary

Attention-deficit/hyperactivity disorder is now viewed as a disorder capable of causing significant distress and/or impairment in a patient's life. In terms of treating ADHD in adults, pharmacotherapy is often responsible for reducing 'core' symptoms, as well as other concurrent psychiatric disorders. The extant literature suggests that agents comprised

primarily of noradrenergic and/or dopaminergic formulations appear to be most beneficial to those adults diagnosed with ADHD. The data also suggest that agents approved by the FDA (some stimulants and ATX) are among the most effective agents for adults with ADHD.

The literature on medication therapy in adults with ADHD echoes many of the findings in pediatric groups with ADHD. However, trials involving ADHD in adults frequently generate findings with greater variability in outcome, and less information on dosing parameters and effectiveness of the various agents that are used. The stimulant medications continue to be the most rigorously investigated treatment with at least 40 studies in 4793 individuals (Tables 1 & 2) and are considered first-line medications of choice for ADHD in adults. The effects of age, dosing, long-term adverse effects and stimulant use in subgroups with ADHD still remain unclear, despite a growing literature.

The nonstimulants, namely ATX, bupropion and TCAs, appear useful for stimulant naive patients, stimulant nonresponders or adults with concurrent psychiatric disorders [117]. Whereas ATX appears to be more responsive in stimulant naive individuals [135], the anti-ADHD response to antidepressants appears to be independent of previous response status to stimulants [122]. Although no adequately powered direct studies comparing stimulants and antidepressants have been completed, comparative data using robust dosing of these compounds in adults, coupled with studies in children, support that stimulants appear slightly more effective in reducing ADHD symptoms [177,178]. While the response to the stimulants is immediate [40,44,63], ATX and the antidepressants have a delayed onset of full therapeutic action of up to 4 weeks, related both to the titration of the medication and the delay in the onset of action of the agent [122,124,129,137,153,179,180]. Generally speaking, MAOIs have been shown to be only minimally useful in adults with ADHD [123]. The α-adrenergic agents, wake-promoting agents and SAMe have yet to establish a critical role in the treatment of ADHD in adults [49]. Cholinesterase inhibitors do not appear to be useful in ADHD [145]. The amino acids appear to be only transiently helpful for ADHD [109,112,114] and are not recommended.

There are few controlled studies that have investigated the treatment of ADHD and comorbidity in adults. This is due, in part, to the inclusion of largely currently noncomorbid individuals into the studies, the bulk of which are commercially funded. Notable exceptions include the multisite controlled study of Adler *et al.* of ATX for ADHD and social anxiety disorder in which both ADHD and anxiety were improved significantly with ATX compared with placebo [150]. Weiss *et al.* similarly found that adults receiving paroxetine or d-AMP and paroxetine demonstrated greater improvement for mood and anxiety symptoms compared with adults receiving d-AMP or placebo alone [70]. Co-occurring nicotine and substance abuse disorders are the most studied comorbidity with adult ADHD: there have been at least 13 controlled studies completed. While these studies generally only show negligible effects on ADHD or substance abuse, some noteworthy exceptions exist. In a study evaluating cigarette smokers, Winhusen *et al.* showed improved ADHD and no worsening or improvement in cigarette use [61]. Wilens *et al.* reported improved ADHD and reduced heavy drinking episodes, but no overall impact on relapse in recently abstinent alcoholics [147]. Of interest, none of the studies of ADHD and substance abuse report worsening of substance use or misuse of medication. Studies of comorbid mood and antisocial disorder have yet to be completed. Only small open studies have been completed on medically compromised adults and few have extended beyond 55 years of age. Investigators have recently reported increased rates of Axis II disorders in adults with ADHD. These investigators observed increased rates of both Cluster B (primarily borderline personality disorder) and Cluster C disorders compared with rates in control subjects without ADHD [181]. Moreover, investigators recently reported that treatment with ATX

under controlled conditions improved core symptoms of ADHD (attention and hyperactivity/impulsivity), as well as symptoms of emotional dysregulation [139].

Methodological differences between studies may account for some of the variance in outcome. The discrepancies in outcome are probably related to the incomplete characterization of study subjects, methodological disparities in assessing ADHD outcome and low medication dosing. Furthermore, it is noteworthy that there continues to be an inconsistent dose–response relationship of stimulants within studies that may be owing to the assignment of individuals to a dose group as opposed to the actual dose achieved. For instance, in studies with MAS ER, a clear dose–response relationship was established if the actual achieved dose was used compared with the assigned dose [69]. Another area of intrigue is the varying placebo response in the various studies of medications for ADHD. Whereas initial studies reported relatively low response to placebo (e.g., typically <20%), more contemporary studies indicate placebo responses as high as 55% [71]. While the etiology of an apparently increasing placebo response is unclear, investigators need to consider this important issue when determining the design and adequate sample size for future controlled clinical trials.

Whereas the pathogenesis of ADHD remains under investigation, it would appear that catecholaminergic effects are necessary for clinical efficacy of anti-ADHD medications [28,182]. AMP and MPH vary in their synaptic mechanisms of action [183], which translates into differing responses between classes of agents in individuals with ADHD [184,185]. Alterations in DA and NE reuptake have also been reported with ATX, modafinil (in pediatric patients), α-agonists, TCAs and bupropion, which have also been shown to be effective for ADHD. The serotonergic antidepressants are not beneficial in terms of improving ADHD [70]. Of interest, these findings add support to the older notion that the pathogenesis of ADHD appears to be mediated by dopaminergic and adrenergic systems, with little direct influence by the serotonergic systems [186].

Whereas early work demonstrated improvement in ADHD with nicotine or related agonists [169,170], more recent large (pediatric) multisite studies have failed to replicate significant improvements [171]. Prohistaminergic agents, while appealing given the endogenous histamine effects on the attention arousal systems, have been disappointing [172].

Owing to lingering psychiatric and ADHD symptoms despite pharmacotherapy, as well as the sequela related to having a chronic disorder, ADHD adults frequently require a more comprehensive and integrated approach to treatment for their ADHD. For instance, the vast majority of studies have used 30% reductions in ADHD symptoms as a threshold for response, indicating that substantial symptomatic residua exist. Structured cognitive-based psychotherapies [23] appear to be helpful, especially when used conjointly with pharmacotherapy, as observed in recent findings in both individual [24] and group settings [25]. For those adults diagnosed with ADHD who are taking steps to advance in their careers or academic pursuits, educational planning and restructuring of the school environment are worth consideration.

Five-year view

Over the next 5–10 years, future studies for the pharmacotherapy of ADHD in adults are anticipated to include the investigation of a variety of compounds that target the diversity of attentional dysfunction in ADHD. For example, open studies with memantine have shown improvement in ADHD and related executive functioning [187]. Agents with selective noradrenergic- and/or dopaminergic-reuptake inhibition should be evaluated for ADHD and related symptoms. Given the consistent findings of nicotine and various aspects of cognitive functioning, further studies with various nicotinic full and partial agonists to specific

subunits of the nicotinic receptor need be evaluated. Further understanding, examination and treatment of many of the associated symptoms and impairment in adults with ADHD are necessary. Similarly, longer-term studies of medication for ADHD in adults need to be undertaken linking symptomatic, functional, physiological and neurobiological systems. Identifying potential long-term effects of chronic medication exposure and later medical disorders related to cognitive or catecholaminergic dysfunction, such as Parkinson's or Alzheimer's disease, is necessary. Moreover, we anticipate that researchers will study those individuals who experience the most significant complications of ADHD, including mood disorders, executive function disorders, personality disorders and substance abuse.

Our review of the literature suggests that medication serves as an effective form of treatment for adults with ADHD. Careful assessment of the adult, including target 'problematic' symptoms, functionality in multiple domains and the degree of impairment, should accompany the incorporation of medication into a treatment plan [188]. To date, effective pharmacological treatments for adults with ADHD include stimulants, noradrenergic agents and antidepressants. Given some parallels in the pharmacological responsivity across the lifespan for ADHD, the testing of compounds in adults prior to exposure in youth provides an effective and ethical manner of examining potential agents in ADHD. Further trials investigating the efficacy of agents for adults with ADHD are necessary. Particular attention to diagnostics, long-term effectiveness and utility in varying adult ADHD populations is required as symptom reduction and clinical outcome are examined in the future.

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• of interest

•• of considerable interest

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Key issues

- In comparison to the more than 300 controlled studies of stimulant efficacy in pediatric attention-deficit/hyperactivity disorder (ADHD), there are at least 25 short-term controlled stimulant trials in adults with ADHD including 2804 subjects and at least 15 longer-term open and controlled stimulant trials including 1989 subjects.
- To date, effective pharmacological treatments for ADHD adults include stimulants, noradrenergic agents and catecholaminergic antidepressants.
- Under controlled conditions, the aggregate literature shows that the stimulants and catecholaminergic nonstimulants have had a clinically significant beneficial effect on treating ADHD in adults.
- At a group level, there appears to be some, albeit not entirely consistent, dose-dependent response to amphetamine and methylphenidate.
- Whereas the pathogenesis of ADHD remains under investigation, catecholaminergic effects appear common in agents that demonstrate clinical efficacy for ADHD.
- There have been at least 47 open and controlled studies of nonstimulant medications in adult ADHD, including as many as 4069 subjects, and generally positive findings have emerged in agents with catecholaminergic effects.

Table 1

Representative short-term controlled clinical studies of stimulants in adults with attention-deficit/hyperactivity disorder[†].

Study (year)	n	Design	Medication	Duration (weeks)	Total dose mean and/or range	Outcome	Comments	Ref.
Wood *et al*. (1976)	15	Double-blind, placebo crossover	MPH	4	27 mg/day	73% response rate	Dx criteria not well defined; low doses of pemoline; mild side effects	[40]
Mattes *et al*. (1984)	61	Double-blind, placebo crossover	MPH	6	48 mg/day	25% response rate	Moderate rate of comorbidity; mild side effects	[41]
Wender *et al*. (1985)	37	Double-blind, placebo crossover	MPH	5	43 mg/day	57% response rate (11% placebo)	68% dysthymia; 22% cyclothymia; mild side effects	[42]
Gualtieri *et al*. (1985)	22	Double-blind, placebo crossover	MPH	2	42 mg/day	Mild–moderate response	No plasma level-response associations	[43]
Spencer *et al*. (1995)	23	Double-blind, placebo crossover	MPH	7	1.0 mg/kg/day	78% response rate, dose relationship (4% placebo)	No plasma level associations; no effect of gender or comorbidity	[44]
Iaboni *et al*. (1996)	30	Double-blind, placebo crossover	MPH	4	30–45 mg/day	Moderate response	Improvement in neuropsychology and anxiety	[45]
Paterson *et al*. (1999)	45	Double-blind, parallel	d-AMP	6	23 mg/day	58% response rate	Weight loss only major adverse effect	[46]
Spencer *et al*. (2001)	27	Double-blind, placebo crossover	AMP salts	7	54 mg/day 20–60 mg/day	70% response rate, dose relationship (7% placebo)	No effect of comorbidity or gender on response; well tolerated	[47]
Taylor (2000); Taylor (2000)	39	Double-blind, placebo crossover	d-AMP	7	22 mg/day	48% response rate	Used as comparator in two studies of nonstimulants; respiratory >30% reduction in scales	[48,49]
Kooij *et al*. (2004)	45	Double-blind, randomized crossover	MPH	3	0.5–1.0 mg/kg/day	38–51% response rate (7–18% placebo)	European study; compare with US high rate of side effects for MPH and placebo	[50]
Carpentier *et al*. (2005)	25	Double-blind, placebo crossover	MPH	8	15–45 mg/day	58% response rate on CGI (32% placebo)	SUD study; positive response to Tx not significantly higher than placebo	[51]
Spencer *et al*. (2005)	146	Double-blind, placebo parallel	MPH	6	1.1 mg/kg/day	76% response rate (19% placebo)	Tx well tolerated despite higher dose	[52]
Biederman *et al*. (2006)	141	Double-blind, placebo parallel	OROS MPH	6	81 mg/day	66% response rate (39% placebo)	Slight SBP, DBP and HR increases with medication	[53]

Study (year)	n	Design	Medication	Duration (weeks)	Total dose mean and/or range	Outcome	Comments	Ref.
Weisler *et al.* (2006)	255	Double-blind, placebo parallel	MAS ER	4	20, 40 or 60 mg/day	55% response rate on CGI (27% placebo)	MAS ER 60-mg group had greatest improvement on ADHD RS	[54]
Spencer *et al.* (2007)	221	Double-blind, fixed-dose, placebo parallel	d-MPH-ER	5	20, 30 or 40 mg/day	54–61% response rate on ADHD RS (34% placebo)	Inconsistent dose response	[32]
Reimherr *et al.* (2007)	45	Double-blind, placebo crossover	OROS MPH	8	57 mg/day (treatment responder mean) 75 mg/day (treatment nonresponder mean)	54% response rate on CGI (22% placebo)	Total ADHD RS score decrease of 41% (vs 14% placebo)	[55]
Jain *et al*. (2007)	39	Double-blind, placebo crossover	MLR MPH	5–11	58mg/day (mean) MLR MPH 65 mg/day (mean) placebo	49% response rate on CGI (23% placebo)	MLR MPH minimal side effects; short trial	[56]
Adler *et al.* (2008); Weber *et al*. (2009)	420	Double-blind, placebo parallel (2:2:2:1)	LDX	4	30, 50 or 70 mg/day	Response rate on CGI: 57, 62 and 61% (29% placebo)	Incidence of AEs highest in first week of LDX treatment	[57,58]
Medori *et al*. (2008)	401	Double-blind, placebo parallel	Prolonged-release OROS MPH	5	18, 36 or 72 mg/day	Responders were 51, 49 and 60% (27% placebo)	AE rates 75, 76 and 82% vs 66% in placebo; most common decreased appetite and headache	[34]
Chronis-Tuscano *et al.* (2008)	23	Double-blind, placebo-controlled	OROS MPH	7	36, 54, 72 or 90 mg/day (mean 84 mg/day)	Significant reduction in CGI scores at all doses	Few AEs	[59]
Adler *et al.* (2009)	226	Double-blind, placebo parallel	OROS MPH	7	68 mg/day OROS MPH (mean) 87 mg/day placebo (mean)	37% response rate on CGI and AISRS (21% placebo)	Mild-to-moderate AE rate, 85% MPH vs 64% placebo; OROS MPH overall effective and well tolerated in dose escalation	[60]
Winhusen *et al.* (2010)	255	Double-blind, placebo parallel	OROS MPH	11	18–72 mg/day	71% response rate on CGI (44% placebo)	Cigarette smoking abstinence not significantly different between groups	[61]
Wigal *et al*. (2010)	105	Randomized, double-blind, crossover	LDX	2	30, 50, or 70 mg/day	77% response on CGI (23% placebo)	After open-label dose optimization (4 weeks), subjects entered 2-week crossover phase	[62]
Spencer *et al.* (2010)	53	Single-blind, parallel	OROS MPH or IR MPH	6	77 mg/day IR MPH (mean) 80 mg/day OROS MPH (mean)	OROS once a day was as efficacious as IR MPH three times per day in adults	OROS well tolerated and similar safety indices as IR; increased adherence with OROS	[63]

Study (year)	n	Design	Medication	Duration (weeks)	Total dose mean and/or range	Outcome	Comments	Ref.
Wender *et al.* (2010)	105	Double-blind, placebo crossover	MPH	2	45 mg/day 10–60 mg/day	74% experienced at least 50% reduction on WRAADDS Sx score (22% placebo)	Participants who improved on MPH IR entered the 12-month, open-label trial	[64]
Total								
25	n = 2804 15–420 (range)	Single: 1 Double: 24	MPH: 19 AMP: 4 LDX: 2	2–11	10–90 mg/day MPH 20–60 mg/day AMP 30–70mg/day LDX	MPH, AMP, and LDX improved ADHD Sxs	AEs mild-to-moderate in severity	

[†]Up to 11 weeks.

Response rate refers to subject reporting much-to-very-much improved (i.e., by CGI) or with clinically significant reduction in symptoms on ADHD rating scales.

ADHD: Attention-deficit/hyperactivity disorder; AE: Adverse event; AISRS: ADHD Investigator Symptom Report Scale; AMP: Amphetamine; CGI: Clinical Global Impression; d-AMP: blood pressure; d-MPH: Dexmethylphenidate; Dx: Diagnosis; ER: Extended release; HR: Heart rate; IR: Immediate release; LDX: Lisdexamfetamine dimesylate; MAS ER: Mixed amphetamine MAS: Mixed amphetamine salt; MLR: Multilayer release; MPH: Methylphenidate; OROS MPH: Osmotic-release oral system methylphenidate; RS: Rating scale; SBP: Systolic blood pressure; SUD: Substance use disorder; Sx: Symptom; Tx: Treatment; WRAADDS: Wender Reimherr Adult Attention-Deficit Disorder Scale.

Table 2

Representative longer-term studies of stimulants in adults with attention-deficit/hyperactivity disorder[†].

Study (year)	n	Design	Medication	Duration	Total dose mean and/or range	Outcome	Comments	Ref.
Levin *et al.* (1998)	12	Open	MPH SR	12 weeks	68 mg/day 40–80 mg/day	Improved ADHD and cocaine use	Cocaine abusers, eight out of 12 completed; no abuse of MPH	[65]
Horrigan *et al.* (2000)	24	Open	AMP salts	16 weeks	11 mg/day	54% response rate on CGI	Low doses used; retrospectively analyzed	[66]
Schubiner *et al.* (2002)	48	Double-blind, placebo parallel	MPH	12 weeks	79 mg/day 30–90 mg/day	77% response rate on global improvement scale (21% placebo)	Comorbid cocaine dependence; CBT for both arms	[67]
Weisler *et al.* (2005); Biederman *et al.* (2005)	223	Open	MAS ER	≤24 months	20, 40 and 60 mg/ day	ADHD RS improved for all ($p < 0.001$)	AEs were mild to moderate, minimal cardiovascular effects; extension of double-blind study	[68,69]
Weiss *et al.* (2006)	98	Double-blind, placebo factorial	Paroxetine and/or d-AMP	20 weeks	Paroxetine (10, 20, 30 and 40 mg/day) d-AMP (5,10, 15 and 20 mg/day)	64% response rate to d-AMP, 44% response rate to paroxetine/d-AMP, 17% response rate to paroxetine (16% placebo)	Patients who received both d-AMP and paroxetine had more severe AEs, but did not show greater improvement overall than patients treated with one medication	[70]
Levin *et al.* (2007)	106	Double-blind, placebo parallel	MPH	14 weeks	40 mg/day 10–60 mg/day	47% response rate on AARS (55% placebo)	SUD study; toxicology revealed decreased probability of cocaine in urine for MPH vs placebo ($p = 0.001$)	[71]
Spencer *et al.* (2008)	274	Double-blind, placebo parallel	Triple bead AMP salts (MAS)	5 weeks (Phase I); 2 weeks (Phase II); 7 weeks (Phase III)	13, 25, 38, 50, 63 or 75 mg/day after dose optimization	52% response rate on CGI (21% placebo)	Mild-to-moderate AEs of insomnia, dry mouth, decreased appetite, headache, weight loss; improved quality of life >12-h duration	[33]
Rösler *et al.* (2009)	359	Double blind, placebo parallel	MPH ER	6 months	41 mg/day	61% response rate (42% placebo)	Relatively low doses used; increased heart rate among MPH ER group	[72]

Study (year)	n	Design	Medication	Duration	Total dose mean and/or range	Outcome	Comments	Ref.
Weisler *et al.* (2009); Ginsberg *et al.* (2011)	349	Open	LDX	12 months	30, 50 or 70 mg/day	84% improvement on CGI	Most AEs were mild to moderate in severity	[73,74]
Adler *et al.* (2009)	170‡	Open	d-MPH ER	6 months	20–40 mg/day	95% response rate on CGI	Open-label extension of Spencer *et al.* [32]	[75]
Bejerot *et al.* (2010)	133	Open	MPH d-AMP	6–9-month follow-up	49 mg/day 18–90 mg/day 28 mg/day 15–70 mg/day	80% response rate	66 of 133 discontinued (38% of which before the 6–9-month time point)	[76]
Marchant *et al.* (2010)	34	Open	OROS MPH	6 months	60 mg/day	85% response rate on CGI	Followed double-blind crossover phase; all 34 included for safety phase	[77]
Wender *et al.* (2010)	78	Open	MPH	12 months	60 mg/day 30–100 mg/day	94% response rate on CGI	Participants who improved on MPH IR double-blind phase entered the 12-month, open-label trial	[64]
Konstenius *et al.* (2010)	24	Double-blind, placebo parallel	OROS MPH	13 weeks	18–72 mg/day	84% retention in treatment completers (59% placebo)	Both groups reduced ADHD Sxs; no difference found between groups in craving for AMP	[78]
Biederman *et al.* (2010)	227	Three-phase, double-blind, placebo parallel	OROS MPH	6 weeks (Phase I); 24 weeks (Phase II); 4 weeks (Phase III)	78 mg/day OROS MPH at Phase I end point (mean)	62% response rate on CGI and AISRS (37% placebo)	Results include Phase I end point response rates only	[79]
Total								
n = 15	n = 1989 12–359 (range)	Double blind: 7 Open: 8	MPH: 10 AMP: 5 LDX: 1	12 weeks – 12 months	10–100 mg/day MPH 5–75 mg/day AMP 30–70mg/day LDX	Long term efficacy of MPH and AMP documented	AEs mild-to-moderate in severity	

Response rate refers to subject reporting much-to-very-much improved (i.e., by CGI) or clinically significant reduction in symptoms on ADHD rating scales.

†At least 12 weeks.

‡Subjects not included in total n.

AARS: Adult Attention-Deficit/Hyperactivity Disorder Rating Scale; ADHD: Attention-deficit/hyperactivity disorder; AE: Adverse event; AISRS: ADHD Investigator Symptom Report Scale; AMP: Amphetamine; CBT: Cognitive behavioral therapy; CGI: Clinical Global Impression; d-AMP: Dexamphetamine; d-MPH: Dexmethylphenidate; Dx: Diagnosis; ER: Extended release; IR: Immediate

release; LDX: dimesylate; MAS: Mixed amphetamine salt; MAS ER: Mixed amphetamine salt extended release; MPH: Methylphenidate; OROS MPH: Osmotic-release oral system methylphenidate; RS: release; SUD: Substance use disorder.

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Table 3

Representative clinical studies of nonstimulants in adults with attention-deficit/hyperactivity disorder.

Study (year)	n	Design	Medication	Duration	Total dose mean and/or range	Outcome	Comments	Ref.
Wood *et al.* (1982)	8	Open	L-DOPA (+ carbidopa)	3 weeks	625 mg/day 62.5 mg/day	No benefit	Side effects: nausea, sedation; low doses	[109]
Wender *et al.* (1983)	22	Open	Pargyline	6 weeks	30 mg/day 10–50 mg/day	68% response rate	Delayed onset; brief behavioral action	[110]
Wender *et al.* (1985)	11	Open	Deprenyl	6 weeks	30 mg/day	66% response rate	Amphetamine metabolite; two dropouts	[111]
Wood *et al.* (1985)	19	Double-blind, placebo crossover	Phenylalanine	2 weeks	587 mg/day	46% response rate (15% placebo)	Transient mood improvement only	[112]
Mattes (1986)	13	Open	Propanolol	Mean: 9 weeks (3–50 weeks)	528 mg/day 40–640 mg/day	85% response rate	Part of ‘temper’ study	[113]
Reimherr *et al.* (1987)	12	Open	Tyrosine	8 weeks	50–150 mg/kg/day	66% response rate	14-day onset of action; tolerance developed; four dropouts	[114]
Shekim *et al.* (1989)	18	Open	Nomifensine maleate	4 weeks	50–300 mg/day	94% response rate	Immediate response; one patient with allergic reaction	[115]
Shekim *et al.* (1990)	8	Open	*S*-adenosyl-L- methionine	4 weeks	≤2400 mg/day	75% response rate	Mild adverse effects	[116]
Wender *et al.* (1990)	19	Open	BPR	6–8 weeks	359 mg/day 150–450 mg/day	74% response rate	Five subjects could not tolerate lowest dose and dropped out; ten subjects with improvement at 1 year	[117]
Wilens *et al.* (1995)	37	Open, Retrospective	Desipramine Nortriptyline	Mean: 50 weeks	183 mg/day 92 mg/day	68% response rate	Comorbidity unrelated to response; 60% on stimulants, 84% on concurrent meds; response sustained in 54% of patients	[118]
Adler *et al.* (1995)	16	Open	Venlafaxine	8 weeks	110 mg/day 25–225 mg/day	83% response rate	Four subjects on other meds; four dropped out; 50% reduction in Sxs	[119]

Study (year)	n	Design	Medication	Duration	Total dose mean and/or range	Outcome	Comments	Ref.
Hedges *et al.* (1995)	18	Open	Venlafaxine	8 weeks	96 mg/day 50–150 mg/day	50% response rate	Side effects led to 39% drop out rate; study divided into two groups, those who could tolerate medication and those who could not	[120]
Findling *et al.* (1996)	10	Open	Venlafaxine	8 weeks	150 mg/day (seven of nine) 75–150 mg/day	70% response rate	Improved anxiety scores; one dropout	[121]
Wilens *et al.* (1996)	43	Double-blind, placebo parallel	Desipramine	6 weeks	147 mg/day	68% response rate (0% placebo)	Comorbidity or levels not related to response	[122]
Ernst *et al.* (1996)	24	Double-blind, placebo parallel	Selegiline	6 weeks	20 mg/day, followed by 60 mg/day	Mild improvement; 60-mg dose better	High placebo response, mild side effects; three arms	[123]
Spencer *et al.* (1998)	22	Double-blind, placebo crossover	ATX	7 weeks	76 mg/day	50% response rate (9% placebo)	Noradrenergic agent; Well tolerated	[124]
Wilens *et al.* (1999)	32	Double-blind, placebo crossover	ABT-418	7 weeks	75 mg/day	40% response rate (13% placebo)	Nicotinic analog; attentional symptoms improved preferentially	[125]
Taylor *et al.* (2000)	22	Double-blind, placebo crossover	Modafinil d-AMP	7 weeks	207 mg/day 22 mg/day	48% response rate 48% response rate	Improved neuropsychology with both Tx	[126]
Cephalon (2000)	113	Double-blind, placebo crossover	Modafinil	7 weeks	100 and 400 mg/day	No difference vs placebo	Cephalon report	[127]
Taylor *et al.* (2001)	17	Double-blind, placebo crossover	Guanfacine d-AMP	7 weeks	1 mg/day 0.25–2 mg/day 10 mg/day 2.5–20 mg/day	Both Tx improved vs placebo	Well tolerated; neuropsychology improved	[128]
Wilens *et al.* (2001)	40	Double-blind, placebo parallel	BPR SR	6 weeks	362 mg/day 100–400 mg/day	52% response rate (11% placebo)	Delayed onset of action; well tolerated	[129]
Upadhyaya *et al.* (2001)	10	Open	Venlafaxine	12 weeks	75–300mg/day	Significant improvement in ADHD and alcohol craving and frequency	SUD study; four out of ten subjects completed 12 weeks	[130]
Kuperman *et al.* (2001)	30	Double-blind, placebo parallel	BPR SR MPH	7 weeks	Maximum 300 mg/day Maximum 0.9 mg/kg/day	64% response rate BPR 50% response rate	Not statistically significant vs placebo; n = 8–11/group	[131]

Study (year)	n	Design	Medication	Duration	Total dose mean and/or range	Outcome	Comments	Ref.
						MPH (27% placebo)		
Wilens *et al.* (2001)	32	Open	BPR SR	6 weeks	385 mg/day	41% response rate	Substance abusers; mild effect on substance abuse	[132]
Levin *et al.* (2002)	11	Single-blind	BPR	12 weeks	400 mg/day 250–400 mg/day	47% response rate	Cocaine abusers; reduced cocaine use	[133]
Wilens *et al.* (2003)	36	Open	BPR SR	6 weeks	370 mg/day 200–400 mg/day	70% response rate by CGI	Bipolar adults with ADHD; no manic activation	[134]
Michelson *et al.* (2003); Simpson *et al.* (2004)	536	Double-blind, placebo parallel	ATX	10 weeks	60, 90 or 120 mg/day	58% response rate	Combination of two, separate multisite studies; improved functioning and less disability	[135, 136]
Adler *et al.* (2005); Adler *et al.* (2008); Marchant *et al.* (2011)	384	Open	ATX	Mean: 40 weeks	99 mg/day	Decrease on CAARS 33%	Continuation of Michelson *et al.* [135]; safety and efficacy established in adults with ADHD	[137–139]
Wilens *et al.* (2005)	162	Double-blind, placebo parallel	BPR ER	8 weeks	393 mg/day	53% response rate on ADHD-RS (31% placebo)	Medicine provided benefit throughout day vs placebo; no serious or unexpected AEs	[140]
Wilens *et al.* (2005)	6 adults	Open	Donepezil	12 weeks	9 mg/day 2.5–10 mg/day	55% improvement on CGI	Not well tolerated	[141]
Reimherr *et al.* (2005)	47	Double-blind, placebo parallel	BPR SR	6 weeks	298 mg/day 100–400 mg/day	41% response rate on CGI (22% placebo)	Not statistically significant vs placebo	[142]
Adler et al. (2006)	218	Double-blind, multicenter	ATX		80 mg once daily versus 40 mg twice daily	Both treatments efficacious, twice daily treatment had greater effect	Changes in dosing are not associated with greater AEs or safety risks	[143]
Wilens *et al.* (2006)	11	Double-blind, placebo crossover	ABT-089	8 weeks	4, 8 and 40 mg/day	ABT-089 was more effective than placebo on CAARS and CGI	Nicotinic partial agonist; no safety or side effect profiles were observed; study interrupted	[144]
Biederman *et al.* (2006)	28	Double-blind, placebo parallel	Galantamine	12 weeks	20 mg/day 8–24 mg/day	22% response rate on CGI (11% placebo)	Study did not support the use of galantamine; no	[145]

Study (year)	n	Design	Medication	Duration	Total dose mean and/or range	Outcome	Comments	Ref.
							statistically or clinically significant greater reduction in ADHD symptoms	
Levin *et al.* (2006)	98	Double-blind, placebo parallel (32 MPH, 33 BPR, 33 placebo)	MPH SR BPR SR	12 weeks	10–80 mg/day 100–400 mg/day	34% MPH and 49% BPR response rates on AARS (46% placebo)	SUD study; MPH & BPR did not provide a clear advantage over placebo	[99]
Wilens *et al.* (2008)	126	Double-blind, placebo parallel	NS2359	8 weeks	0.5 mg/day	33% response rate on ADHD-RS (27% placebo)	Triple amine-reuptake inhibitor; no serious AEs; some attentional improvement on neuropsychological testing	[146]
Wilens *et al.* (2008)	147	Double-blind, placebo parallel	ATX	12 weeks	90 mg/day 25–100 mg/day	Improved ADHD; ATX reduced cumulative heavy drinking days 26% vs placebo	SUD study; no serious AEs or specific drug–drug reactions related to current alcohol use; no effect on relapse rate vs placebo	[147]
Levin *et al.* (2009)	20	Open	ATX	12 weeks	80 mg/day 20–100 mg/day	50% response rate on AARS	Cocaine abusers; little to no effect on cocaine abuse	[148]
Johnson *et al.* (2009)	20	Open	ATX	10 weeks–1 year	85 mg/day 40–100 mg/day	50% response rate on CGI	Side effects led to 95% drop-out rate by 10 weeks; only one patient continued treatment for 1 year	[149]
Adler *et al.* (2009)	442	Double-blind, placebo parallel	ATX	14 weeks	83 mg/day 40–100 mg/day	ATX monotherapy improved ADHD Sx and comorbid social anxiety disorder	Rates of insomnia, nausea, dry mouth and dizziness were higher with ATX than with placebo	[150]
Adler *et al.* (2009)	501	Double-blind, placebo parallel	ATX	6 months	85 mg/day 25–100 mg/day	Once-daily morning- dosed ATX was efficacious when measured 10 weeks and 6 months after initiating Tx	AEs similar to previous trials	[151]

Study (year)	n	Design	Medication	Duration	Total dose mean and/or range	Outcome	Comments	Ref.
Wilens *et al.* (2010)	32	Open	BPR SR	6 weeks	100–400 mg/day	66% response rate on ADHD RS	SUD study; 19 out of 32 completed 6-week protocol; no clinically significant reductions observed in self-report of SUD or CGI SUD scores	[152]
Surman *et al.* (2010)	45	Open	ATX	6 weeks	79 mg/day 50–120 mg/day	64% response rate on CGI and AISRS	ADHD-NOS population, similar outcome vs full ADHD; no serious AEs	[153]
Adler *et al.* (2010)	18	Open	ATX	10 weeks	25–120 mg/day	Improvement in ADHD, reduced cravings	SUD study; 12 out of 18 completed	[154]
McRae-Clark *et al.* (2010)	38	Double-blind, placebo-controlled	ATX	12 weeks	25–100 mg/day	Improvement in ADHD, not marijuana use	SUD study; 16 out of 38 completed	[155]
Takahashi *et al.* (2011)	45	Open	ATX	8 weeks	114 mg/day 40–120 mg/day	Statistically significant changes in CAARS and CGI scores	No serious AEs were reported	[156]
Young *et al.* (2011)	502	Double-blind, placebo-controlled	ATX	24 weeks	90 mg/day 40–100 mg/day	68% response rate (42% placebo)	AEs overall and for on-label or slow titration ATX were similar and consistent with previous adult ATX studies	[157]
Total								
n = 47	4069 6–536 (range)	Double: 23 Single: 1 Open: 23	BPR:10 ATX:14 Others: 23	2 weeks–1 year	BPR: 100–450 mg/day ATX: 25–320 mg/day	Variable response	Some delay in therapeutic response – may be related to titration schedule. Response rates typically less than stimulants	

Response rate refers to subject reporting much-to-very-much improved (i.e., by CGI) or clinically significant reduction in symptoms on ADHD rating scales.

AARS: Adult Attention-Deficit/Hyperactivity Disorder Rating Scale; ADHD: Attention-deficit/hyperactivity disorder; AE: Adverse event; AISRS: Adult Attention-Deficit/Hyperactivity Disorder Investigator Symptom

Rating Scale; ATX: Atomoxetine; BPR: Bupropion; CAARS: Conner's adult ADHD rating scale; CGI: Clinical Global Impression; d-AMP: Dextroamphetamine; Dx: Diagnosis; L-DOPA: L-3,4- ER: Extended dihydroxyphenylalanine; MPH: Methylphenidate; NOS: Not otherwise specified; RS: Rating scale; SR: Sustained release; SUD: Substance use disorder; Sx: Symptom; Tx: Treatment.