Treating Attention-Deficit/Hyperactivity Disorder in Adults: Focus on Once-Daily Medications

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ABSTRACT

Objective: To review the efficacy, safety, and abuse liability of approved treatments in adults with attention-deficit/hyperactivity disorder (ADHD), with a focus on once-daily medications.

Data Sources: PubMed was searched for relevant studies/reviews in English from 2002 to 2011 on adult ADHD treatments.

Study Selection: Keywords used in the search were *ADHD*, *adults*, and *treatment*. Limits included only clinical trials, meta-analyses, randomized controlled trials, and reviews including adults (aged ≥ 19 years).

Data Extraction: Selection criteria returned 471 publications. Retrieved studies were excluded if they primarily focused on children, treatments not indicated for ADHD, or ADHD and comorbid conditions.

Data Synthesis: An epidemiologic survey revealed that 10.9% of adults identified with ADHD had received treatment during the prior 12 months. Treatments for ADHD in adults include pharmacologic and nonpharmacologic options. US Food and Drug Administration–approved long-acting stimulants and a nonstimulant with proven efficacy and safety profiles have been developed and include osmotic-release oral system methylphenidate hydrochloride (OROS-methylphenidate), extended-release dexmethylphenidate hydrochloride, mixed amphetamine salts extended release (MAS-XR), the nonstimulant atomoxetine hydrochloride, and the prodrug lisdexamfetamine dimesylate. Long-acting stimulants differ in formulation characteristics used to achieve extended release, with OROS-methylphenidate employing an osmotic-release technology, extended-release dexmethylphenidate hydrochloride and MAS-XR using pH-dependent beads, and lisdexamfetamine dimesylate using prodrug technology. These features variably affect pharmacokinetic characteristics, duration of action, and abuse liability. While all long-acting medications have varied pharmacokinetic features, mechanism of action, and duration of effect, all are generally efficacious and safety profiles are similar.

Conclusion: Approved long-acting treatments in adults with ADHD were effective in improving symptoms and were generally well tolerated.

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Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral disorder,[1] with a prevalence of approximately 3% to 7% in school-aged children.[2] ADHD persists into adulthood in up to 65% of cases,[3] causing impairments in multiple domains of functioning in various settings.[2] An epidemiologic study[4] of adults with ADHD reported a prevalence of 4.4%. Of those with ADHD, 25.2% reported ever having received treatment, and only 10.9% received treatment during the prior 12 months.[4]

Treatment options encompass psychosocial and pharmacologic treatments approved by the US Food and Drug Administration (FDA) for adults with ADHD including long-acting stimulants (osmotic-release oral system methylphenidate hydrochloride [OROS-methylphenidate],[5] extended-release dexmethylphenidate hydrochloride,[6] and mixed amphetamine salts extended release [MAS-XR]),[7] the nonstimulant atomoxetine hydrochloride,[8] and the stimulant prodrug lisdexamfetamine dimesylate.[9] Each option has its own clinical advantages and limitations and except for atomoxetine has abuse liability. This review provides a discussion of the clinical evidence supporting use of each treatment for ADHD in adults.

METHOD

PubMed searches identified relevant studies and critical reviews published in English between 2002 and 2011 on the treatment of ADHD in adults. Keywords used in the search were *ADHD*, *adults*, and *treatment*, and limits included only clinical trials, meta-analyses, randomized controlled trials, and reviews including adults (aged ≥ 19 years). These criteria returned 471 publications. Studies on children were excluded, as were studies of medications not indicated for ADHD treatment and studies on ADHD treatment and comorbid conditions. The remaining citations relevant to this review are described here. Relevant abstracts presented at annual professional meetings of the American Academy of Child and Adolescent Psychiatry, American Psychiatric Association, New Clinical Drug Evaluation Unit, Society of Biological Psychiatry, and US Psychiatric and Mental Health Congress between 2007 and 2009 not published elsewhere also were included.

RESULTS

Treatment Options for ADHD

Effective ADHD management requires recognition of its chronic nature. Treatment may include nonpharmacologic (psychosocial) therapy and/or pharmacologic therapy (stimulant or nonstimulant agents),[10] singly or in combination.

Nonpharmacologic therapy. Pharmacotherapy is generally considered first-line treatment for ADHD; however, some adults

Clinical Points

- Attention-deficit/hyperactivity disorder (ADHD) causes substantial functional impairments in everyday life for many adults.
- An understanding of the available nonpharmacologic adjunctive or alternative options and the unique characteristics of various long-acting pharmacotherapy options is critical to the ongoing management of ADHD in clinical practice.
- The potential for functional clinical improvement with effective treatment underscores the value of appropriate diagnosis and treatment of adults with ADHD.

may continue to have residual symptoms and functional impairments.[10] There is renewed interest in evidence-based, nonpharmacologic strategies to supplement pharmacotherapy, particularly for adults. Cognitive-behavioral therapy (CBT) can interrupt a patient's cycle of symptoms by providing effective compensatory strategies. CBT can help patients identify thoughts and behaviors exacerbating their symptoms and provide strategies to restructure their work and/or home environments to become better organized and less distracted.[10]

One controlled study[11] assessed the efficacy of CBT in adults with ADHD; 44 adults with ADHD received either no therapy or a program of group CBT focusing on psychosocial skills, individual coaching, and workbook exercises. Approximately 50% of each group was also receiving pharmacotherapy. Participants who received CBT had significantly greater improvement in ADHD symptoms than did controls (effect size [d] = 1.4).[11] Effect sizes of 0.2, 0.5, and 0.8 can be categorized as small, medium, and large magnitude of drug effect, respectively,[12,13] suggesting that this effect size of 1.4 was large. Clinical significance was assessed by determining the number of treatment responders, defined as a 33% decrease in ADHD symptoms as assessed by the *DSM-III-R* ADHD checklist.[11] One year after treatment, 50% of participants in the CBT group were classified as clinical responders (d = 1.4).[11]

In another study, 31 adults on a stable medication regimen for ADHD were randomized to receive individual CBT with continued pharmacotherapy or pharmacotherapy alone.[10] The CBT was customized to the individual's symptoms, addressing cognitive skills such as organization/planning, managing distractions, cognitive restructuring, time management, anger/frustration management, and communication skills. Participants in the adjunctive CBT group scored significantly lower on the ADHD Rating-Scale-IV (ADHD-RS-IV) (P < .01), Clinical Global Impressions (CGI)–Severity of Illness scale (P < .002), Current Symptom Scale (P < .0001), Hamilton Depression Rating Scale (P < .01), Hamilton Anxiety Rating Scale (P < .04), and Beck Anxiety Inventory (P < .04) versus pharmacotherapy alone. Effect sizes for differences between pharmacotherapy alone or combined with CBT were 1.2, 1.4, 1.7, 0.65, 0.55, and 0.43, respectively.[10]

Recently, metacognitive therapy, a form of psychosocial therapy using cognitive-behavioral principles to encourage and support development of executive self-management skills, has also been proven effective in reducing the severity of ADHD symptoms in adults.[14] A cohort of 88 adults with ADHD received 12-week metacognitive therapy or supportive psychotherapy group-based intervention. Participants who received metacognitive therapy showed greater improvement in measures of inattention (eg, inattention subscale of the Adult ADHD Investigator Symptom Rating Scale [AISRS] and the Conners' Adult ADHD Rating Scales–Self-Report: Long Version [CAARS-S] inattention/memory subscale) versus supportive psychotherapy. Clinical responder analyses indicated that therapeutic clinical response was achieved by 19 (42%) and 24 (53%) participants in the metacognitive therapy group but by only 5 (12%) and 12 (28%) participants in the supportive psychotherapy group using AISRS and CAARS-S criteria, respectively. Metacognitive therapy was also associated with larger improvements versus supportive psychotherapy on measures of ADHD symptoms such as the AISRS.[14]

Another form of therapy that may be used to manage ADHD in adults is dialectical behavioral therapy (DBT)–based psychotherapy developed in Germany.[15,16] As noted by Hirvikoski and colleagues in the DBT study,[16] the majority of available psychotherapy options for adults with ADHD have been CBT based, with many studies limited by small sample sizes and omission of appropriate placebo arms. The Hesslinger et al manual[15] was used in the DBT study by Hirvikoski et al[16] with minor modifications on the basis of pilot group feedback. Adults with ADHD (n = 51) on stable pharmacotherapy or taking no medication were randomized to either the DBT-based skill training group (n = 26) or the control group (parallel loosely structured discussion; n = 25). Participants were administered self-rating scales prior to randomization and posttreatment. The themes and content of the 14 DBT sessions in the study included clarification, 3 mindfulness acceptance tool sessions (neurobiology and mindfulness I, homework and mindfulness II, and mindfulness III), 2 change tool sessions (dysfunctional behavior/behavior analysis), emotion regulation, depression/medication in ADHD, impulse control, stress management, chaos and control, dependency, ADHD in relationships/self-respect, retrospect, and outlook.[16] For study completers who remained stable with their initial pharmacotherapy, a significant improvement in ADHD symptoms occurred in the DBT versus control group. However, no reduction in comorbidity occurred in either study group.[16] Furthermore, due to limited research, the effectiveness of DBT versus CBT or other forms of psychotherapy has yet to be determined. However, these findings suggest that "ADHD-specific, skill-based, structured, and brief psychological interventions for adults are effective."[17(p649)]

Pharmacotherapy. Pharmacotherapy, with demonstrated efficacy and safety, continues to be a mainstay of ADHD treatment.[3] At present, there are no officially sanctioned guidelines for pharmacologic treatment of adult ADHD.[18] All FDA-approved stimulants for treatment of ADHD in adults contain either methylphenidate or amphetamine. Both drugs are believed to enhance neurotransmission of dopamine and norepinephrine, but they do so in different ways: methylphenidate blocks dopamine reuptake,[19,20] whereas amphetamines block dopamine reuptake and increase dopamine release.[19] Among adults, the median treatment duration may be longer with amphetamine-based treatments than with methylphenidate-based treatments.[21] There are no current clinical predictors of which patients will respond preferentially to particular stimulants.[3] If close relatives have been treated successfully for ADHD, clinicians sometimes empirically rely on clinical treatment response seen in a new patient's relatives to guide initial treatment choice. The choice of methylphenidate- or amphetamine-based products should be left to the physician and the patient.[18]

While stimulants are generally effective in treating ADHD symptoms, in clinical practice some patients show poor response; some others may refuse medication due to fear of dependence or treatment-emergent adverse events (TEAEs). The only currently FDA-approved nonstimulant for adult ADHD is atomoxetine, a highly specific inhibitor of presynaptic norepinephrine reuptake with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors.[8]

All FDA-approved medications for ADHD treatment in adults are long acting and include: OROS-methylphenidate,[5] extended-release dexmethylphenidate,[6] MAS-XR,[7] atomoxetine,[8] and lisdexamfetamine dimesylate.[9] Long-acting stimulants show effectiveness and side effects similar to those seen with immediate-release stimulants.[22] Although immediate-release medications are not FDA approved for use in adults with ADHD, an analysis from Verispan's Vector One National program[23] of total retail prescriptions for ADHD medications in March through May of 2008 (representing approximately 7 million prescriptions in the United States) revealed that 46% of adults were prescribed an immediate-release stimulant versus only 14% of pediatric patients.

Osmotic-Release Oral System–Methylphenidate

OROS-methylphenidate has an immediate-release outer coating and a core that delivers methylphenidate based on osmotic pressure.[24] This technology combines the benefits of immediate-release and extended-release formulations by providing a sustained drug release over 6 to 8 hours. In part 1 of a 2-part study, an open-label, randomized, 3-treatment, 3-period, crossover pharmacokinetics study in 36 healthy adults compared OROS-methylphenidate versus immediate-release methylphenidate and a sustained-release methylphenidate. OROS-methylphenidate increased mean methylphenidate plasma concentrations gradually, with time to maximum concentrations (T_{max}) at approximately 6 to 8 hours.[25] Peak concentrations for the sustained-release formulation were observed at approximately 4 hours. For the immediate-release regimen (dosing every 4 hours for 3 doses), plasma concentrations fluctuated along with the oral dosing, and peak concentrations were at approximately 6.5 hours. The maximum plasma concentration (C_{max}) for OROS-methylphenidate was significantly lower than immediate-release methylphenidate and the sustained-release formulation.[25] The second part of the study, an open-label trial of 32 healthy adults, demonstrated that terminal half-life and mean area under the curve for methylphenidate were similar after single and multiple doses of OROS-methylphenidate.[25]

A randomized, crossover pharmacokinetic study comparing extended-release dexmethylphenidate to OROS-methylphenidate in 36 adults showed a biphasic plasma concentration–time profile for both and equivalent total exposure.[26] Extended-release dexmethylphenidate exhibited greater earlier exposure and maximum plasma concentration versus OROS-methylphenidate, while OROS-methylphenidate had higher plasma methylphenidate concentrations at later time points.[26]

In a randomized, placebo-controlled, 6-week trial of OROS-methylphenidate, 149 adults with ADHD received either OROS-methylphenidate titrated as needed (up to 1.3 mg/kg/d) or placebo.[27] In the OROS-methylphenidate group, 66% were clinical responders (defined as Clinical Global Impressions–Improvement scale [CGI-I] ratings of much or very much improved and a ≥ 30% reduction in ADHD symptom scores on the AISRS), and 39% in the placebo group were responders ($P = .002$).[27] Treatment-emergent adverse events that occurred more frequently with OROS-methylphenidate versus placebo were decreased appetite (34% vs 3%, $P < .001$); dry eyes, nose, and mouth (34% vs 7%, $P < .001$); gastrointestinal symptoms (28% vs 14%, $P = .03$); tension/jitteriness (18% vs 0%, $P < .001$); sleep problems (18% vs 5%, $P = .02$); cardiovascular complaints (9% vs 1%, $P = .04$); depression (8% vs 0%, $P = .02$); dizziness (7% vs 0%, $P = .02$); and anxiety (6% vs 0%, $P = .03$). No clinically significant episodes of depression or anxiety occurred.[27] A higher proportion of participants in the OROS-methylphenidate group versus controls (9% vs 1%, $P = .04$) had clinically significant heart rate elevations (> 100 bpm).[27] Mean changes in heart rate at endpoint were 4.5 bpm and –2.7 bpm ($P < .001$) for OROS-methylphenidate and placebo, respectively.[27] Of note in this trial, as with other stimulant trials, participants with known chronic medical conditions including cardiovascular disease were excluded.[27]

In a 5-week, fixed-dose study, 402 adults with ADHD received OROS-methylphenidate (18, 36, or 72 mg/d) or placebo.[28] For each OROS-methylphenidate group, scores for the CAARS Observer forms total score were better versus placebo ($P < .015$), although they were not significantly different from each other. For the 18-, 36-, and 72-mg/d methylphenidate groups, 50.5%, 48.5%, and 59.6%, respectively, were clinical responders (≥ 30% reduction in

ADHD symptoms using the CAARS Observer total score). The percentage of clinical responders in all 3 treatment groups significantly differed from the placebo group (27.4%, $P < .001$).[28] The effect sizes (d) for the 18-, 36-, and 72-mg/d groups were 0.38, 0.43, and 0.62, respectively. Of TEAEs observed in > 10% of participants receiving OROS-methylphenidate, only decreased appetite and dry mouth were dose related; most TEAEs were mild or moderate in intensity. No significant differences in change of cardiac parameters between the OROS-methylphenidate groups and placebo were reported.[28]

In 20 women with ADHD who were mothers of children with ADHD and who received OROS-methylphenidate (maximum tolerated dose following a 5-week titration period) or placebo for 2 weeks, OROS-methylphenidate resulted in improved inattention and ADHD index scores ($d = 0.48$ and 0.38, respectively) versus placebo.[29] Treatment also improved scores on several domains of the Alabama Parenting Questionnaire versus placebo: parental involvement ($d = 0.52$), poor monitoring/supervision ($d = 0.70$), inconsistent discipline ($d = 0.71$), and corporal punishment ($d = 0.42$).[29]

Extended-Release Dexmethylphenidate

Extended-release dexmethylphenidate contains the *d-threo*-enantiomer of methylphenidate, which is considered to be responsible for most clinical effects of methylphenidate.[6] It employs a beaded technology using 50% immediate-release and 50% pH-dependent enteric-coated delayed-release beads.[6] Pharmacokinetics of extended-release dexmethylphenidate indicated a similar absorption rate to 2 doses of immediate-release dexmethylphenidate administered 4 hours apart.[30] The first peak C_{max} was in the range of 1 to 4 hours, and the second peak ranged from 4.5 to 7 hours. However, peak and trough fluctuation with the extended-release formulation exhibited lower plasma concentration than the immediate-release formulation. Due to first-pass effect, oral extended-release dexmethylphenidate had a mean absolute bioavailability of 22% to 25%.[30]

In a multicenter, randomized, fixed-dose, double-blind, placebo-controlled study, adults with ADHD (N = 221) received 20, 30, or 40 mg/d of extended-release dexmethylphenidate or placebo for 5 weeks.[31] Participants in all 3 extended-release dexmethylphenidate groups had significantly greater improvements in mean ADHD-RS-IV scores versus placebo: changes were 7.9 for placebo versus 13.7 ($d = 0.53$, $P = .006$), 13.4 ($d = 0.49$, $P = .012$), and 16.9 ($d = 0.83$, $P = .001$) for 20-, 30-, and 40-mg/d extended-release dexmethylphenidate, respectively.[31] The proportion of clinical responders (very much or much improved on the CGI) was 47.4% with extended-release dexmethylphenidate 20 mg/d ($P = .027$), 37.0% with 30 mg/d (P not significant), 55.6% with 40 mg/d ($P = .003$), and 26.4% with placebo.[31] Common TEAEs with extended-release dexmethylphenidate versus placebo included headache (23.0% vs 11.3%), decreased appetite (18.2% vs 11.3%), and dry mouth (15.8% vs 3.8%). Most adverse events in the extended-release dexmethylphenidate groups were mild or moderate in intensity. There were no clinically significant changes in laboratory tests, electrocardiograms, or blood pressure.[31] Mean heart rate increased (4.4 bpm) in the extended-release dexmethylphenidate groups versus a mean decrease (–1.4 bpm) with placebo ($P = .0007$).[31] In a 6-month, open-label extension (N = 170), there were no clinically notable changes in vital signs and serious cardiac adverse events or clinically remarkable changes in laboratory tests.[32]

Mixed Amphetamine Salts Extended Release

Mixed amphetamine salts extended release, which contains various salts of *d*- and *l*-amphetamine, is mechanically formulated with 2 types of drug-containing beads: immediate-release beads and enteric-coated, pH-dependent beads that release drug in the intestine wherein pH is higher. This mechanism creates a pH-dependent system designed to give a double-pulsed delivery of amphetamine, prolonging medication release.[7] In a randomized, open-label pharmacokinetics study in healthy adults, exposure to either isomer of amphetamine was considered equivalent between triple-bead MAS and MAS-XR that was supplemented 8 hours later with immediate-release MAS.[33] Moreover, median time to maximum observed concentration was approximately 8 hours for triple-bead MAS versus approximately 10 hours for MAS-XR plus immediate-release MAS.[33] MAS-XR demonstrated a rapid onset of action of approximately 1.5 hours and provided 12-hour coverage in children (aged 6 to 12 years) with ADHD.[34]

In a 4-week clinical trial, 255 adults received MAS-XR (20, 40, or 60 mg/d) or placebo.[35] Reductions in ADHD-RS-IV total scores at endpoint were significantly greater for each MAS-XR group versus placebo ($P < .001$); placebo-adjusted differences from baseline were –6.6, –7.2, and –7.8 for the 20-, 40-, and 60-mg/d groups, respectively. On the basis of ADHD-RS-IV total scores at endpoint, the mean effect size for 20-, 40-, and 60-mg/d MAS-XR was 0.8.[35] Commonly reported TEAEs in any group were dry mouth (27.4%), anorexia/decreased appetite (25.5%), insomnia (23.9%), and headache (23.6%). Most TEAEs were mild to moderate in intensity.[35] MAS-XR was associated with significant increases in pulse ($P = .025$) and systolic blood pressure ($P = .015$) versus placebo. Mean changes in pulse rate were 4.2, 5.3, 6.2, and 1.9 bpm in the 20-, 40-, and 60-mg/d and placebo groups, respectively; mean changes in systolic blood pressure were 0.3, 4.3, 0.9, and –1.9 mm Hg, respectively. These changes were not considered clinically meaningful.[35]

Atomoxetine

Clinical trials have established the efficacy of the nonstimulant atomoxetine in adults with ADHD using both twice-daily and once-daily dosing.[36,37] Oral atomoxetine is completely and quickly absorbed, demonstrating a median T_{max} of approximately 1 to 2 hours.[38] Absolute oral bioavailability of atomoxetine ranged from 63% to 94%.[38]

Although food may not affect the extent of absorption of atomoxetine, it has been reported to decrease C_{max} and delay T_{max} by approximately 3 hours.[38] It is also important to note that the bioavailability and clearance of atomoxetine can be affected by cytochrome P450 2D6 enzyme activity, which is responsible for the enzymatic clearance of atomoxetine. Whether an individual is a fast or slow metabolizer can significantly alter the plasma half-life of atomoxetine from 5.2 hours in fast metabolizers up to 21.6 hours in slow metabolizers.[38]

In 2 identically designed 4-week trials, participants were randomized to receive either atomoxetine twice daily (titrated to 60–120 mg/d) or placebo.[36] In both studies, there was a greater decrease in investigator-rated CAARS total scores relative to baseline for the atomoxetine group versus placebo (study 1: –9.5 vs –6.0, $P = .005$; study 2: –10.5 vs –6.7, $P = .002$). Mean diastolic blood pressure changes from baseline to endpoint with atomoxetine treatment versus placebo were 2.3 mm Hg versus 0.5 mm Hg for study 1 ($P = .063$) and 1.2 mm Hg versus 0.6 mm Hg for study 2 ($P = .556$).[36] Mean changes in systolic blood pressure with atomoxetine versus placebo at endpoint were 2.3 versus −0.8 for study 1 ($P = .015$) and 3.5 versus 0.9 for study 2 ($P = .059$).[36]

A 6-month study evaluated the efficacy of once-daily atomoxetine in adults with ADHD (N = 501).[37] Participants received atomoxetine (titrated to 25 mg/d–100 mg/d) or placebo. The atomoxetine group showed greater reduction in AISRS total scores by endpoint (–14.1) versus placebo (–10.5, $P = .002$). Atomoxetine was associated with greater weight loss versus placebo at both 10 weeks (1.3 kg, $P < .001$) and 6 months (1.6 kg, $P < .001$). Change in diastolic blood pressure from baseline at 10 weeks was 1.7 mm Hg with atomoxetine and 0.2 mm Hg with placebo ($P = .02$) and at 6 months was 1.2 mm Hg for atomoxetine and 0.5 mm Hg for placebo (P not significant).[37] Atomoxetine was associated with greater increases in heart rate versus placebo at both 10 weeks (4.5 vs 0.4 bpm, $P < .001$) and 6 months (3.8 vs 1.5 bpm, $P < .001$). Nausea (29%), dry mouth (27%), fatigue (14%), decreased appetite (13%), erectile dysfunction (10%), dizziness (8%), and urinary hesitation (6%) occurred more often with atomoxetine versus placebo ($P \leq .036$).[37]

A 6-week trial compared the safety profile of once-daily versus twice-daily atomoxetine dosing.[39] Adults with ADHD (N = 218) received either atomoxetine 40 mg twice daily or 80 mg once daily. There was no between-group difference in the frequency of any of the 4 most common TEAEs (dry mouth, insomnia, nausea, and erectile dysfunction), although nausea occurred more frequently in the once-daily group versus the twice-daily group (32.4% vs 16.4%, $P = .007$). For treatment-emergent abnormal laboratory values, the only significant difference was higher incidence of low bicarbonate in the twice-daily group (8.3% vs 0%, $P = .028$). Mean change in baseline to endpoint scores on the CAARS investigator-rated screening version, the primary efficacy measure for this study, was reduced in both the twice-daily atomoxetine group (mean baseline and endpoint values of 37.2 and 20.2, $P < .001$) and the once-daily atomoxetine group (mean baseline and endpoint values of 38.4 and 25.1, $P < .001$). However, the reduction in scores was greater in the twice-daily group compared with the once-daily group (mean decrease of 17 vs 13 points, $P < .001$).[39]

Prodrug Technology

The clinical usefulness of therapeutically effective drugs can be limited by undesirable properties such as low oral absorption, low site specificity, toxicity, instability, or poor patient acceptance.[40] Prodrugs were designed to overcome pharmacologic or pharmacokinetic barriers that may limit the use of a particular drug.[41] Prodrugs are generally compounds with little or no pharmacologic activity prior to biotransformation to the therapeutically active metabolite.[42] They have become an established tool for overcoming barriers to the utility of the associated parent drug molecule; approximately 5% to 7% of drugs approved worldwide are prodrugs.[43] They are activated in vivo by hydrolysis, oxidation, or reduction.[42] One of the nontoxic promoieties currently used as a carrier for active agents is the naturally occurring amino acid L-lysine. Prodrugs can provide improved clinical predictability by improving solubility and reducing variability of absorption.[42]

The Prodrug Stimulant Lisdexamfetamine Dimesylate

Lisdexamfetamine dimesylate is the first long-acting prodrug stimulant that is FDA approved for the treatment of ADHD in adults.[9] The therapeutically inactive prodrug is converted to L-lysine and therapeutically active *d*-amphetamine following oral ingestion.[9,44,45] The conversion of lisdexamfetamine dimesylate to *d*-amphetamine is unlikely to be affected by gastrointestinal pH and variations in normal gastrointestinal transit times.[44,46] In adults, lisdexamfetamine dimesylate has demonstrated consistent *d*-amphetamine delivery from participant to participant and within participants.[47] Absorption of lisdexamfetamine dimesylate occurs primarily in the small intestine, and conversion of lisdexamfetamine dimesylate into active *d*-amphetamine occurs in the blood.[45]

The efficacy of lisdexamfetamine dimesylate in treating adult ADHD symptoms was established in a randomized, 4-week trial involving 420 adults aged 18–55 years with moderate to severe ADHD.[48] All 3 lisdexamfetamine dimesylate dose groups (30, 50, and 70 mg/d) demonstrated significant reductions in least-squares mean ADHD-RS-IV scores of 16.2 to 18.6 versus 8.2 for placebo ($P < .0001$). CGI-Improvement scores were improved at endpoint in the lisdexamfetamine dimesylate groups versus placebo ($P < .01$). Treatment effect sizes at endpoint versus placebo were 0.73, 0.89, and 0.99 for the 30-, 50-, and 70-mg/d groups, respectively. TEAEs with an incidence > 5% in the lisdexamfetamine dimesylate group and twice that in the placebo group were decreased appetite, anorexia, dry mouth, insomnia, nausea, diarrhea, feeling jittery, and anxiety.

There were no clinically significant QTcF (Fridericia) measurements. From baseline to endpoint, least-squares mean (95% CI) changes for systolic blood pressure were 0.8 (−0.7 to 2.3), 0.3 (−1.2 to 1.8), and 1.3 (−0.2 to 2.7) mm Hg for 30-, 50-, and 70-mg/d lisdexamfetamine dimesylate and −0.5 (−2.6 to 1.5) mm Hg for placebo (*P* not significant). For diastolic blood pressure, least-squares mean (95% CI) changes were 0.8 (−0.4 to 2.0), 1.1 (−0.1 to 2.3), and 1.6 (0.4 to 2.7) mm Hg for all 3 lisdexamfetamine dimesylate groups, respectively, and 1.1 (−0.1 to 2.3) mm Hg (*P* not significant) for placebo.[48]

Participants who completed at least 2 weeks of the short-term trial[48] had the option of continuing in a 1-year, open-label extension.[49] Significant improvements in ADHD-RS-IV total scores relative to baseline were observed at all visits as early as 1 week ($P < .0001$). At endpoint, 84.1% of participants had CGI-Improvement scores showing improvement relative to baseline. Most TEAEs were of mild or moderate severity.[49] Cardiovascular effects in participants without significant known cardiovascular risks revealed a mean increase in heart rate of approximately 3.4 bpm from baseline to endpoint. However, this increase was not deemed clinically meaningful. The mean changes in systolic and diastolic blood pressure from baseline to endpoint were 3.1 and 1.3 mm Hg, respectively.[49,50]

A double-blind, placebo-controlled crossover Adult Workplace Environment trial[51] studied the efficacy, duration of effect, and safety of lisdexamfetamine dimesylate in adults (N = 142) with ADHD. This adult workplace environment design was used for the first time in a trial to assess the duration of action of an ADHD medication in adults. Lisdexamfetamine dimesylate treatment resulted in improvements in least-squares mean (SE) change from predose of Permanent Product Measure of Performance total scores versus placebo ($P < .001$) and was effective from 2 to 14 hours postdose.[51] Lisdexamfetamine dimesylate also improved mean ADHD-RS-IV scores versus placebo ($P < .0001$).[51] Additionally, recent data demonstrated that lisdexamfetamine dimesylate may improve executive function behavior and quality of life in adults.[52,53] Most TEAEs were mild to moderate in severity.[51] Any TEAEs occurred in 79.6% of participants with lisdexamfetamine dimesylate (all doses) treatment. The most common TEAEs with an incidence ≥ 10% in the dose-optimization phase of the study were decreased appetite (37%), dry mouth (30%), headache (20%), insomnia (18%), and upper respiratory tract infection (10%). There were no TEAEs reported by ≥ 10% of participants who received lisdexamfetamine dimesylate in the crossover phase, while 12% reported fatigue in the placebo group.[51]

Abuse Liability Studies

Stimulants are associated with a high abuse potential, and prolonged use may lead to dependence. Stimulants such as methylphenidate were considered a public concern on the basis of the rationale that stimulants may be abusable or addictive as intranasal or intravenous (IV) preparations.[54] Consequently, all stimulants indicated for the treatment of ADHD are US Drug Enforcement Agency Schedule II controlled substances. However, abuse liability varies with the delivery system of these formulations.[55] Generally, drugs with a more rapid rate of onset are associated with greater potential for abuse.[55] Long-acting stimulant formulations with a preferential pharmacokinetic profile and pharmacologic characteristics may decrease the potential for abuse if they provide prolonged onset time.[56] A large-scale community study of stimulant abuse among individuals enrolled in an ADHD treatment center indicated that the most frequent mode reported for stimulant abuse was "crushing" and "snorting," which may be decreased with long-acting formulations.[56] This survey concluded that prescription agents abused most often were short-acting agents that have pharmacologic and pharmacokinetic profiles, allowing the user to obtain a rapid high.[56] Nonstimulants (such as atomoxetine), inactive prodrugs (such as lisdexamfetamine dimesylate), or OROS-methylphenidate may decrease somewhat the potential for abuse on the basis of their mechanisms of action and/or delivery design.

Stimulants, as a class, may be abused on the basis of reinforcing effects due to rapid and robust dopamine increases in the brain as seen with commonly abused stimulants (eg, cocaine and methamphetamine). However, in clinical practice, stimulants may be administered at a low dose and then titrated slowly to decrease abuse potential.[57] Moreover, methylphenidate formulations did not seem to induce a reinforcing effect as did cocaine, although IV methylphenidate had an ED50 (amount that is required to block 50% of the dopamine transporter) dose half that of cocaine, indicating higher potency than cocaine for dopamine-transporter blockade.[57] These data suggest that route of administration affects the pharmacokinetic properties and ultimately abuse liability. Long-acting methylphenidate formulations with controlled delivery, such as OROS-methylphenidate, provide a means for slow ascending and sustained plasma concentrations, which mimic slow dopamine release and hence decrease abuse potential, versus the peak and trough plasma concentrations of immediate-release preparations.[57]

Lower abuser potential and diversion of OROS-methylphenidate versus immediate-release formulations have been demonstrated.[58] In a double-blind, placebo-controlled, randomized crossover study in 49 healthy adults, OROS-methylphenidate demonstrated decreased abuse liability versus immediate-release methylphenidate. These data suggest that the pharmacokinetic profile of OROS-methylphenidate contributed to slower absorption and brain entry and sustained dopamine receptor occupancy.[58] The tough shell of OROS-methylphenidate may be difficult to crush for snorting or to extract pure drug for IV or intranasal use.[58,59] A study conducted in 12 healthy adults treated with OROS-methylphenidate versus immediate-release methylphenidate indicated longer T_{max} and dopamine

receptor occupancy and no likeability effects, suggesting that abuse liability is predictable based on the delivery system.[59] Another placebo-controlled, randomized, double-blind, crossover study conducted in adult recreational drug users suggested that OROS-methylphenidate may have a lower abuse potential as indicated by lower subjective effects due to slower methylphenidate delivery.[60]

The high norepinephrine transporter affinity of atomoxetine suggests a decreased abuse liability potential; unlike stimulants, atomoxetine does not increase dopamine concentrations in brain regions (eg, the striatum or nucleus accumbens).[61,62] In 1 study of 16 recreational or light drug users that assessed various doses of atomoxetine, treatment did not indicate pleasurable subjective drug effects versus placebo,[62] but the highest dose of atomoxetine (90 mg) was below the maximum recommended 100-mg adult dose.[63] In a double-blind study of 40 participants, atomoxetine was similar to placebo in liking scores as indicated by the Drug Rating Questionnaire-Subject; it also did not have a greater abuse liability versus desipramine. Atomoxetine in doses up to 180 mg (above the recommended adult dose) demonstrated less abuse liability than methylphenidate or phentermine.[63] Overall, atomoxetine has demonstrated low abuse liability in study participants, is not classified as a controlled substance by the US Drug Enforcement Agency, and is a clinical option when stimulant abuse may be of concern.

Lisdexamfetamine dimesylate also demonstrated decreased drug liking in studies of drug abusers. In a crossover study[9,64] of 12 adult stimulant abusers with a history of IV drug abuse, lisdexamfetamine dimesylate 50-mg IV produced abuse-liking effects that were greater than placebo, but the difference was nonsignificant. In contrast, the abuse-liking effects of immediate-release *d*-amphetamine 20-mg IV were greater than placebo ($P = .01$).[64] The abuse liability of orally administered lisdexamfetamine dimesylate (50, 100, and 150 mg), *d*-amphetamine sulfate (40 mg), and diethylpropion (200 mg) were examined in a study[9,65] of 36 adults with a history of stimulant abuse. Although the amphetamine base content of 100 mg of lisdexamfetamine dimesylate is equivalent to that of 40 mg of *d*-amphetamine sulfate, study participants reported lower mean abuse-liking scores with lisdexamfetamine dimesylate 100 mg than *d*-amphetamine 40 mg ($P < .05$).[9,65] Abuse-liking scores were not significantly different between lisdexamfetamine dimesylate 150 mg and *d*-amphetamine 40 mg.[9,65]

In contrast to extended-release stimulants, which often contain immediate-release stimulant components that are susceptible to mechanical manipulation such as crushing, conversion of the lisdexamfetamine dimesylate prodrug to its active component requires conversion in the blood, potentially reducing abuse or diversion.[65] While likeability for lisdexamfetamine dimesylate is lower and dosages needed to get an equivalent effect for drug abusers are higher, clinicians still must consider the potential for abuse of stimulant medications. Another amphetamine prodrug formulation in development, KP106, demonstrated a similar decreased abuse liability profile on the basis of preclinical studies.[66]

DISCUSSION

Development of long-acting treatments for ADHD has significantly advanced the current treatment armamentarium for ADHD in adults. Moreover, the inclusion of various nonpharmacologic treatments to long-acting pharmacotherapy, such as CBT, metacognitive therapy, and DBT, has proven to be a useful alternative treatment for adults who are unable or unwilling to consider pharmacotherapy or as an adjunctive therapy to optimize treatment response. Yet, unmet patient and clinical needs remain. Most currently approved long-acting stimulant formulations rely on encapsulated matrix or beaded formulations to prolong the absorption period of the active drug,[24] potentially compromising delivery such as seen with MAS-XR by alterations in gastric pH or gastrointestinal transit if coadministered with proton-pump inhibitors.[67,68] Concurrent food intake, especially a high-fat meal, has variable effects on bioavailability of long-acting stimulants depending on the formulation tested, with MAS-XR demonstrating decreased dose exposure, OROS-methylphenidate relatively unaffected, and lisdexamfetamine dimesylate unaffected (see Ermer et al[69] for a review). In addition to concerns over consistent drug delivery, the classification of long-acting stimulants as schedule II drugs reflects their inherent risk for abuse or diversion. Several studies[58,59,63–65] have been conducted to examine the abuse potential of long-acting medications. Results from these studies suggest that while the abuse potential attributable to long-acting stimulants is lower than that observed for immediate-release stimulants, these medications are associated with potential for abuse.[58,59,63,65] Despite the advantages offered by extended-release medications with their longer duration of action and reduced potential for abuse compared with short-acting formulations and FDA approval of only long-acting stimulants, adults with ADHD are as often prescribed short-acting medications as long-acting formulations.[23]

The lack of head-to-head clinical trials comparing stimulants and nonstimulants and amphetamine- and methylphenidate-based agents makes drawing conclusions regarding relative efficacy difficult. A meta-analysis[70] compared the efficacy of long-acting stimulants, short-acting stimulants, and nonstimulant medications in the treatment of adult ADHD. The study suggested that stimulant medications were more effective than nonstimulant medications, as indicated by the number needed to treat (NNT) to obtain a positive clinical outcome. Moreover, the NNTs for most long-acting stimulants compared were similar, all having NNTs between 2 and 3. This finding suggests that one would expect to treat 2 to 3 ADHD participants with long-acting stimulants and to have 1 more success than another treatment regimen, such as nonstimulants in this case.[71] For

context, the pooled NNT for the most frequently prescribed second-generation antidepressants of the serotonin reuptake inhibitor class, consisting of treatments such as fluoxetine and sertraline, for the management of major depressive disorder ranged from 4 to 6.[72] However, such a meta-analysis of studies using different methodologies is not a substitute for head-to-head studies, and the investigators advised caution when comparing the effects of different medications across studies.[70]

When assessing the data identified and described in this review, as in any literature search, ours was limited by the selected keywords and search parameters and may have resulted in relevant articles not being recovered during the search process.

CONCLUSION

ADHD, a common disorder, causes substantial impairments in everyday functioning. Although it first presents in childhood, for many it persists into adulthood. Long-acting medications are effective options with the benefits of once-daily dosing; and they have been confirmed by existing international guidelines as the suggested first-line pharmacotherapy for the management of ADHD in adults.[73,74] Long-acting stimulants differ in formulation characteristics on the basis of extended-release technology used to deliver active medication. While all formulations support once-daily dosing, differences in pharmacokinetic features across the day and duration of action should be considered when identifying optimal treatment choices for individual patients.

Clinical trial evidence supports the efficacy and tolerability of long-acting treatments. The efficacy and safety profiles of the various long-acting stimulants appear similar. However, comparative duration of effect may be an important factor to consider on the basis of typically long adult days that mix work and home responsibilities. Abuse potential is an important concern. Treatment options for adults with ADHD regarding abuse potential include a nonstimulant with low abuse liability and long-acting stimulants, of which OROS-methylphenidate and lisdexamfetamine dimesylate have features that may provide some benefit over short-acting stimulant agents, on the basis of clinical findings of lower abuse-related liking effects. As with all stimulants, prudent clinical prescribing and monitoring are indicated for all patients, especially those with histories or risk factors for drug abuse.

Moreover, inclusion of nonpharmacologic treatment as alternative treatments or as an adjunct to long-acting stimulant pharmacotherapy provided increased benefit to participants in the management of ADHD. Treatment of adult ADHD with effective medications can rapidly lead to significant symptom improvement in many patients and may also result in improved functioning in home, social, academic, and work settings. Moreover, sustained improvement was seen for most patients in long-term studies. For patients and clinicians, the potential for such meaningful clinical improvement underscores the value of collective efforts to diagnose and appropriately treat adult ADHD.

Drug names: atomoxetine (Strattera), desipramine (Norpramin and others), fluoxetine (Prozac and others), lisdexamfetamine dimesylate (Vyvanse), methylphenidate (Focalin, Daytrana, and others), osmotic-release oral system methylphenidate hydrochloride (Concerta), sertraline (Zoloft and others).

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