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REVIEW

Once-daily medications for the pharmacological management of ADHD in adults

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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed psychiatric disorder in children and adolescents. Symptoms of ADHD often persist beyond childhood and present significant challenges to adults. Pharmacotherapy is a first-line treatment option for ADHD across all age groups. The current review's goals are (a) to critically examine the current state of knowledge regarding once-daily formulations of pharmacotherapies for treatment of adults with ADHD and (b) to provide clinicians with evidence-based information regarding the safety, efficacy and tolerability of once-daily medications for adult ADHD. The reviewed body of evidence strongly supports the use of pharmacotherapy as a first-line therapeutic option for the treatment of adults with ADHD. The once-daily pharmacological agents are effective therapeutic options for the treatment of adults with ADHD. In the US, based on the available evidence, once-daily medications are currently underutilized in adults with ADHD compared to pediatric population.

Keywords: adults, attention deficit/hyperactivity disorder, once-daily pharmacotherapies

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed neurodevelopmental psychiatric disorders in children and adolescents characterized by a variety of behavioral and cognitive symptoms, including poor impulse control, hyperactivity and inattention. According to the National Health and Nutrition Examination Survey on the prevalence, recognition, and treatment of ADHD in children age 8–15 in the US, an estimated 2.4 million children, or 8.7% of all children in this age group meet the diagnostic criteria for ADHD, based on the *Diagnostic and Statistical Manual of Mental Disorders –Fourth Edition Text Revision* (*DSM-IV- TR*).[1,2] Prior to its introduction in the DSM-III in 1980, ADHD and its core symptoms, when conceptualized as minimal brain dysfunction, were viewed by many clinicians to be specifically related to childhood and adolescence, with a tendency to gradually disappear before adulthood.[3] However, most of the adult patients, between 40% and 65%, continue to experience clinically significant symptoms of ADHD beyond their youth.[4] Today, with an estimated prevalence of this disorder of about 4.4%, approximately nine million adults in the US may meet the diagnostic criteria of ADHD, with only 11% of those adults currently in treatment.[4] According to the DSM-IV-TR criteria, diagnosis of ADHD requires a presence of six or more symptoms of inattention or hyperactivity/impulsivity, in addition to a history of impairment prior to seven years of age, with clear evidence of significant impairment in social, school

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or work functioning, at least in two different settings, and symptoms are not better accounted for by another mental illness. Three subtypes of ADHD are recognized: ADHD predominantly inattentive type (ADHD-I), ADHD predominantly hyperactive–impulsive type (ADHD-H) and ADHD combined type (ADHD-C; both inattentive and hyperactive–impulsive symptoms), with the ADHD-I subtype being the most common diagnosis in adults.[1,5]

The current diagnostic criteria for ADHD in adults have been previously criticized for its lacking of both clinical specificity and developmental sensitivity, since the diagnostic criteria were developed to be primarily applied in children and young adolescents.[6] It is also imperative to acknowledge that many of the individuals who continue to experience symptoms of ADHD during adulthood commonly no longer have the same subsets of symptoms that were present during childhood and adolescence. Therefore, it has been difficult to estimate the rate of persistence of ADHD from childhood into adulthood, as prospective studies have produced mixed results.[7,8]

Most of the adults with ADHD tend to report a marked decrease in the severity of symptoms of hyperactivity and impulsivity, but continue to emphasize the severity of inattention symptoms.[9,10] In addition, as environmental demands become more complex (eg, needs to balance families and careers, issues related to time management, and encoding and manipulating information), adults with ADHD report more cognitive deficits as well a variety of symptoms such as procrastination, low tolerance to frustration, poor motivation, and insomnia, but these symptoms are not included in the DSM-IV-TR criteria. Not surprisingly, significantly fewer adults with ADHD attend college, twice as many are divorced and half as many are completely satisfied with their professional lives and career tracks.[11] Of those adults with ADHD who do attend college, studies suggest that they are at greater risk for academic and psychological difficulties.[12] In a community sample, adults with ADHD also were found to have a high level of unemployment and educational deficits.[11] These findings could be explained, at least partially, by differences in the baseline of academic achievement and social functioning between youth with and without ADHD, since deficits in these areas are associated with lower educational achievements, which often limit future employment opportunities.[13,14] However, some of these problems also may be related to deficits in executive functioning, including sustained attention, working memory, verbal fluency, as well as motor and mental processing speed in adults with ADHD.[15–17] These deficits are found to be similar to the patterns of neuropsychological and executive function deficits observed in children and are commonly associated with significant functional impairments.[18–20] For instance, the results from a recently conducted study looking at the driving performance of individuals with ADHD using a simulated driving procedure confirmed that adults with ADHD exhibit generally poorer driving performance than controls. Although both adults with ADHD and controls demonstrated signs of impairment in response to alcohol, the findings provide compelling evidence to suggest that the cognitive and behavioral deficits associated with ADHD might impair driving performance in such a manner as to resemble that of an alcohol-intoxicated driver. Moreover, alcohol might impair the performance of drivers with ADHD in an additive fashion that could considerably compromise their driving skill even at blood alcohol concentrations below the legal limit.[21]

Gender differences in adults with ADHD have received much less attention. Based on the available data, it appears that the male to female ratio in an adult sample is close to 1.6:1, which is more similar to the gender ratio in epidemiological samples of children and adolescents, which range from 1.5:1 to 3:1, but opposite to the gender ratio reported in clinical studies with children and adolescents, where the male to female ratio is heavily skewed toward boys, ranging from 4:1 to 10:1.[22,23] At any rate, there is an ample body of evidence that ADHD affects a significant number of female patients and is as much a source of morbidity and disability for females as has been documented for males.[24]

Across the life span, ADHD has been shown to be associated with a high risk for comorbid disorders.[25–27] Based on the National Co-morbidity Survey Replication, an epidemiological study of numerous psychiatric disorders, lifetime prevalence rates of psychiatric comorbidities of adult ADHD were 45% for mood disorders, 59% for anxiety, 36% for substance use disorders (SUD), and 70% for impulse disorders, including antisocial personality and intermittent explosive disorders.[26] Data regarding the prevalence of comorbid conditions in adults with ADHD are derived from two different types of studies. In retrospective studies, the comorbid conditions are commonly identified and assessed in individuals diagnosed with ADHD in their adulthood, while in prospective studies, individuals are diagnosed with ADHD in their childhood, and the comorbid conditions are assessed and followed during the entire developmental course of the disorder.[28–30] Interestingly enough, the rates of comorbid conditions tend to be lower in prospective studies than those in retrospective studies. This discrepancy could be explained, at least partially, by the impact of the

early therapeutic interventions.[31] However, the overall relationships between different types of symptoms and behaviors within ADHD and its comorbidities are still not fully understood. Undoubtedly, the comorbid conditions contribute to the delay in diagnosis of ADHD and further complicate the clinical course of this disorder. In addition, these comorbid conditions may have a pervasive impact on the overall therapeutic response to treatment and often may require additional therapeutic modalities independent of the treatment for ADHD.

Methods

A review of relevant studies was done by searching PubMed database from January 1980 to December 2008 using the terms: *pharmacotherapy of adult ADHD* (1027 publications were identified), *once-daily medications for ADHD* (25 papers were identified), and *medications for adult ADHD* (286 publications were identified), restricting papers to English. PubMed is a service of the US National Library of Medicine and the National Institute of Health. The individual studies were too clinically heterogeneous and methodologically variable to justify a quantitative meta-analysis. For the purpose of this article, the authors chose to examine these studies based on the following empirically derived inclusion criteria:

- Study design: randomized controlled trials and quasi-randomized trials involving alternate allocation or assignment by time period.
- Participants: adults with ADHD.
- Types of interventions: once-daily pharmacological agents.
- Exclusion criteria: trials that were neither randomized nor quasi-randomized.

Selection of the studies for inclusion in this paper involved two steps. First, the authors independently reviewed the abstracts of all studies identified by the literature search, based on inclusion criteria, and excluded those for which they agreed that the eligibility criteria were not met. Next, the remaining articles were reviewed in detail and the two authors made a final decision about inclusion or exclusion by consensus.

Once-daily medications for the treatment of adult ADHD

The pharmacotherapy remains the primary therapeutic modality for ADHD, particularly in the adult population. An analysis of data on the total prescriptions for ADHD medications in the US indicated that almost seven million patients filled their prescriptions at least once in 2007. In adults alone, an increased prevalence rate of the pharmacological treatment of 15.3% has been reported for each year between years 2000 and 2005, reaching up to 0.8% of the total adult population.[32,33]

In general, there are two main classes of pharmacological agents available to treat ADHD: stimulants (ie, methylphenidate and amphetamine compounds) and nonstimulants (ie, atomoxetine).

Stimulants

For nearly fifty years, since methylphenidate (MPH) was first introduced to treat hyperactive children with behavioral problems, stimulants have remained the mainstay of treatment for ADHD.[34] Their therapeutic efficacy is generally attributed to the ability of stimulants to block the re-uptake of dopamine (DA) and norepinephrine (NE) into the presynaptic neuron and increase the release of these monoamines into the extra-neuronal space.[35] The clinical efficacy and safety of this class of drugs in both pediatric and adult populations were repeatedly demonstrated in numerous clinical and research studies.[36,37] At the same time, the therapeutic utility of this class of drugs is commonly undermined by a major concern that long-term stimulant administration might increase the risk for the development of SUD. Consistent with these concerns, epidemiological studies have demonstrated that between 17%–45% of adults with ADHD have histories of alcohol abuse and dependence, and 9%–30% have histories of drug abuse or dependence.[38] In addition, adults with ADHD and comorbid SUD have been reported to have earlier onset of substance abuse relative to adults without ADHD.[39] There is also the issue of potential misuse and diversion of stimulants. Based on data from the 2002 National Survey on Drug Use and Health conducted in the US, 2.6% of individuals 12–17 years of age and 5.9% those of 18–25 years of age had misused ADHD stimulants during some period of time.[40] Therefore, when selecting the most optimal therapeutic agent for the treatment of ADHD, particularly stimulants, there are a number of considerations. For example, most studies in adults effectively demonstrated that MPH produces subjective effects similar to cocaine and dexamphetamine in both healthy volunteers and individuals with histories of substance abuse.[41] In general, the speed of the onset of drug effects plays a significant role in determining the reinforcing efficacy of the drug and the overall risk for drug abuse or dependency. The central nervous system (CNS)-acting pharmacological agents with rapid onset of actions and short duration appear to have greater abuse liability than similar

pharmacological agents with longer duration of actions and slower onset of action.[42,43] This led to the development of a number of reformulated, long-acting agents for the treatment of ADHD with an increased duration of therapeutic action. The rationale behind this strategy is based on the ability of new delivery systems to ensure a more gradual onset and sustained delivery of medication in the brain, which may potentially contribute to decreased drug abuse potential of this class of pharmaceuticals.[44,45] In the US, there are only four extended-release once-daily preparations of stimulants approved by the Food and Drug Administration (FDA) for the treatment of adults with ADHD.

Methylphenidate

In June 2008, the FDA approved the use of an osmotic release oral system formulation of MPH (OROS-MPH) in adults with ADHD. The OROS-MPH formulation is an extended-release preparation of MPH, designed to increase the duration of therapeutic action up to 12 hours as opposed to 3–4 hours for the immediate release (IR) formulation of MPH with a once-daily administration, which is thought to reduce the potential for abuse. The clinical efficacy and safety of OROS-MPH were assessed in a randomized, six-week, placebo-controlled parallel-design study of OROS MPH in 141 adult subjects with ADHD.[46] OROS-MPH or placebo was initiated at 36 mg/day and titrated to optimal dose response, depending on efficacy and tolerability, up to 1.3 mg/kg/day. The results demonstrated that OROS-MPH is an effective option in the treatment of adults with ADHD. Treatment with OROS-MPH was associated with clinically and statistically significant reductions in DSM-IV symptoms of inattention and hyperactivity/impulsivity compared to subjects treated with placebo. Forty-four of the subjects (66%) receiving OROS-MPH and 23 subjects (39%) (n = 23) receiving placebo met *a priori* definition of response of "much" or "very much improved" on the Clinical Global Impression–Improvement Scale (CGI-I) plus a >30% reduction in Adult ADHD Investigator System Report Scale score. In terms of side effects, the treatment with OROS-MPH was associated with statistically significant increases in systolic and diastolic blood pressure, as well as heart rate.

In a double-blind study by Medori and colleagues, 401 adults 18–63 years of age with ADHD randomized in four treatment groups to receive OROS-MPH in three fixed doses (18 mg, 36 mg, or 72 mg/day), or placebo daily for five weeks.[47] The primary measure of treatment response was the Conners Adult ADHD Rating Scale (CAARS; investigator-rated) at end point compared with baseline. Treatment with 18 mg, 36 mg, and 72 mg/day OROS-MPH, compared with placebo, was associated with significantly larger improvement in CAARS total symptom score from baseline to end point than placebo. Responders (≥30% decrease of total score) were 50.5%, 48.5%, and 59.6% in 18-mg, 36-mg, and 72-mg/day groups, respectively, versus 27.4% in placebo. Incidence of adverse events was 75%, 76%, and 82% in treatment arms and 66% in placebo. The most frequent adverse events included decreased appetite (25% OROS-MPH; 7% placebo) and headache (21% OROS-MPH; 18% placebo). In OROS-MPH-treated patients, 4.3% discontinued due to adverse events. In all groups, change from baseline in blood pressure occurred at week 1, with only slight further increases or decreases from week 1 through week 5. In the 18-mg group, one serious adverse event, a cerebrovascular accident, possibly related to the study drug, was reported in a 59-year-old man who temporarily stopped treatment and recovered in 16 days.

For some period of time, heritability of ADHD has been an important topic of research endeavors.[48] Available data from a number of family studies suggest that both parents with ADHD are more likely to have their offspring diagnosed with ADHD, and children with ADHD are more likely to have parents with ADHD.[49,50] These observations coupled with the results from the studies on cognitive deficits and functional impairment in adults with ADHD provided a clinical and scientific rationale for examining the effects of pharmacological treatment on parental style.[51,52] To achieve this objective, the effects of OROS-MPH on symptoms and parenting style in mothers with ADHD were evaluated in 23 mother-child dyads in which both were diagnosed with ADHD based on the DSM-IV criteria.[53] Mothers underwent a double-blind titration of placebo or OROS-MPH (doses: 36, 54, 72, 90 mg/day) for a five-week period to an optimal dose (phase 1), followed by a two-week random assignment of placebo or maximum effective dose (phase 2). The primary outcome measures were based on CAARS ratings of maternal ADHD symptoms and Alabama Parenting Questionnaire. Secondary outcomes included side effects measures. In terms of the core ADHD symptoms in mothers during phase 1, the results indicated that OROS-MPH produced statistically significant decreases in symptoms of inattention in doses of 54, 72, and 90 mg/day ($p < 0.001$) and symptoms of hyperactivity/impulsivity in doses of 72 ($p < 0.001$) and 90 mg/day ($p < 0.01$). In addition, in doses of 72 and 90 mg/day, OROS-MPH produced significant reduction in inconsistent discipline ($p < 0.01$) and corporal punishment ($p < 0.001$). The dose of 54 mg/day and above of OROS-MPH also produced decreases in inconsistent discipline and corporal punishment ($p < 0.05$). In Phase 2, estimates

of effect size (Cohen d) were employed due to the limited power to detect statistically significant differences. Effect size was determined as the difference between the two treatment conditions: those randomly assigned to placebo compared to those randomly assigned to their most effective dose. Small effects on inattention (d = 0.48) and ADHD Index (d = 0.38) were found in those who were randomly assigned to medication versus placebo. In terms of parenting, during Phase 2, treatment with OROS-MPH was associated with medium size effects on maternal involvement (d = 0.52), poor monitoring/supervision (d = 0.70), and inconsistent discipline (d = 0.71), and much smaller effects on corporal punishment (d = 0.42) when compared to placebo. Overall, participants tolerated the medication well and reported few side effects during titration, such as irritability, stomach aches, headaches, and skin picking. No symptoms of psychosis, mania, depression or serious adverse events were reported. Pairwise comparisons suggested significant weight loss from baseline to 54 mg ($p < 0.05$), 72 mg ($p < 0.001$), and 90 mg ($p < 0.01$), from baseline to 90 mg from 0 to 6.9 kg, with a mean ± SD loss of 2.31 ± 1.62 kg.

Dexmethylphenidate

The IR-MPH preparation is a racemic mixture of the d-threo and l-threo enantiomers. The ability of MPH to enhance neurotransmission of DA and NE is largely attributed to d-theo-MPH, which led to the development of dexmethylphenidate (d-MPH).[54] Although, in some instances, it was assumed that a single enantiomer is identical to half of the racemic preparation in terms of its clinical efficacy, which, in turn, provides clear advantages of smaller doses and fewer side effects, pos hoc studies revealed a possibility of distinctly different properties between these two.[55] Consequently, the clinical efficacy, tolerability and safety of d-MPH underwent testing in clinical populations.[56] In general, the results were similar to those of racemic MPH. However, due to a short half-life, frequent administration of d-MPH was needed, which provided a rationale for the development of a long-lasting formulation (extended release or ER). The efficacy and safety of d-MPH-ER in adults with ADHD were examined in a randomized, double-blind, parallel-group, placebo-controlled study conducted by Spencer and colleagues using 20, 30, and 40 mg daily doses versus placebo.[57] The change in scores on the ADHD Rating Scale (ADHD-RS) was used as the primary efficacy variable. The instrument consists of 18 items adapted directly from the DSM-IV ADHD symptom list, modified for use in adults. Secondary efficacy outcomes included the proportion of patients with improvement ≥30% in ADHD-RS total score and final scores on CGI-I scale. Of the 221 patients randomized (127 men; 94 women; mean age 38.7 years), 184 completed the double-blind phase. For all randomized patients, the mean baseline DSM-IV ADHD-RS total score (37.0 on a scale of 0 to 54) indicated moderate to marked severity of ADHD symptomatology. Their mean baseline Global Assessment of Functioning (GAF) score was 54.6. The GAF is a numeric scale (0 through 100) used by mental health clinicians and physicians to subjectively rate the social, occupational and psychological functioning of adults, eg, how well or adaptively one is meeting various problems-in-living. The score in a range of 51–60 corresponds to moderate symptoms of disorder OR any moderate difficulty in social, occupational, or school functioning. The results indicated that all dosages of d-MPH-ER were significantly superior to placebo on both the DSM-IV ADHD-RS inattentive and hyperactive-impulsive subscales. The highest dose of 40 mg showed a trend toward being the most efficacious. All three doses of d-MPH-ER produced increases from baseline in GAF scores when compared with placebo. Mean changes were 5.4 with placebo, 11.1 with d-MPH-ER 20 mg ($z = -3.714$, $p < 0.001$), 8.7 with 30 mg ($z = -2.864$, $p = 0.004$), and 11.3 with 40 mg ($z = -2.957$, $p = 0.003$). An improvement of 10 points on the GAF scale is considered to be very significant, particularly, since the duration of this trial was only five weeks. Importantly, the average patient's score at study end point rose to above 60, a range that does not generally indicate a need for clinical treatment. Overall, the d-MPH-ER was well tolerated in all three doses. Most adverse events in the d-MPH-ER group were mild (33.3%) or moderate (45.5%) in severity. The severity of adverse events was similar across dosage groups. The most commonly reported adverse events, including headache (23.0% with d-MPH-ER and 11.3% with placebo), decreased appetite (18.2% and 11.3%, respectively), dry mouth (15.8% and 3.8%, respectively), were consistent with the well-known side effects of stimulants. No clinically significant changes in ECG or laboratory parameters occurred.

Mixed amphetamine salts

Amphetamines compounds are commonly used as a first-line treatment option for ADHD.[58] Amphetamine compounds are available in IR and extended release (XR) preparations. Mixed amphetamine salts XR (MAS XR) capsules contain a 1:1 ratio of immediate-to-delayed-release MAS pellets. Delayed-release beads are designed to release drug content approximately four hours after administration. With the delayed-release component, the capsule, taken once/day, MAS XR produced similar pharmacokinetic and pharmacodynamic effects to immediate-release MAS taken twice/day.

The safety profile and rapid onset of action of MAS XR are similar to those of the IR tablets, but the long-acting formulation provides a persistent 12-hour therapeutic effect with once-daily dosing.[57] For instance, the pharmacokinetic profile of one MAS XR 20-mg capsule is equivalent to that of two MAS IR 10-mg tablets dosed 4–6 hours apart.[60]

The efficacy, safety, and tolerability of MAS XR in adults were evaluated during a 4-week randomized, double-blind, placebo-controlled study.[61] A total of 255 patients with ADHD, combined type, were randomized to receive placebo, MAS XR 20, 40, or 60 mg daily in a 1:1:1:1 ratio using a block randomization schedule. The outcome measures included the ADHD-RS (primary) and CAARS-Short Version Self-Report (secondary). Results indicated that once-daily MAS XR 20, 40, and 60 mg daily doses were safe and effective in the treatment of adult ADHD, combined type. Subjects treated with MAS XR had significantly improved symptoms compared with placebo, as determined by the ADHD-RS. This improvement was detected as early as the first week of treatment and was maintained throughout the study. The dose-response efficacy seemed to be related to symptom severity: adults with mild symptoms had significant greater improvements with the lowest MAS XR (20 mg/day), whereas those with severe symptoms had significantly greater improvements with the highest dose (60 mg/day). Importantly, daily symptom relief continued for up to 12 hours in all three doses of MAS XR. This is an important benefit for individuals with ADHD, given the potential for missed doses with multiple daily dose regimens. Additionally, compliance with XR stimulant medications is improved and the XR platform of these formulations may result in a lower abuse liability relative to IR stimulant formulations.[62] The most commonly reported side effects included dry mouth (27.4%), decreased appetite (25.5%), insomnia (23.9%), and headache (23.6%). Most of the reported side effects were mild or moderate in intensity. There are no clinically significant cardiovascular effects associated with MAS XR in adults.

Lisdexamfetamine

Lisdexamfetamine (LDX) is the first stimulant prodrug and is indicated for the treatment of ADHD. This pharmacological agent was developed to provide a longer duration of the therapeutic effect with less of a propensity to drug abuse and drug diversion. After oral ingestion, LDX, a therapeutically inactive molecule, is converted to L-lysine, an essential aminoacid, and d-amphetamine, a main therapeutic component, during first-pass metabolism.[63]

To evaluate the efficacy and safety, LDX was compared to placebo in 3 therapeutic doses, 30, 50, and 70 mg/day, in 420 adults aged 18 to 55 years with moderate to severe ADHD.[64] Following a 7- to 28-day washout, the participants were treated with 30, 50, or 70 mg/day LDX or placebo, respectively, for four weeks (N = 119, 117, 122, and 62, respectively). The 50- and 70-mg/day groups underwent forced-dose titration. The primary efficacy measure was the clinician-determined ADHD-RS total score. The results indicated that all 3 doses produced larger changes in ADHD-RS scores than placebo (placebo = −8.2; 30 mg/day LDX = −16.2; 50 mg/day LDX = −17.4; 70 mg/day LDX = −18.6; all $p < 0.0001$ vs placebo). Importantly, these significant differences relative to placebo were observed in each treatment group, beginning at week 1 and for each week throughout. LDX was generally well-tolerated. Adverse events included dry mouth, decreased appetite, and insomnia.

Nonstimulants

The current evidence base strongly supports the use of stimulant medications as first-line agents, even though adults with ADHD do not respond to stimulants at the rate of 10%–30%. In addition, some of the patients also have a low tolerance to the most common side effects of stimulants, such as appetite suppression, dry mouth, gastrointestinal discomfort, anxiety/irritability, sleep difficulties, headache as well as the considerable clinical concerns related to impact of this class of medications on the cardiovascular system. In February 2007, the FDA instructed manufacturers of all drug products approved for the treatment of ADHD to include warnings about possible cardiovascular risks and the possibility of adverse psychiatric symptoms. The patient medication guide for MPH preparations includes a warning that MPH has been associated with a risk of stroke and heart attack in adults. In addition, in individuals with ADHD and comorbid bipolar disorder, stimulants have demonstrated a worsening of mood instability. The recurrence of manic symptoms following the initial stabilization inhibited ADHD response to medications.[65]

These concerns and unmet needs in the pharmacotherapy of ADHD in special populations (eg, patients with psychiatric comorbidities, patients with histories of SUD) have led to the development of the new generation of pharmacological agents with different mechanisms of action and lower potentials for misuse.

Atomoxetine

Atomoxetine (ATX), the first drug in the emerging class of nonstimulants, was approved by the FDA in the US for the treatment of ADHD in children, adolescent, and adult populations in 2002. A potent and selective inhibitor of the

presynaptic NE transporter, ATX has also demonstrated increases of DA in the prefrontal cortex in preclinical studies. However, in contrast to stimulants, ATX does not affect the nucleus accumbens and striatum, the areas of brain associated with the reward system. Consequently, ATX has a low potential for abuse.[66,67]

The efficacy and tolerability of ATX in adults with ADHD were examined in two clinical trials using randomized, double-blind, placebo-controlled designs during a 10-week treatment period.[68] Five hundred thirty six adults (N = 280 *study I* and N = 256 *study II*) with a diagnosis of ADHD based on DSM-IV criteria were randomized to receive ATX or placebo. The primary outcome measure for this was the sum of the Inattention and Hyperactivity/Impulsivity subscales of CAARS rated by the investigator. At each visit, clinicians also administered the CGI-Severity Scale, Hamilton Anxiety (HAM-A) and Hamilton Depression Scales (HAM-D) to assess symptoms of anxiety and depression. In addition, the self-rated version of Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) was also completed at baseline and end points. ATX was administered in two even doses (morning and late afternoon) at a total daily dosage of 60 mg. However, for some patients, based on their symptomatology, the daily dosage was increased to 90 mg/day after two weeks and 120 mg/day after four weeks. In both studies, ATX improved ADHD symptoms as measured by the Attention and Hyperactivity/Impulsivity subscales compared with placebo groups. These changes were independent of the gender and age of participants. Statistically significant changes also were observed in both studies in the ATX arms on secondary measures, including the CAARS, the WRAADS, and the CGI-S. The administration of ATX was associated with a number of side effects, including dry mouth, increased blood pressure and heart rate, insomnia, nausea, decreased appetite, and constipation. Eleven patients discontinued their participation due to the side effects in study I (six in placebo arm) and 12 patients in study II (three in placebo arm). Based on these data, the authors concluded that although the tolerability profile in an adult population is different compared to children and adolescents, overall tolerability was satisfactory, as evident by a discontinuation rate less than 10% over the 10-week treatment period.

If the pivotal studies discussed above have unequivocally demonstrated the overall safety and efficacy of ATX for the treatment of symptoms of ADHD in adult population, a number of newly published studies have also supported the notion that treatment with ATX has been associated with an improvement in quality of life. For example, Adler and colleagues examined the quality of life in adults with ADHD following their treatment with ATX using a measure of health-related quality of life (HRQL; the Medical Outcomes Study 36-item short-form health survey [SF-36]).[69] A well-recognized and validated instrument, it consists of 36 questions with a four-week recall covering eight health domains (subscales): physical functioning, bodily pain, role limitations due to physical problems, emotional problems, general health perceptions, mental health, social functioning, and vitality. Based on the scores of these subscales, two major components were calculated, the Physical Component Summary (PCS) and the Mental Component Summary (MCS).[70] The primary outcome measure for ADHD symptoms was the total symptom score based on the CAARS-Investigator Rated. A total of 218 subjects were enrolled into the initial period of three to 28 days used to ensure that all subjects met the entry criteria. Upon completion of the initial period, the participants entered a six-week, double-blind (not placebo-controlled), acute-treatment period. At the beginning of this study period, the patients were randomly assigned in a double-blind fashion to one of two treatment dosage groups of ATX therapy (40 mg twice a day or 80 mg once a day). No other dose changes were permitted during this study. If necessary, the participants were allowed to switch between the treatment arms, but only once. The decision to switch was made between the clinician and the patient. Patients unable to tolerate either of these treatment arms or requiring a dose reduction due to tolerability were discontinued from the study. Study HRQL measures were taken at the baseline and at the end of the study period. The CAARS data were collected at each post-baseline visit. As expected, the results indicated that ATX was clinically effective in reducing the overall ADHD symptoms, as measured by the CAARS. The results suggested that treatment with ATX also improved the subject's perceived quality of life. This improvement was also accompanied by statistically significant improvement in HRQL, as measured on the SF-36, in four domains of the MCS (ie, vitality, social function, role-emotional, and mental health). In addition, for those subjects with the most severe ADHD symptoms at baseline, the improvement in the MCS measure most strongly correlated with the improvement of ADHD symptoms. Clinical improvement in ADHD symptoms did not correlate significantly with changes in four domains of the PCS (ie, physical function, role physical, bodily pain, and general health).

The considerable disability and the overall negative impact of ADHD are not limited to the academic and vocational settings, but also can be evident in social situations and

recreational activities.[71] Studies of adults with ADHD have found them to be more likely to be involved in automobile accidents due to their poorer driving habits, to have more frequent accidents, and to have had more traffic violations, such as speeding, compared to control groups.[72] In view of this problem, Barkley and colleagues examined the effects of ATX on driving performance in a small sample of adults.[73] Eighteen participants (8 males and 10 females), between ages 22 to 60, diagnosed with ADHD combined type (72%) and predominantly inattentive type (28%) were included in a final sample. To test the original hypothesis, the within-subject reversal design was employed. Therefore, all participants were exposed to placebo or ATX in a counterbalanced order. Either placebo or ATX were titrated upward after one week for three additional weeks. The ATX was initiated in a subtherapeutic dose of 0.6 mg/kg/daily for a period of one week. Then, medication was adjusted upward to 1.2 mg/kg/daily for at least a three-week period. The placebo was titrated in the same fashion. The outcome measures included ADHD-RS, Safe Driving Behavior Rating Scale, Driving Anger Scale, and virtual reality driving simulator. The driving simulations tests were conducted using a virtual reality 12-minute scenario. Participants were exposed to a number of virtual driving conditions, such as driving through the highway, country, and city while following verbal directions administered by the simulator. The driving performance was assessed by an independent examiner and the self-rating of simulator driving performance. The results indicated that ATX improved the self-reported measures of ADHD symptoms, impairments ratings, and ratings of driving behavior in natural settings. However, no effects of ATX were noted on other measures of driving behavior or on the simulator. In addition, the design of this study did not allow the investigators to determine the potential impact of the practice effects on the simulator measures under both placebo and drug conditions.

Antidepressants

Wilens and colleagues evaluated the efficacy and safety of an extended-release, once-daily formulation of bupropion XL (BUP-XL) in the treatment of adults with ADHD. One hundred and sixty-two adults diagnosed with ADHD (combined and inattentive types) participated in an eight-week placebo-controlled, prospective study examining the therapeutic efficacy and safety of BUP-XL in doses up to 450 mg/day. The primary efficacy measure was the proportion of ADHD responders, defined as at least a 30% reduction in the investigator-rated ADHD-RS, at week 8. The results indicated that BUP-XL responders (53%) exceeded placebo responders (31%) ($p = 0.004$ at week 8) with a significantly greater proportion of BUP-XL responders at week 2 ($p = 0.01$). Therapeutic benefits of BUP-XL sustained throughout the day compared with placebo (morning $p = 0.033$, afternoon $p = 0.004$, evening $p = 0.024$). In addition, BUP-XL was well-tolerated, as evident by a low rate of drug-related study discontinuation (5%), with no serious or unexpected adverse events reported.[74]

Desipramine, a tricycle antidepressant, has been previously found to be clinically effective in the treatment of ADHD in children and adolescents and has been used as an alternative therapeutic agent to stimulants for more than two decades.[75,76] In adults, the clinical efficacy of desipramine was examined in a double-blind, six-week, placebo-controlled trial.[77] Forty-three patients (out of the 168 subjects screened) were initially enrolled in this study. The final group of patients consisted of 41 patients (20 women and 21 men) ranging in age from 21 to 60, with only two patients diagnosed with ADHD during childhood. Importantly, most of the patients were also diagnosed with at least one comorbid psychiatric condition. The average number of comorbid conditions was 2.8 per subject. Subsequently, in addition to the ADHD-RS, the HAM-D, and HAM-A, and the Beck Depression Inventory (BDI) were administered. Desipramine was administered once-daily and initially titrated up 100 mg/day during week 1, and up to 200 mg/day by week 2. At the end of the six-week trial, most of the patients in the treatment arm (68%) were considered much to very much improved. Therapeutic response was noted at week 2 and continued through the duration of the study. Interestingly, the therapeutic response to desipramine in this sample was independent of gender, socioeconomic status, and lifetime history of depression and anxiety disorders.

Emerging once-daily pharmacological agents

The increasing awareness of adult ADHD and the unmet medical needs for once-daily pharmacological agents have led to the development of new long-lasting stimulant medications. Triple-bead mixed amphetamine salts (SPD465) is an oral, once-daily, extended-release preparation developed to control symptoms of ADHD for up to 16 hours.[78] It contains three types of beads: 33.3% – immediate pulse-release, 33.3% - delayed pulse-release, and 33.3% – delayed extended-release beads. This combination provides symptom control not only during morning and afternoon activities, but for evening activities as well. The efficacy and safety of SPD465 were evaluated during a seven-week, randomized, double-blind,

placebo-controlled, parallel-group, dose-optimization study of 272 adults with ADHD. The primary outcome measure was change in ADHD-RS-IV, which consists of 18 items designed to reflect and assess current ADHD symptomatology.[79]

Secondary outcome measures included CGI, Time-Sensitive ADHD Symptom Scale (TASS) (measuring extended duration), Brown Attention-Deficit Disorder Scale (BADDS) (measuring executive function), Adult ADHD Impact Module (AIM-A) (measuring quality of life [QOL]), and ADHD-RS-IV hyperactivity-impulsivity and inattentiveness subscales. The results indicated that SPD465 was effective in controlling symptoms of adult ADHD up to 16 hours when compared to placebo. Importantly, the investigators reported significant improvements in executive function and QOL. The most common adverse events were typical for this class of medications and included insomnia, dry mouth, decreased appetite and weight, and headache.

Given that the well-established efficacy of the currently available once-daily pharmacological agents for the treatment of adult ADHD has been determined through the results of clinical trials in which generalizations to typical patient populations are difficult, alternative therapeutic options and approaches toward the treatment of adult ADHD are being investigated. These limitations in treatment options are further complicated by the warnings from the FDA that stimulants may be associated with sudden death and serious cardiovascular events. These concerns, for example, lead to the recent suspension of MAS-XR from the market by the health authorities in Canada. In 2005, ATX received a "black box warning", a type of warning that indicates that the drug carries a significant risk of serious or even life-threatening events, from the FDA similar to that of antidepressant medications based on reports of increased suicidal thoughts, ideations and behavior, though no such warning was required based on the results from adult studies.

Guanfacine immediate release (GIR) is a nonstimulant adrenergic agonist commonly prescribed to control hypertension and has been also used for a number of years for the treatment of ADHD as an off-label alternative to stimulants, particularly in children and adolescent populations.[80,81] The mechanism of action of guanfacine is largely attributed to its selective effects on α2a-adrenoreceptors in the prefrontal cortex (PFC). Disruption in the PFC and its projections to other brain structures can cause distractibility, inattention, impairment in memory, and impulsivity, the core symptoms of ADHD.[82]

In an adult population, the clinical utility of GIR for the treatment of ADHD was assessed in a double-blind, placebo-controlled, crossover study comparing its efficacy with that of dextroamphetamine (DAMP).[83] Seventeen adults diagnosed with ADHD based on the DSM-IV participated in three randomized two-week treatment periods of placebo, GIR, and DAMP, separated by four-day washout intervals. The primary outcome measures were based on the DSM-IV ADHD Behavioral Checklist and the Copeland Symptom Checklist for Adult ADHD. The results indicated that both drugs significantly reduced ADHD symptoms on the DSM-IV Adult Behavior Checklist for Adults over placebo ($p < 0.05$). The improvement of symptoms did not differ significantly between the two drugs. Both medications were also well tolerated. No subjects discontinued this trial due to side effects. The most commonly reported side effect of DAMP was muscle tension (N = 5), and of GIR was fatigue (N = 4). At the completion of the study and before unblinding, participants were asked about their drug preference. Four subjects chose GIR, 12 chose DAMP, and one chose placebo. All subjects choosing DAMP reported that preference to DAMP was based on the positive effects of DAMP on motivation while GIR did not have this effect. Despite the encouraging results, the investigators concluded that the overall clinical utility of guanfacine in adults with ADHD was limited by the need to administer this medication more than once daily.

Guanfacine extended-release formulation (GXR) has been specifically developed for the treatment of ADHD, and it is designed to allow once-daily dosing and improve tolerability. Initially, the single-dose pharmacokinetic properties and dose proportionality of GXR following oral administration were assessed in 49 healthy adults.[84] The single-dose pharmacokinetic properties of GXR 1-, 2-, and 4-mg tablets appeared to be statistically linear. In all three doses, GXR appeared to be well tolerated, with no serious adverse events, withdrawal, or discontinuation from study participation due to adverse events reported.

Although our search failed to identify any double-blind placebo-controlled randomized studies of GXR in adults with ADHD, the results indicated that safety, efficacy, and tolerability of GXR for the treatment of ADHD have been recently examined in two large, double-blind pivotal studies conducted in pediatric population.[85,86] In addition, an open-label extension study was also conducted to examine the long-term (up to two years) safety profile and efficacy of GXR children and adolescents.[87] Based on the outcomes from these studies, the investigators concluded that the administration of GXR significantly improved clinical symptoms of ADHD compared to placebo and commonly reported adverse

events, such as somnolence, sedation, and fatigue, were mild to moderate in severity. GXR 2–4 mg/day was generally safe over a long-term (two year) period.

Conclusions

The increasing amount of evidence regarding the impact of the persistent symptoms of ADHD from childhood into adulthood on critical areas of functioning, including education, employment, relationships with family and peers, and the development of comorbid conditions such as disorders of anxiety, depressive spectrum, and SUD, have led to better recognition of ADHD worldwide and even, in some instances, to the development of new treatment guidelines.[88]

In this light, it is imperative to acknowledge that childhood-onset and persistent ADHD was found to be associated with an early onset of alcohol use disorders, which, in turn, was associated with the developmental pathway to SUD. Individuals with ADHD were significantly more likely than controls to make the transition from an alcohol use disorder to a drug use disorder (hazard ratio = 3 .8) and were also more likely to continue to abuse psychoactive substances following a period of dependence. Consequently, a lack of treatment, inadequate treatment, or premature treatment discontinuation during childhood, adolescence, and/or early adulthood may increase a risk for the development of SUD.[89]

The long-lasting and once-daily pharmacological agents recently introduced into the clinical practice have provided clinicians with new options for the treatment of ADHD. On a practical level, these newer stimulant and nonstimulant medications can enhance compliance and even decrease the likelihood of drug misuse, abuse, and diversion. However, in comparison to the pediatric population, these pharmacological agents are still largely underutilized. According to the most recent analysis of US prescribing patterns, the long-acting agents account for 78% of ADHD prescriptions in the pediatric population (patients prior to 17 years of age), but only for 49% of adult ADHD prescriptions, in spite of the fact that adults may have even greater difficulties with medication compliance and issues related to drug abuse and diversion than those of younger age patients.[32] A number of studies have examined the patterns of compliance in adults with ADHD. The results reported by Perwien and colleagues suggested that in clinical settings, newly treated adult patients continued their treatment for ADHD for several months, but they did not consistently adhere to their therapeutic regiment for more than two months.[90] The poor adherence to the treatment also impacts its effectiveness. In a study conducted by Ramos-Quiroga and colleagues, patients were initially treated with MPH-IR for three times daily for three months and then switched to MPH-OROS once daily.[91] The results indicated that the percentage of responders went drastically up from 28.6% from MPH-IR to 91.4% for the OROS formulation. The mean numbers of days when no medicine was taken was seven-fold higher with IR than with the OROS formulation. Almost all of the patients that participated in this trial preferred the OROS formulation based on the fact that it was easier to take, which in turn, resulted in better compliance and higher effectiveness of this therapeutic option according to the authors.

The neurobiological basis of ADHD is complex. The insights from molecular genetics, neuroimaging, neurochemistry, neuropsychology, behavioral pharmacology, and epidemiological studies have unequivocally demonstrated the heterogeneity of ADHD.[92,93] For researchers and practitioners alike, this heterogeneity makes it difficult to decide on the most appropriate therapeutic agent from the arsenal of currently available medications, select the most efficacious dose, and predict the therapeutic response or side effects of their patients. To address some of these concerns, future studies are needed involving the adult population of patients with ADHD, similar to the recently reported study by Newcorn and colleagues.[94] In this large double-blind, randomized, placebo-controlled study, the therapeutic response to the commonly prescribed OROS-MPH was prospectively compared to ATX in children and adolescents with ADHD. In addition to the results indicating a differential response between the two treatments (OROS-MPH is more effective in decreasing symptoms of ADHD than ATX), there was also some evidence for preferential response, with one-third of the patients responding to either OROS-MPH or ATX, but not both. It should also be noted that the results from this study add to and extend the currently available body of evidence regarding the superiority of stimulants over nonstimulants from the earlier reports conducted under less rigorous methodological conditions. The preferential therapeutic response, which is likely based on genetic determinates, further underlines the importance of the most recent attempts to identify the phenotypes and endophenotypes associated with ADHD. These efforts are likely to pave the way for more individualized ADHD treatments with a significant therapeutic response in a large percentage of patients. It is also plausible that some subgroups of patients with ADHD will respond differently from the majority. Therefore, additional studies will be warranted to examine these differences, including the safety and efficacy studies in specific sub-populations of patients

(eg, individuals with co-morbid mood, anxiety, personality, eating disorders, and SUD).

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