

Management of attention-deficit hyperactivity disorder in adults: focus on methylphenidate hydrochloride

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Abstract: Attention-deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorders in young adults and causes significant psychosocial impairment and economic burden to society. Because of the paucity of long-term evidence and lack of national guidelines for diagnosis and management of adult ADHD, most of the data are based on experience derived from management of childhood ADHD. This article reviews the current evidence for the diagnosis and management of adult ADHD with special emphasis on the role of methylphenidate hydrochloride preparations in its treatment. Methylphenidate hydrochloride, a stimulant that acts through the dopaminergic and adrenergic pathways, has shown more than 75% efficacy in controlling the symptoms of adult ADHD. Although concern for diversion of the drug exists, recent data have shown benefits in preventing substance use disorders in patients with adult ADHD.

Keywords: adult ADHD, treatment, stimulants, methylphenidate hydrochloride

Introduction

Attention-deficit hyperactivity disorder (ADHD), characterized by inattention, hyperactivity and/or impulsivity, causes significant impairment in psychological, occupational and social functioning in adults.¹⁻³ It is estimated that 1% to 36% of children diagnosed with ADHD will continue to manifest symptoms into adulthood depending on the diagnostic criteria used.⁴ Estimates increase to between 40% and 60% when considering persistence rates in adults experiencing partial remission.⁴ Recent data suggest an adult ADHD prevalence rate of 4.4% with increased incidence in males.⁵ A retrospective analysis of National Ambulatory Medical Care survey over an 8-year period from 1996 to 2003 estimated a total of 10.5 million ambulatory adult ADHD visits accounting for 3.5% of 301 million adult mental health disorder visits.⁶ Adult ADHD diagnosis and management pose unique challenges to physicians because of an increased incidence of comorbid psychiatric and substance use disorders in this population. These comorbidities may result in substantial undertreatment in patients with adult ADHD because of providers attributing symptoms to the comorbid psychiatric disorder rather than adult ADHD.⁷ As a result, patients' ADHD may remain untreated, which has been shown to result in impairment in patients' self-care, mobility, cognition, and role functioning.^{3,5} Stimulants including methylphenidate, amphetamine and dextroamphetamine salts were the mainstay of treatment until atomoxetine, a nonstimulant, selective noradrenaline reuptake inhibitor, was approved for adult ADHD treatment. In this paper, we will briefly review the diagnosis and management

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of adult ADHD and detail the role of methylphenidate hydrochloride in the treatment of ADHD and comorbid disorders in adults.

Diagnosis

The diagnosis of adult ADHD poses challenges to clinicians as symptoms in adulthood may differ from those in childhood.^{8–10} For example, the DSM criteria require behaviors such as running or climbing excessively, which are unlikely to be symptoms present in adults.¹ Further, many ADHD adults learn over time to compensate for their symptoms and thus may not manifest symptoms seen in childhood.^{9,10} Diagnosis can be further complicated when adults present without a childhood diagnosis of ADHD and have comorbid psychiatric and substance use disorders.^{3,8} In a study by Faroane et al, most patients with adult ADHD were self-reported and self-referred, and there was significant delay in time to first diagnosis and initiation of treatment, especially in the primary care setting.³

Diagnostic criteria

The *Diagnostic and Statistical Manual for Mental disorders, Fourth Edition Text Revision* (DSM-IV-TR) requires 6 out of 9 symptoms of inattention (ie, failure to attend to detail, difficulty sustaining attention, not listening when spoken to, failure to follow through on tasks, organizational deficits, difficulty concentrating, losing items, distractibility, forgetfulness) or hyperactivity/impulsivity (ie, fidgeting, difficulty staying seated, excessive running/climbing, difficulty playing quietly, acts as though “driven by a motor”, excessive talking, difficulty awaiting one’s turn, interrupting frequently, prematurely responding to questions) be present for a diagnosis of ADHD.¹ In addition, the symptoms must be present before age 7 and result in significant impairment observable in at least two settings. The three ADHD subtypes according to DSM criteria are: predominantly hyperactive-impulsive type, inattentive type and combined type.¹ However, it is important to note that the DSM criteria were developed based on childhood presentation and may not adequately represent symptoms in adults.^{9–14}

The Utah criteria, developed for identification of adult ADHD, may be utilized as an alternative to DSM criteria. According to these criteria, an adult must have a childhood history of ADHD and current motor hyperactivity, attention deficits and 2 of the following: labile affect, temper outbursts, excessive emotional reactivity, disorganization, impulsivity and associated features of ADHD.¹⁵ One disadvantage of these criteria is the focus on affective symptoms and

requirement for hyperactivity, particularly given that these symptoms may decline more quickly over time than symptoms of inattention.¹¹ Further, according to Utah criteria, ADHD may be diagnosed only in the absence of other psychiatric disorders, posing a diagnostic challenge given the increased incidence of comorbid psychiatric disorders.^{2,16}

Assessment

Unfortunately, there are currently no assessments diagnostic of adult ADHD. Therefore, a multi-pronged approach including interviews, rating scales and checklists may be helpful in establishing a diagnosis.^{2,17} The first step is to be aware of common clinical presentations of adult ADHD. Adults with ADHD may present with cognitive (eg, difficulty concentrating, poor memory) or affective complaints (eg, anxiety, irritability, depressed mood) and/or behavioral difficulties (eg, disorganization, failure to complete projects, poor school/work performance).^{2,3,8} Further, adults with ADHD experience higher rates of disruption in their interpersonal relationships, driving-related problems (eg, accidents, citations) and substance abuse.^{18–21} Employing a screening measure, such as the World Health Organization’s Adult ADHD Self-Report Scale Screener, may be helpful in identifying patients for further evaluation.²²

Upon suspicion of an ADHD diagnosis, it is important to first conduct a thorough interview. Patients should be queried about past and present ADHD symptoms, with information gathered from family members and previous school records if possible to establish a childhood diagnosis.^{3,23} Functional impairment can be assessed by querying patients about their performance in a variety of situations during the prior week, the level of effort required to function and coping strategies utilized.^{23–25} Assessing family history of ADHD may also be helpful given that ADHD has approximately 70% heritability.^{2,26} Diagnostic interviews are available to assist with the interview process, including the Brown ADD Scale, Connor’s Adult ADHD Diagnostic Interview for DSM-IV and the Diagnostic Interview Schedule.²⁴ Rating scales, many of which require no special training and take less than 5 minutes to administer (eg, Brown ADD Scale for Adults, Connor’s Adult ADHD Rating Scale, Adult ADHD Self Report Scale, ADHD Rating Scale-IV), are available for administration to patients and their family members and can serve as useful adjuncts in the diagnostic process.^{22,27} Providers should take care to determine that symptoms are not due to other psychiatric diagnoses, such as mood disorders, anxiety disorders and personality disorders, many of which share symptoms with ADHD.^{2,3,17,25} Routine laboratory and radiological tests

are useful for differentiating ADHD from common medical conditions that can mimic symptoms of ADHD, including thyroid disorder, seizure disorders, drug interactions, hepatic diseases, lead toxicity, post-head injury, sleep disorders and hearing deficits.^{2,17} A complete blood count, metabolic profile and thyroid function studies can identify anemia, thyroid disorders or liver disorders. Routine radiological evaluation including computed tomography is not required for the initial diagnosis of ADHD and should be reserved for patients with a recent history of head trauma.^{2,17}

Treatment

Similar to the diagnostic challenges mentioned above, most recommendations for the management of adult ADHD are derived from clinical experiences in childhood ADHD treatment. Currently, there is no practice guideline available in the United States for adult ADHD management. However, the British Association for Psychopharmacology (BAP) published a guideline in 2007 for ADHD management in adults and adolescents in transition to adult services.²⁸

Adult ADHD results in significant functional and psychosocial impairment; treatment therefore consists of pharmacological, behavioral or combination interventions. As mentioned previously, comorbid psychiatric disorders and substance use disorders are not uncommon, posing unique challenges to the physician utilizing pharmacological management.³ Physicians' concerns about prescribing medications with the potential for abuse further complicate and may delay initiation of appropriate treatment.²⁹ In addition to physician bias, insurance reimbursement sources other than private or self-pay significantly reduce the likelihood of ADHD treatment, including ADHD-specific pharmacotherapy.⁶

Nonpharmacological treatment

Several behavioral strategies for assisting adults with managing their ADHD symptoms have been suggested, including organizational and time management strategies.^{17,30} Though the research is still in its relative infancy, cognitive behavioral strategies are the most commonly investigated of the nonpharmacologic strategies. Cognitive-behavioral therapy includes identification and modification of patients' maladaptive thought patterns and behaviors and has shown statistically significant improvements in ADHD symptoms, functional impairment, depression, anxiety, hopelessness, health status and self-esteem.^{30,31} Skills typically taught during cognitive-behavioral therapy include education about symptoms and medications, emotional regulation, self-esteem

building, problem-solving skills, mindfulness and strategies for improving motivation, concentration, listening, impulsivity, organization and time management.^{3,30,31} It is important to note that cognitive behavioral therapy alone may be insufficient, and thus combining it with pharmacological interventions is recommended.^{31,32} Family therapy and support groups may also prove a useful adjunct in adult ADHD management.^{2,17}

Pharmacologic treatment

Stimulants and atomoxetine are the mainstay of pharmacological adult ADHD treatment and have been shown to improve symptoms of ADHD and comorbid psychiatric disorders. They have also been shown to improve associated symptoms of adult ADHD, including self-esteem, social and family functioning, driving skills and substance use risk.^{32–35}

The most commonly used stimulants in the treatment of adult ADHD include methylphenidate hydrochloride preparations (MPH), dextroamphetamines (DEX) and mixed amphetamine salts levo amphetamine and dextroamphetamine (AMP). Pemoline, a weak stimulant medication, has been withdrawn from the market because of hepatotoxicity.³⁶ Stimulants have shown a response rate of 25% to 78% depending on the diagnostic criteria, dose of medication administered and the presence of comorbid psychiatric disorders. Response rates of greater than 75% have been demonstrated with higher doses of both methylphenidate and mixed amphetamine salts.^{37–40} Lisdexamphetamine (Vyvanse®; Shire Pharmaceuticals), the once daily prodrug stimulant, was approved by the United States Food and Drug Administration (FDA) for treatment of adult ADHD in 2007. In a study of 420 adults with moderate to severe ADHD by DSM-IV criteria, lisdexamphetamine was superior to placebo in all 3 doses, and patients tolerated it well with minimal side effects.⁴¹

Despite their benefit, it is important to note that one barrier to appropriate treatment with stimulant medications is physician discomfort with prescribing controlled substances with the potential for abuse. In one study, 38% of physicians surveyed preferred prescribing a nonstimulant medication, and 58% preferred prescribing a noncontrolled medication with no evidence of abuse potential in patients with ADHD.²⁹

Atomoxetine, a selective noradrenergic reuptake inhibitor, is the only nonstimulant medication approved by the FDA for ADHD treatment and has the benefit of not being a controlled substance. It has demonstrated efficacy in reducing

inattentiveness, hyperactivity and impulsivity with minimal side effects in children and adolescents with ADHD. Among adults with DSM-IV criteria for ADHD, administration of atomoxetine in 2 randomized controlled trials of 10-week duration (study I, $n = 280$; study II, $n = 256$) resulted in significant improvements in both inattentive and hyperactive/impulsive symptoms on the Connor's Adult ADHD Rating Scales. The discontinuation rate was less than 10% in both the studies.⁴² The most common side effects were dry mouth, decreased appetite, insomnia, erectile dysfunction and nausea with no significant cardiovascular side effects. A recent 4-year open label study of 384 adult patients demonstrated statistically significant improvement in ADHD symptom scores with minimal side effects, demonstrating the long-term efficacy and safety of atomoxetine.⁴³ Despite being recommended as a first-line treatment for pediatric patients with ADHD because of its comparable efficacy with stimulant medications and low abuse potential, among adult patients its use has primarily been limited to patients with comorbid substance use, psychiatric and tic disorders.^{32,44}

Antidepressants have demonstrated less comparable efficacy than stimulants in the treatment of adult ADHD. The response is dose-related and delayed in comparison to stimulant preparations.^{45–47} Bupropion has been the most extensively studied of the antidepressants. In a meta-analysis of 5 clinical trials comparing the efficacy of bupropion to placebo, bupropion was 2.4 times more likely to result in improved clinical outcomes.⁴⁷ The alpha-agonist clonidine has also been used in the treatment of ADHD, primarily as an adjunct to stimulants in cases of comorbid aggression, insomnia or tics.^{32,48}

Modafinil, a novel cognitive enhancer approved for the treatment of narcolepsy, has been found to improve neuropsychological task performance in children and adults with ADHD with minimal side effects and low abuse potential. An analysis of 4 randomized control trials showed significant improvement in primary outcomes and cognitive function in ADHD patients. Insomnia and headache were the more common side effects, seen in 20% of the patients. There are no data on modafinil's long-term efficacy, and hence it may be considered in patients with ADHD who do not respond to standard treatment.^{17,49}

Nonstimulants can also be combined with stimulants for patients with inadequate response and for treatment of comorbid psychiatric disorders.^{28,32,44} Patients who fail to respond to appropriate doses of stimulants may have comorbid psychiatric or developmental disorders; hence a careful re-evaluation of the patient's diagnosis is warranted. A trial of behavioral therapy may be initiated prior to adding nonstimulants

in such situations. Clonidine may alleviate symptoms of impulsivity or hyperactivity and sleep disturbance or tics from use of stimulants. Bupropion may be combined with stimulants for treatment of comorbid mood disorders, bipolar or substance use disorders.^{28,32,44}

Methylphenidate in the management of adult ADHD

Psychostimulants, especially amphetamines, were the most effective treatment for hyperactivity syndromes in children from the 1930s until methylphenidate (Ritalin®) received FDA approval in 1968.⁴⁵ Since its introduction, methylphenidate has become the most prescribed medication for ADHD treatment in children and adults.³³

Mechanism of action

Methylphenidate hydrochloride (MPH) is a piperidine derivative, structurally related to amphetamines. The exact mechanism of action of stimulants in ADHD is not completely understood, but they are presumed to act through the dopaminergic and adrenergic pathways of the frontostriatal areas in the brain.^{50,51} Unlike amphetamines which can cause a direct release of dopamine and norepinephrine into the presynaptic cleft, MPH is a mild central nervous system stimulant which acts by blocking the reuptake of dopamine and norepinephrine into the presynaptic cleft by blocking the dopamine transporter protein (DAT). MPH has also been shown to reduce the availability of striatal dopamine transporter proteins in adults with ADHD. In 10 patients treated with MPH, single photon emission computed tomography (SPECT) imaging demonstrated that MPH lowered striatal DAT availability in adults with ADHD.⁵²

MPH oral preparations are readily absorbed after oral administration with a peak plasma concentration in 2 hours. It crosses the blood-brain barrier, and 80% of the dose is excreted through urine as ritalinic acid, the main urinary metabolite.¹⁷

Preparations and dosage

MPH is available in short-, intermediate- and long-acting preparations and through a transdermal delivery system.

Short-acting preparations of MPH:

- i. Dexmethylphenidate or Focalin® (Novartis) (2.5, 5, 10 mg capsules)
- ii. Methylin® (5, 10, 20 mg tablets)
- iii. Ritalin® (5, 10, 20 mg).

Intermediate-acting preparations:

- i. Metadate® ER (10, 20 mg capsules)
- ii. Methylin® ER (10, 20 mg capsules)

- iii. Ritalin® SR (20 mg)
- iv. Metadate® CD (10, 20, 30, 40, 50, 60 mg)
- v. Ritalin® LA (10, 20, 30, 40 mg).

Long-acting preparations:

- i. Concerta® (Ortho-McNeil-Janssen) [extended-release oral osmotic release system (OROS) tablets] (18, 27, 36, 54 mg capsules)
- ii. Focalin® XR (5, 10, 15, 20 mg capsules)
- iii. Daytrana® (Shire Pharmaceuticals), the transdermal drug delivery system (10, 15, 20, 30 mg patches).

Dexmethylphenidate (Focalin®) is a more potent d-threo enantiomer of racemic methylphenidate approved for ADHD treatment with a high affinity for dopamine transporter (DAT) and requires only half the total dose of immediate acting MPH preparations. Focalin® XR is the extended-release formulation with a bimodal release pattern with bead delivery system. Each capsule of Focalin® XR contains half the dose as immediate-release MPH beads and the other half as enteric coated delayed-release beads. OROS methylphenidate (Concerta®) was approved by FDA in 2008 for use in adults and uses an oral osmotic release system for its longer duration of action. Each capsule contains 2 drug compartments and a water absorption compartment. 22% of the drug is coated on the outside of the capsule and results in immediate relief of symptoms; the remaining 78% of the medication is released more slowly.¹⁷ Due to this unique drug delivery system it cannot be crushed, injected or inhaled, further reducing the abuse potential. Daytrana is the transdermal delivery system of MPH and is well tolerated. Methylin® and Ritalin® SR are available in generic format; Metadate® CD and Ritalin® LA capsules can be opened and sprinkled on soft food. All MPH preparations are schedule II controlled substances due to the potential for abuse.³²

The initial starting dose is 10 mg/day for short-acting preparations, and the dose is titrated by 5 to 10 mg weekly to a maximum dose based on response and side effects (Table 1). The first dose is typically given in the morning with the additional dose in the afternoon or early evening for optimal symptom control. Late evening doses may exacerbate symptoms of insomnia and hence should be avoided. Long-acting preparations maybe ideal for adolescents and adults due to increased compliance and lesser abuse potential. Short-acting preparations can be combined with long-acting preparation for optimal symptom control during the day time.¹⁷

Efficacy of methylphenidate in adult ADHD

MPH has been shown to reduce symptoms of hyperactivity, impulsivity and inattentiveness and to improve on-task

behavior, academic performance and social functioning in children and adolescents.^{32,53} Although earlier studies on the efficacy of MPH in the management of adult ADHD showed equivocal results due to low doses of medication, the presence of comorbid disorders and the varying diagnostic criteria used, recent results have been promising (Table 2).^{40,54} In 1995, Spencer and colleagues conducted a randomized, 7-week, placebo-controlled, crossover study of MPH in 23 adult patients meeting DSM-III-R ADHD criteria. A daily dose of 1.0 mg/kg per day of MPH resulted in a marked therapeutic response as compared to placebo (78% vs 4%, $P < 0.0001$) in 18 of the 23 subjects, independent of gender, comorbid anxiety or depression or family history of psychiatric disorders.⁴⁰ Similar results (76% MPH vs 19% placebo) were reported by these authors in a later study of 146 adult patients with ADHD with a daily dosing of 1.1 mg/kg/day of MPH.³⁸ A 2004 meta-analysis of 6 studies (140 MPH treated adults and 113 placebo treated adults) showed a mean effect size of 0.9 ($z = 4.3$, $P < 0.001$), which was similar to the effects observed with earlier studies in children and adolescents. Larger effect sizes (1.3, $P < 0.02$) were associated with physician ratings of outcomes and larger doses of MPH (0.9 mg/kg/day or higher).⁵³

Long-acting preparations have a similar efficacy rate with greater convenience and compliance due to single daily dosing.^{32,55–59} In one study, once daily dosing of equipotent extended-release OROS MPH tablets (Concerta®) had similar efficacy to 3 times per day dosing of immediate-release MPH.⁵⁹ In a double-blind trial of 401 adults with ADHD, those treated with OROS methylphenidate (18 mg, 36 mg, or 72 mg/day), demonstrated significant improvement in total symptom score as measured by Connor's Adult ADHD Rating Scale (mean change = -10.6 for 18 mg, $P = 0.01$; -11.5 for 36 mg, $P = 0.01$; -13.7 for 72 mg, $P < 0.001$; -7.6 for placebo).⁵⁵ Improvement in executive function and oppositional/defiant symptoms has also been demonstrated in adults treated with OROS MPH.^{57,59} Most of the earlier studies were of short duration, thus data on the long-term efficacy and safety of these drugs are limited. However, a recent study of extended-release methylphenidate (methylphenidate ER) in 359 subjects for 24 weeks showed clinically and statistically significant sustained improvements in ADHD symptoms.⁶¹

Some differences in efficacy have been suggested depending on time of ADHD onset and ADHD subtype. However, in a recent study, when MPH was administered to children and adults meeting DSM-IV ADHD criteria, those meeting the childhood onset criterion had no better response

Table 1 Treatment of adult ADHD

Medication	Duration of action	Dose	Side effects	Comments
Methylphenidate (MPH) Short-acting: (Focalin, Ritalin, Methylin)	3 to 8 h	10 to 80 mg/day	Insomnia; loss of appetite; weight loss; headache; nervousness; increase in pulse rate and blood pressure	Titrate dose weekly by 5 to 10 mg; monitor pulse rate and blood pressure; ^a pregnancy risk: category C; contraindicated in lactation
Intermediate-acting: (Ritalin SR, Methylin ER, Metadate ER, Metadate CD, Ritalin LA)	8 to 12 h	10 to 80 mg/day		
Long-acting: Concerta, Daytrana (patch)	10 to 12 h	18 to 72 mg/day 10 to 60 mg/day patch		Patch on for 9 h and off for 15 h
Dextroamphetamine (DEX) Short-acting (Dexedrine)	4–6 h	5 to 45 mg/day	Insomnia; loss of appetite; weight loss; headache; nervousness; increase in pulse rate and blood pressure	Titrate by 5 mg per week; pregnancy category C; monitor blood pressure and pulse
Long-acting (Dexedrine spanules)	6 to 8 h	5 to 45 mg/day		
Mixed amphetamine salts (AMP) Adderall	4 to 6 h	5 to 40 mg/day	Insomnia; loss of appetite; weight loss; headache; nervousness; palpitation; tachycardia; elevation of blood pressure	Pregnancy category C; monitor blood pressure and pulse; dosing in the morning to reduce sleep disturbances; titrate by 2.5 to 5 mg/week
Adderall XR Lisdexamfetamine (Vyvanse)	8 to 10 h	5 to 60 mg/day 30 to 70 mg/day		
Bupropion (Wellbutrin)	12 h	37.5 to 450 mg/day	Insomnia; increase risk of seizures; headache	Pregnancy category B; effect on lactation unknown; contraindicated in patients with seizures and bulimia; response after 4 to 5 weeks
Atomoxetine (Strattera)	24 h	40 to 80 mg/day	Sleep disturbance; nausea; vomiting; dyspepsia; abdominal pain; headache; changes in blood pressure and pulse rate; jaundice and hepatotoxicity	Pregnancy category C; effect on lactation unknown; should be discontinued in patients who develop jaundice or elevated liver function tests
Tricyclic antidepressants (TCA) Desipramine or imipramine Nortriptyline (Pamelor)	24 h	10–150 mg/day 10 to 150 mg/day	Dry mouth; constipation; changes in pulse rate, blood pressure; conduction abnormalities Effects on blood pressure and heart rate, dry mouth, dizziness	Monitor therapeutic levels; response after 4 weeks; monitor ECG before and after stabilization on treatment Effective for impulsivity and hyperactivity, tics and sleep disturbances
Clonidine		0.2 to 0.4 mg/day		

Notes: ^aFDA Use in Pregnancy Ratings: Category A: No risk indicated in controlled studies; B: No evidence of risk in humans; C: Inability to rule out risk; D: Positive evidence of risk; X: Contraindicated in pregnancy.

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to methylphenidate at doses of 0.5 mg/kg/day than subjects with late-onset ADHD (eg, not meeting the childhood onset criterion).⁶² A comparative analysis of the efficacy of MPH on the subtypes of ADHD in children (ADHD inattentive type vs ADHD combined type) indicated that MPH's predominant effect was on hyperactivity and aggression in children with ADHD combined type. Effect on inattention and task performance was equal among the two groups in children.⁶³

As previously mentioned, adult ADHD patients have high rates of comorbid substance use disorders and, as a result, physicians are sometimes hesitant to initiate stimulant treatment in this population. However, research indicates that

this hesitation may not be well-founded. In a meta-analysis of 6 studies of children, adolescents and adults treated with stimulants for a minimum of 4 years (2 with follow-up in adolescence and 4 in young adulthood) and with information on childhood treatment with stimulants, a substantial reduction in subsequent alcohol and other substance use disorders was found.³⁵ Similarly, a recent 10-year prospective follow-up study of 140 children with ADHD treated with stimulants found no significant increase or decrease in alcohol, drug or nicotine use disorders.⁶⁴ In patients diagnosed with comorbid substance use disorders, the results are also promising. In one study, long-acting MPH was shown

Table 2 Efficacy of methylphenidate (MPH) in the treatment of ADHD^{38,53,55–58,60,61}

Study	N	Method	Duration	Conclusion
Faraone ⁵³	253	Meta-analysis of 6 randomized placebo controlled trials		Mean effect size for MPH was 0.9 ($P < 0.001$) and larger effect size of 1.3 was noticed with higher doses of MPH (>0.9 mg/kg/day)
Spencer ³⁸	146	Randomized, placebo-controlled, parallel study	6 weeks	Therapeutic response (76% vs 19%)
Medori ⁵⁵	401	Randomized, double blind, placebo controlled study of 18, 36 and 72 mg of OROS MPH	5 weeks	Change in total score on Connor's Adult ADHD Rating Scale: mean change -10.6 ($P = 0.01$) for 18 mg, -11.5 ($P = 0.01$) for 36 mg, and -13.7 ($P < 0.001$) for 72 mg vs -7.6 for placebo
Rosler ⁶¹	359	Randomized, placebo controlled, parallel study of methylphenidate ER	24 weeks	Response of more than 30% reduction of the WRAADDS score, 61% compared to 42% in the placebo group. 55% of subjects on MPH and 37% placebo showed improvement in CGIS
Biederman ⁵⁸	141	Randomized placebo controlled, parallel study of OROS MPH	6 week	66% of subjects ($n = 44$) on OROS MPH and 39% of subjects ($n = 23$) on placebo showed improvement in CGIS and $>30\%$ reduction in Adult ADHD Investigator System Report Scale Score
Jain U ⁵⁶	50	Double blind, placebo controlled, cross over study using once daily novel biphasic multilayer release (MLR) methylphenidate	6 weeks	Improvement in CGIS (Global Improvement: 2.6 vs 3.7; $P = 0.0015$), CAARS-S (12.2 vs 5.4; $P = 0.0083$), and CAARS-O (10.9 vs 6.6; $P = 0.1404$)
Reimherr ⁵⁷	47	Double blind, placebo controlled, crossover trial of OROS MPH		40% ($N = 19$) had ADHD with both significant emotional and oppositional symptoms. OROS methylphenidate superior to placebo for all clinical measures: total WRAADDS score decrease of 42% vs 13%, $P < 0.001$ and total ADHD-RS score decrease of 41% vs 14%, $P = 0.003$
Fallu ⁶⁰	30	Pilot, uncontrolled, open label	38 days	Statistically significant improvements observed in executive function

Abbreviations: ADHD-RS, Adult ADHD-Rating Scale; CAARS-S, Conners' Adult ADHD Rating Scales Self-rated; CAARS-O, Conners' Adult ADHD Rating Scales Observer Rated; CGI-I, Clinical Global Impressions-Improvement scale; WRAADDS, Wender-Reimherr Adult Attention Deficit Disorder Scale.

to be effective in controlling the symptoms of ADHD in patients with cocaine dependence in complete remission without any relapse of abuse.³³ Interestingly, a 14-week trial comparing the efficacy of sustained-release MPH to placebo in the treatment of cocaine-dependent adults with ADHD failed to demonstrate a significant reduction in ADHD symptoms, but did result in a reduction in cocaine use among MPH-treated patients.⁶⁵ However, MPH is still considered a second line agent for treatment of patients with adult ADHD and comorbid substance abuse disorder who do not respond to antidepressants or atomoxetine. Long-acting preparations with less abuse potential and close monitoring of patients is required if initiated on MPH.^{2,17,33}

Comparison of methylphenidate with other pharmacological agents for ADHD

Data comparing the different pharmacological agents available for the treatment of adult ADHD are very limited. Most of the clinical evidence is derived from studies on children and adolescents. When studies among adults do exist, the majority are placebo-controlled trials and not direct comparisons of the different drugs. In a meta-analysis seeking to provide an indirect comparison of short-acting immediate-release MPH with longer-acting stimulants, bupropion and atomoxetine, 22 placebo controlled trials ($n = 2203$) were evaluated. The relative risk of clinical response was 4.32 for short-acting stimulants (95% CI 3.03, 6.16), 1.87 for long-acting bupropion (95% CI 1.36, 2.58) and 1.35 for longer-acting stimulants (95% CI 0.997, 1.84). The authors concluded immediate-release MPH was more effective for the treatment of ADHD and comorbid substance use disorders with no significant adverse effects.⁶⁶

Amphetamines

There are minimal data comparing the efficacy of amphetamines with MPH preparations in adults and children, but available data suggest no significant difference in efficacy, side effect profiles or response rates between MPH preparation and amphetamine salts.^{38,40,54} In a study comparing the efficacy of OROS MPH (72 mg), extended-release amphetamine salts (30 mg) and placebo in improving simulated driving performance among 35 adolescent drivers with ADHD, OROS MPH resulted in a significant improvement in driving performance among adolescents with ADHD. Mixed amphetamine salts did not exhibit statistical significance over placebo in the driving performance of adolescents.³⁵

Atomoxetine

There are no data directly comparing atomoxetine and MPH in the treatment of adult ADHD. Earlier studies in children and adults demonstrated response rates similar to MPH in ADHD symptom reduction with minimal side effects.^{31,42} Despite comparable efficacy, there is some indication of bias in atomoxetine prescription practices. A 2006 utilization study compared prescribing practices of atomoxetine versus long-acting stimulants for adult ADHD three years after the introduction of atomoxetine for the treatment of adult ADHD. Results indicated that younger patients and females were less likely to receive atomoxetine, and patients with past-year claims for alcohol and drug dependence, psychosis, bipolar disorder and anxiety disorders were more likely to receive atomoxetine.⁴⁴

Bupropion

Sustained-release bupropion has been used off-label in the treatment of adult ADHD, particularly when patients present with comorbid depression or substance abuse disorders. However, there are very limited data comparing the efficacy of bupropion to MPH in adult ADHD treatment. In a 7-week randomized controlled trial, adult ADHD symptom reduction as measured by the Clinical Global Impression scale was 50% for methylphenidate, 64% for sustained-release bupropion and 27% for placebo.⁶⁷ A 12-week trial comparing the efficacy of sustained-release MPH or sustained-release bupropion to placebo in treating ADHD symptoms in methadone-maintained subjects with cocaine dependence or abuse did not show any significant difference between treatments because of a high placebo response. Further, there was no misuse of medication or worsening of cocaine use in subjects treated with MPH.⁶⁸

Clonidine

Clonidine is commonly used in the treatment of ADHD, particularly when patients present with comorbid aggression, insomnia or tic disorder. However, data on its use in adult ADHD are lacking. In a clinical trial of 122 children aged 7 to 12, subjects were randomly assigned to clonidine, MPH, combined clonidine/MPH or placebo. Results indicated no significant benefit of clonidine over MPH as measured by the Connor's Teachers Abbreviated Symptom Questionnaire.⁶⁹

Side effects

Similar to other stimulants, MPH can cause mild disturbances in mood, appetite and sleep which can be minimized by using the lowest effective dose and using

long-acting preparations.^{2,17,32,33} The most common side effects of long-acting preparations include headache, decreased appetite, insomnia, nervousness and nausea.^{32,55,56} Patients appear to be fairly tolerant of side effects, one study showing only 4.3% of patients treated with OROS MPH discontinuing treatment due to an adverse event.⁵⁵ MPH preparations should be used with caution in patients with prior history of seizure disorders as it can initiate seizures in higher doses.³³ MPH and other stimulants are contraindicated in patients with glaucoma, hyperthyroidism, hypertension, acute psychosis and those using monoamine oxidase inhibitors.³³

Diversion of stimulants has been a significant concern among physicians in initiating treatment for adult ADHD. These medications, particularly the short-acting preparations, are abused orally, through nasal insufflations after grinding or by injecting the dissolved drug. Approximately 7% to 11% of adolescents and young adults have reported diverting their stimulant medications. Further, approximately 11% of students without ADHD reported using MPH or amphetamine for recreational purposes.⁷⁰

Drug holidays, or the discontinuation of treatment during weekends and holidays in an effort to minimize adverse effects, should be discouraged due to lack of evidence supporting their benefit.^{2,8,17,32,33}

Monitoring parameters

Because of the effects of MPH and other stimulants on weight, blood pressure and heart rate, patients' vital signs should be closely monitored prior to therapy initiation and at periodic intervals thereafter (AHA recommendation Class I recommendation, level of evidence C).^{32,37,58,71–73} Although adult data are not available, the estimated rate of sudden death in children treated with MPH between January 1992 and December 2004 was calculated to be 0.2/100,000 patient-years, well below the rate of sudden death in the general pediatric population.³² Despite this, it is important to exercise caution when initiating treatment. In April 2008, the American Heart Association recommended evaluation for cardiac disease in children prior to initiating therapy with MPH and other stimulants and atomoxetine due to FDA warnings of cardiac deaths in children. Most of these mortalities occurred in patients with underlying structural heart disease (eg, hypertrophic cardiomyopathy). Cases of sudden cardiac death have been reported when prescribing MPH in combination with clonidine; however, such events are rare when MPH is used as a single agent. Patients should be queried about a personal history of heart disease,

symptoms of palpitation, dizziness or syncope and a family history of sudden cardiac death prior to age 40, long QT syndrome, arrhythmias and hypertrophic cardiomyopathy. A detailed medication and substance abuse history should be elicited prior to the initiation of treatment. A baseline electrocardiogram, though not mandatory, is also recommended prior to initiation of stimulant treatment (Class IIa recommendation, level of evidence C).⁷³

Due to the increased incidence of psychotic and manic symptoms among patients receiving stimulant treatment, the FDA warns that patients should also be monitored closely for psychosis and suicidal ideation while on stimulant medications.⁷⁴ It should be noted that patients treated with atomoxetine should also be closely monitored for these symptoms, as they are more commonly reported with atomoxetine than MPH. Patients should also be closely monitored for compliance with their medication regimen and for medication and other substance abuse, including random drug screens.^{2,32}

Effect of methylphenidate on pregnancy and lactation

To date, there are limited human studies examining prenatal and breastfeeding risk. Earlier drug monitoring studies did not observe increased incidence of birth defects due to MPH exposure.⁷⁵ The National Toxicology Program Center for the Evaluation of Risks to Human Reproduction reported in 2005 that there are insufficient data for pregnancy loss and reproductive effects with MPH use in pregnancy.⁷⁶ However, because of limited human data and animal data suggesting moderate risk during pregnancy, all stimulants (including MPH) carry category C risk in pregnancy.^{75,76} Despite potential for risk, there is no recommendation for termination of pregnancy for maternal exposure to MPH. However, patients should be closely monitored and counseled about the possibility of emergence of symptoms or unfavorable physiological side effects (such as changes in heart rate, blood pressure) owing to sudden withdrawal of stimulant drugs during pregnancy.⁷⁹

Data on MPH safety during lactation is limited, but it is presumed to be passed to the nursing infant due to its low molecular weight. The American Academy of Pediatrics recommends against breastfeeding while on MPH and other stimulant medications.⁷⁵

Cost

Earlier cost and efficacy studies of drug treatments for ADHD in children and youth indicated no significant

differences among treatments; however, immediate-release MPH and extended-release MPH preparations had lower total expected costs.^{78,79} In a 6-month follow up of 4569 patients receiving 3 alternative drug therapies for ADHD (OROS MPH, extended-release mixed amphetamine salts, atomoxetine), adults treated with OROS MPH had slightly lower medical and total medical and drug costs than those treated with MAS-XR or atomoxetine after adjusting for patient characteristics including substance abuse, depression, and comorbid disorders. The comparison of risk-adjusted total direct costs, including drug cost, was on average US\$156 less (8.0%, US\$1,782 vs US\$1,938) for OROS-MPH compared with extended-release mixed amphetamine salts ($P = 0.017$) and \$226 less (11.3%, \$1,782 vs. \$2,008) compared with atomoxetine ($P < 0.001$).⁸⁰

Conclusions

Adult ADHD causes academic, occupational and social dysfunction with significant economic burden to society. Currently, there are no national guidelines to aid physicians in the diagnosis and management of adult ADHD, and most of the treatment principles are based on evidence from childhood ADHD treatment. In spite of the advent of longer-acting and nonstimulant medications for the treatment of ADHD, MPH remains the most cost-effective treatment with clinically significant outcomes. Amid concerns for diversion of drugs for potential abuse, MPH (particularly short-acting, immediate-release MPH) has been shown to decrease substance use disorders in children and young adults. Long-acting preparations are beneficial because of their potential for increased compliance and lower potential for abuse. Compared with the childhood ADHD literature, there is a significant paucity of evidence on the cardiovascular and psychiatric adverse effects in adults. Further, there is limited evidence of the comparative efficacy, including long-term efficacy, and safety of different pharmacological agents. Until more data are available, immediate-release and long-acting MPH and other stimulant medications remain the mainstay of treatment for adult ADHD.

Disclosures

The authors declare no conflicts of interest.

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