Pharmacotherapy for Attention-deficit–Hyperactivity Disorder

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Abstract

Attention-deficit–hyperactivity disorder (ADHD), one of the most common psychiatric disorders worldwide, is characterised by developmentally inappropriate levels of inattention and/or hyperactivity–impulsivity. Pharmacotherapy is an important treatment option for ADHD, either on its own or in combination with behavioural, educational and family interventions. Although stimulants are the most widely prescribed medications for ADHD, with numerous studies demonstrating their efficacy and safety in children, adolescents and adults, there are other agents that have been shown to be effective and that can be useful when stimulants are not indicated. Differences exist between Europe and North America in terms of the availability of pharmacological agents, guidelines for the use of drugs and perceptions about therapeutic options. This article describes the pharmacological and clinical characteristics of different medications approved globally for the treatment of ADHD and the factors that contribute to varying treatment choices, therapeutic options and perceptions about ADHD in Europe and North America.

Keywords

Attention-deficit–hyperactivity disorder (ADHD), stimulants, children, adults, pharmacotherapy

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Attention-deficit–hyperactivity disorder (ADHD), one of the most common psychiatric disorders worldwide, is characterised by developmentally inappropriate levels of hyperactivity–impulsivity and/or inattention. ADHD has been estimated to affect 5–12% of children worldwide, with approximately 30–70% of those with ADHD in childhood showing persistence of ADHD symptoms into adolescence and up to 66% into adulthood. Children diagnosed with ADHD are impaired across a number of major domains, including their functioning at school, at home and with their peers. Children with ADHD perform less effectively in school than unaffected children in that they achieve poorer grades in academic subjects, have to repeat school grades more frequently, have more special educational placements and require more out-of-class tutoring. The behavioural difficulties associated with ADHD include continuous friction with peers, parents and teachers, often leading to placement in special classes, suspension and/or expulsion, and social rejection by their peers due to aggression, impulsivity and non-compliance with rules. As they grow up, children with ADHD become disproportionately involved in the consumption of cigarettes, alcohol and illicit drugs, and appear to maintain their risk of continued addictions later in life.

Adults diagnosed with ADHD may still be hyperactive, impulsive or inattentive, but their symptoms usually manifest in different ways from children. Symptom-wise, adults with ADHD often show overt hyperactivity symptoms less frequently than inattention-based symptoms; however, as in children, adults with ADHD experience significant impairments across several domains. These include immaturity, social maladjustment, higher rates of separation and divorce, fewer years of education, lower socioeconomic status, lower occupational achievement, lower rates of professional employment, increased work difficulties, poor work performance, more frequent changes in employment and higher rates of quitting or being fired from jobs.

In a recent World Health Organization (WHO) survey, investigators found that ADHD was associated with 22.1 excess days of lost role performance annually (as defined by both lost work time and lower efficiency). Another survey found that adult subjects with ADHD tend to have poorer driving habits, evidenced by their having received more traffic citations, particularly for speeding, than non-ADHD control subjects and a greater likelihood of being involved in, and at fault for, automobile accidents, including those involving bodily injury. Adults with ADHD are also significantly more likely than controls to have co-morbid psychiatric diagnoses of anxiety, bipolar disorder, depression, drug or alcohol abuse or antisocial disorder, which often make treatment more difficult. Finally, the economic impact of untreated adult ADHD is high and includes increased inpatient, outpatient, prescription drug and other medical costs compared with non-ADHD controls, as well as more days of unexplained work absence. It should be noted that although ADHD
clearly affects quality of life, as outlined above, studies have yet to be conducted that systematically evaluate treatment effects on these end-points.

Pharmacotherapy for Attention-deficit–Hyperactivity Disorder

Pharmacotherapy is an important component in the treatment for ADHD and is often combined with behavioural, educational and family interventions. Currently, stimulants are the most widely prescribed medications for treatment of ADHD when pharmacological treatment is indicated, and numerous studies have demonstrated their efficacy and safety in children and adults.26–28

Stimulants
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Stimulants can be classified based on chemical structure and on duration of action. There are two structural classes of stimulant used therapeutically: amphetamines (AMP) and methylphenidate (MPH). The therapeutic effects of stimulants in ADHD are primarily due to their inhibition of the presynaptic neuronal re-uptake of dopamine and norepinephrine.29 However, there are differences between these two classes in some pharmacological characteristics. The actions of MPH are limited to inhibition of neuronal re-uptake, while AMP has additional neuronal actions including presynaptic release of norepinephrine and dopamine.30

There are also differences in plasma half-life and metabolic and elimination profiles, with MPH undergoing extensive first-pass hepatic metabolism, whereas, depending on the formulation, a considerable portion (~50%) of AMP is excreted unchanged in the urine.30 Arnold found that while some treatment characteristics tended to differ between AMP and MPH, few of these differences reached statistical significance, and the author concluded that there was no basis to recommend either MPH or AMP over the other.30 AMP and MPH both have relatively short half-lives of four to six hours and two to three hours, respectively, and were initially available as immediate-release (IR) short-acting formulations. Recently, a number of extended-release (ER) formulations of these stimulants were developed. Table 1 illustrates IR and ER formulations of AMP and MPH, along with the durations of action that are available in various countries.

<table>
<thead>
<tr>
<th>Agent</th>
<th>US Trade Name</th>
<th>European Products</th>
<th>Tmax (hours)</th>
<th>Single Dose Duration of Action (hours)</th>
<th>Doses per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>dAMP</td>
<td>Dexedrine®</td>
<td>Dexadrine®</td>
<td>1.5</td>
<td>3–4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dextrostat®</td>
<td></td>
<td>1.9</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>MAS</td>
<td>Adderall®</td>
<td></td>
<td>3</td>
<td>4–6</td>
<td>1–3</td>
</tr>
<tr>
<td>MPH</td>
<td>Ritalin®</td>
<td>Equasym®</td>
<td>2</td>
<td>2–4</td>
<td>1–3</td>
</tr>
<tr>
<td></td>
<td>Medikinet®</td>
<td>Rubifen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methylphenidate</td>
<td>Tifrinat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dMPH</td>
<td>Focalin®</td>
<td></td>
<td>3</td>
<td>4–6</td>
<td>1–3</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

Table 1: Immediate-release and Extended-release Stimulants – US and European Approvals

a. Not all products are available in all countries.
b. The drug has a 13-hour duration based on nine-hour wear time.111
IR = immediate-release; ER = extended-release; dAMP = d-amphetamine; MAS = mixed amphetamine salts; MPH = methylphenidate; dMPH = d-methylphenidate; MAS XR = mixed amphetamine salts extended release; OROS-MPH = osmotic-release methylphenidate; MTS = methylphenidate transdermal system; LDX = lisdexamfetamine dimesylate.

Comparative Efficacy

Although the clinical efficacy and safety of pharmacological treatment of ADHD has been well researched, few studies evaluating medications in head-to-head comparisons are available. Therefore, the best evidence comes from an indirect comparison of the randomised, double-blind, placebo-controlled studies for each medication. Effect size, a statistical method that measures the difference in improvement between drug and placebo (adjusted for the scale and accuracy of the measurements used in each study), is often employed as a useful technique for comparing the effectiveness of pharmacological agents.26,31 There are, of course, limitations to comparing studies when design features differ substantially.26,31 The strength of this type of analysis is as a comparative tool. While the clinical significance of the absolute values of effect size may vary depending on factors specific to various disease states and clinical populations, for pharmacological agents used to treat ADHD effect sizes above approximately 0.5 are generally considered moderate and those above 0.8 are considered large.32 Additionally, relative efficacy or effect size is only one of a number of factors, including patient-specific factors, severity of disease, relative tolerance of individuals for adverse effects,
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Table 2: Common Adverse Events Associated with Stimulant Agents

<table>
<thead>
<tr>
<th>Agents</th>
<th>Study Citation</th>
<th>Type</th>
<th>Number of Subjects</th>
<th>Duration</th>
<th>Comparison</th>
<th>Findings</th>
<th>Discontinuations Due to AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate-release Stimulants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPH</td>
<td>Barkley et al.</td>
<td>RCT</td>
<td>83</td>
<td>1 week</td>
<td>Versus placebo</td>
<td>Decreased appetite, insomnia, abdominal pain</td>
<td>3.6%</td>
</tr>
<tr>
<td>Ahmann et al.</td>
<td>RCT</td>
<td>206</td>
<td>1 week</td>
<td></td>
<td>Versus placebo</td>
<td>Decreased appetite, insomnia, abdominal pain, headache, dizziness</td>
<td>2%</td>
</tr>
<tr>
<td>Schacher et al.</td>
<td>RCT</td>
<td>91</td>
<td>16 weeks</td>
<td></td>
<td>Versus placebo</td>
<td>Decreased appetite, abdominal pain, reduced weight gain, affective symptoms</td>
<td>10%</td>
</tr>
<tr>
<td>Charach et al.</td>
<td>RCT</td>
<td>91</td>
<td>12 months</td>
<td></td>
<td>Versus placebo</td>
<td>Decreased appetite</td>
<td></td>
</tr>
<tr>
<td>dAMP</td>
<td>Gillberg et al.</td>
<td>RCT</td>
<td>62</td>
<td>2 weeks</td>
<td>dAMP versus baseline</td>
<td>dAMP versus baseline: decreased appetite, insomnia</td>
<td>1.6% dAMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MPH versus baseline</td>
<td>MPH versus baseline: decreased appetite</td>
<td>1.6% MPH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>dAMP versus MPH</td>
<td>dAMP versus MPH: insomnia, irritability, prone to crying, anxiousness, sadness, nightmares: dAMP-MPH</td>
<td></td>
</tr>
<tr>
<td>MAS</td>
<td>Spencer et al.</td>
<td>RCT</td>
<td>27</td>
<td>7 weeks</td>
<td>Versus placebo</td>
<td>Decreased appetite, agitation, insomnia</td>
<td></td>
</tr>
</tbody>
</table>

Extended-release Stimulants

| OROS MPH      | Weishoff et al. | RCT    | 360                | 4 weeks  | OROS MPH versus IR MPH | Decreased appetite, headache, abdominal pain                             | <1%                         |
| MPH ER (Metadate CD) | RCT    | 321    | 3 weeks            |          | Versus placebo         | Decreased appetite                                                        | <1%                         |
| MPH ER (Equasym® XL) | RCT    | 318    | 3 weeks            |          | Versus IR MPH          | Headache, decreased appetite, abdominal pain: 2.2% MPH ER               | 3% IR MPH                   |
| dMPH ER       | Greenhill et al. | RCT    | 97                 | 7 weeks  | Versus placebo         | Decreased appetite, headache, abdominal pain                             | 2.2% MPH ER                |
| MPH Transdermal | RCT    | 282    | 7 weeks            |          | Versus placebo         | Appetite, nausea, vomiting, insomnia                                     | Decreased                   |
| MAS XR        | McGough et al. | RCTs   | 51                 | 4 weeks  |versus placebo         | Decreased appetite, headache, insomnia, abdominal pain, irritability     | 15%                         |
| LDX           | Biederman et al. | RCT    | 290                | 4 weeks  | Versus placebo         | Decreased appetite, headache, insomnia, abdominal pain, irritability     | 7%                          |

AE = adverse event; IR = immediate release; ER = extended release; dAMP = d-amphetamine; MAS = mixed amphetamine salts; MPH = methylphenidate; dMPH = d-methylphenidate; MAS XR = mixed amphetamine salts extended release; OROS-MPH = osmotic-release methylphenidate; MTS = methylphenidate transdermal system; LDX = lisdexamfetamine dimesylate; RCT = randomised clinical trial.

Adverse Event Profiles

Relative tolerability profile of various agents and the availability and appropriateness of non-pharmacological treatments, that must be weighed when making treatment choices. Throughout this article, effect sizes for various agents will be included whenever available.

Cardiovascular Effects of Stimulant Agents

Relative to stimulant treatment and, as described in the American Academy of Child and Adolescent Psychiatry (AACAP) guidelines, stimulants may either improve or worsen such symptoms. Common AEs seen in adult patients receiving stimulants are similar to those described above for children, although abdominal pain is generally not as prevalent in adults as in children. In the discussion of specific stimulant agents below, specific effects of particular agents will be noted when they differ from the general profile.
monitoring. In a review by Rapport and Moffitt of 15 studies reporting cardiovascular effects of MPH, they found that seven studies reported significant increases in heart rate, five studies reported significant increases in systolic blood pressure and six studies reported significant increases in diastolic blood pressure. Additionally, in a two-year study of children with ADHD receiving mixed amphetamine salts extended release (MAS XR), short- and long-term mean increases in heart rate, blood pressure and QT interval were insignificant, with no apparent dose relationship. In adults, treatment with stimulants was associated with small statistical increases in blood pressure in one analysis of data from controlled trials. In an open-label study of adults with ADHD (n=223) receiving MAS XR, mean increases in blood pressure and other cardiovascular parameters were small and were judged to be clinically insignificant. Authors of these studies concluded that the cardiovascular effects of stimulants were mild and minimal in studies of children and adults with ADHD.

Recommendations in both North America and Europe suggest regular (at least every six months in European recommendations) monitoring of blood pressure and pulse rate in children treated with stimulants. Although the changes in blood pressure and heart rate of the magnitude seen in the studies above is likely not of clinical concern, if sustained such increases may be associated with long-term negative consequences. Available evidence suggests that these effects of stimulants are readily resolved by discontinuing the medication.

**Growth Effects of Stimulants**

In a qualitative review of 29 studies, Poulton found that 11 presented results suggestive of height attenuation following stimulant treatment. She hypothesised that both weight loss and attenuation in height velocity may be associated with a single adaptive mechanism, with weight loss followed by conservation of energy through restricting increase in height. A quantitative review of this literature by Faraone et al. found that stimulant medication led to delays in expected growth in height and weight. Although patients continued to grow, they grew less than expected for their age. This effect was greatest for taller and heavier children and was greater for children compared with adolescents. The studies reviewed also suggested that these deficits were attenuated over time. They did not suggest differences in the magnitude of growth deficits between methylphenidate and amphetamine, although this conclusion was tenuous due to the scarcity of comparative studies. As most studies examined growth in childhood or early adolescence, they could not provide information about the effects of stimulants on height and weight attained in adulthood. Although most of the growth literature is based on short-acting stimulants, the three available studies of long-acting stimulants showed a similar pattern of growth deficits.

In the review by Faraone et al., the mean height and weight deficits for each study were positively correlated. This suggested that these deficits may share some common sources of variance. This finding raises the possibility that some failure to make expected height gains could be attributed to the lack of interest in eating and inadequate nutrition that contributes to weight loss. If true, clinical strategies used to improve nutrition and encourage weight gain could possibly reduce deficits in expected height. However, the impact of such strategies would likely be small given that the height-weight correlation in individual data, albeit significant, is not large.

Physicians should advise patients and their parents about the potential for growth delays. They should monitor growth for all stimulant-treated youths, and emerging deficits should be treated based on the clinical considerations of each patient. Current data do not support specific guidelines for the magnitude of growth deficit that should trigger clinical concern. Insight into this issue is provided by the American Association of Clinical Endocrinologists (AACE) medical guidelines for clinical practice for growth hormone use in adults and children, which listed growth delay criteria that should trigger clinical concern:

- severe short stature (i.e. height more than two standard deviations below the population mean);
- height more than 1.5 standard deviations below the average of the mother’s and father’s heights;
- height more than two standard deviations below the mean and a one-year height velocity more than one standard deviation below the mean or a one-year decrease of more than 0.5 standard deviations in height;
- in the absence of short stature, a one-year height velocity more than two standard deviations below the mean or a two-year height velocity more than 1.5 standard deviations below the mean.

The circumstances of individual cases would determine whether the stimulant treatment regime should be changed or a referral to an endocrinologist is warranted.

In communicating the magnitude of growth deficits to patients, clinicians should note that deficits are most prominent among the tallest and heaviest children, and treatment with stimulants does not markedly increase the number of children who are seriously thin or short, as indicated by being below the fifth percentile of the population. Also, unlike height, decreased weight is not always a problem. Some children on stimulants are overweight and their decrease in weight growth may be an acceptable outcome.

As emerging growth deficits are easy to identify, they can be corrected by implementing appropriate clinical strategies. Drug holidays should result in rebound growth, but they can also be problematic because symptoms may re-emerge or worsen. For individual patients, physicians need to determine whether the risks of switching to another stimulant or a non-stimulant outweigh the risks associated with growth delays.

**Suicidal Thinking**

James et al. found an increased risk of suicide in children and adolescents with ADHD, which is consistent with the increased risk of depression among ADHD patients. However, no studies have specifically linked stimulant medications to an increase in suicidality.

**Abuse Liability**

The impact of ADHD and of the use of stimulants on the incidence and course of stimulant abuse is complex and controversial. Many cross-sectional and follow-up studies show that ADHD children and adults are at high risk of substance use disorders. It is equally well documented that stimulant medications have the...
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potential for abuse, but one cannot conclude from these data that stimulants cause subsequent substance use.

Several naturalistic, longitudinal studies have addressed the issue of substance abuse. An early study reported a higher likelihood of substance use problems and cigarette smoking in patients using stimulants than in those not using stimulants. On the other hand, a subsequent study found that ADHD patients who were medicated were at a lower risk of developing substance abuse disorder than unmedicated patients. The data from these and other studies were combined in a meta-analysis of six studies. The meta-analysis concluded that stimulant treatment in childhood reduced the risk of substance use disorders in adolescence and had no effect on the risk of these disorders in adulthood.

Although the therapeutic use of medications does not cause substance abuse, concerns remain about the potential for misuse of these medications by ADHD patients. The literature review by Faraone and Wilens noted that all of the studies examining this issue found evidence for either the misuse or diversion of ADHD medications by some ADHD patients. Risk factors for misuse and diversion were pre-existing conduct or substance use disorders, use of an immediate-release stimulant, male gender, Caucasian race and membership of a fraternity or sorority.

When working with patients at risk of misuse or diversion, clinicians should discuss these issues with either parents or, for adolescents and adults, with the patients themselves. Co-ordination of pharmacotherapy with non-pharmacological management, including counseling for adolescent and adult patients, may be helpful to reinforce these discussions and to help monitor the progress of therapy. Clinicians need to monitor high-risk patients for the appropriate use of their stimulant medications. In addition, the use of a non-stimulant alternative should be considered.

Agents

IR stimulant formulations are effective in reducing ADHD symptoms, with an average effect size of 0.91. However, these preparations have limitations associated with their relatively short duration of action. With effects lasting only approximately four to six hours, IR stimulants are usually given in multiple daily doses, including midday and/or afternoon doses. This can result in peaks and troughs in the plasma concentrations and clinical actions of patients. The need for multiple daily doses can also lead to poor dosage compliance and stigma for children who are required to take medication at school. Missed doses and poor compliance are also problematic for a variety of reasons, including forgetfulness and volitional avoidance. IR formulations may also be associated with pharmacological rebound (i.e., deterioration in behavior/increase in ADHD symptoms beyond unmedicated baseline that occurs as the therapeutic effects of medication wear off). Another concern with IR stimulants has been an increased potential for misuse, diversion and abuse, as described above. ER formulations were designed to extend the therapeutic effects of stimulants over the course of the day and to alleviate the drawbacks associated with IR formulations. Effect sizes for ER stimulant formulations averaged 0.95 and were not statistically different from the effect sizes of IR stimulants. A discussion of the comparative effects of various IR and ER agents over the day will be addressed in a later section that focuses on studies utilizing structured school and classroom settings and other daily assessments to gain insight into the relative efficacy in ADHD treatments for symptom control over the course of the day.

Amphetamines

Several IR amphetamine-based products that have been useful pharmacotherapeutic agents for ADHD are currently available. Dexamphetamine (dAMP), the d-isomer of d,l-amphetamine sulphate, has a time to peak plasma concentration of approximately 1.5 hours and provides symptom relief for approximately four to six hours (see Table 1). dAMP showed similar efficacy to MPH in a cross-over study of children with ADHD (n=125). While the incidence of AEs was similar between the dAMP and MPH groups, the severity of AEs, particularly negative emotional side effects, was significantly greater in patients receiving dAMP than in those receiving MPH. In two randomised, placebo-controlled studies in naturalistic settings, dAMP had significant efficacy compared with placebo in adults with ADHD. Other small (n=22 and n=17, respectively) randomised, placebo-controlled studies that also included other active drug groups (modafinil and guanfacine, respectively) have also demonstrated the efficacy of dAMP in treating adults with ADHD.

Mixed amphetamine salts (MAS) is a racemic mixture of three amphetamine salts with a different pharmacokinetic profile from the IR formulations of AMP (e.g., longer time to peak plasma levels related to the differential absorption of the mixed salts). The results of four trials found MAS to have minor but statistically significant advantages over standard-release MPH in children in clinician and parent ratings, but not in teacher ratings. These advantages were observed for both symptom measures and global ratings but were greater for the latter; in addition, the clinical advantages of MAS were significant for both fixed-dose and best-dose designs. In an open-label preliminary study (n=24) and a randomised, placebo-controlled study (n=30) of adults with ADHD, MAS demonstrated efficacy versus placebo and tolerability similar to that of other stimulant agents. Although an association between MAS treatment and anxiety in susceptible individuals was noted in the open-label study, the link was not corroborated in the placebo-controlled study.

A two-component ER capsule formulation of MAS (MAS XR) was developed to provide once-daily dosing of amphetamine, with a single dose of MAS XR in the morning producing similar pharmacokinetic and pharmacodynamic effects to IR MAS given twice daily. In large randomised, placebo-controlled trials (n=584 and n=259, respectively), MAS XR has been shown to be effective compared with placebo and well tolerated in children and adults with ADHD, including adults with severe symptoms (ADHD Rating Scale [ADHD-RS] score ≥32 at baseline). The mean MAS XR effect size was 0.8. The AE and safety profiles of ER amphetamines in both paediatric and adult studies were similar to those of other stimulant agents used to treat ADHD. Among the AEs commonly observed with MAS XR were nausea, decreased appetite and insomnia, without evidence of the increased incidence or severity of psychiatric AEs seen with IR dAMP.

Methylphenidate

The IR formulation of MPH provides relief from ADHD symptoms for approximately four hours; thus, multiple daily dosing is necessary to maintain improvements across the day. A number of
double-blind, cross-over, placebo-controlled studies have demonstrated that IR MPH is effective in children and adults.87,94 A European study in adults also demonstrated efficacy for IR MPH.87 Dextmethylphenidrate (dMPH), the d-isomer of MPH, has been shown to be as effective and safe as the more commonly prescribed d/L-MPH in treating children with ADHD.87 Moreover, the d-MPH formulation was also effective compared with placebo in adults with ADHD.87 Effect size estimates for IR d/L-MPH and d-MPH formulations are approximately 0.9.60

Several ER MPH formulations have been developed to address the shortcomings of the IR formulations that were described earlier. A formulation that delivers MPH via OROS® osmotic technology has been developed. The efficacy and safety of osmotic-release MPH (OROS-MPH) in children with ADHD were established in randomised placebo- and active-controlled studies.40,41,97 Two studies (n=282 and n=68, respectively) reported that children receiving OROS-MPH had significantly better performance compared with placebo in terms of teacher/parent assessments.40,41

In a randomised, open-label comparison (n=147) of OROS-MPH with IR MPH, OROS-MPH showed significantly greater efficacy compared with IR MPH.64 Both studies also showed that OROS-MPH was well tolerated in children. In a large randomised, placebo-controlled comparative study of OROS-MPH (n=220), atomoxetine (ATX, discussed below; n=222) and placebo (n=74), OROS-MPH and ATX both showed efficacy compared with placebo, and OROS-MPH showed a significant advantage over ATX.64 In a randomised, placebo-controlled trial, OROS-MPH was found to be safe and effective in adults (n=141) with ADHD.87 In children, the OROS-MPH effect size has been reported as 1.1.64

Other ER MPH formulations that utilise a different formulation technology (e.g. microbead dual-phase release) have also been shown to be effective in subjects with ADHD.64 A MPH-ER once-daily preparation (available only in Europe) showed similar efficacy to IR MPH twice daily in a randomised, placebo- and active-controlled trial (n=79).64 An MPH transdermal delivery system has been developed in which the drug is contained within a multipolymeric adhesive and is released continuously when applied.68-70 This system has been shown in an open-label, dose-optimisation continuation study over a 12-month period.104 AEs were generally mild to moderate and were consistent with those observed for other stimulant medications.68,71,76,104 Similarly to MAS XR and long-acting MPH formulations, psychiatric AEs (particularly those related to emotionality) do not appear to occur with increased incidence or severity compared with IR stimulants. In a recent clinical trial of LDX in adults with ADHD, improvements in ADHD-RS were significantly greater at end-point for all LDX doses compared with placebo.105,106 AEs were generally mild or moderate and included dry mouth, decreased appetite and insomnia.

An ER formulation of dexamphetamine (dMPH-ER) has been studied in children and adults.65,77 In children and adolescents with ADHD (n=97), dMPH-ER was studied for seven weeks in a randomised placebo-controlled trial using scales rated by teachers, parents and physicians.65 At end-point, improvements in teacher- and parent-rated scales were reported for dMPH-ER compared with placebo. In a placebo-controlled trial in adult ADHD subjects (n=221), dMPH-ER showed efficacy versus placebo.65 AE profiles were similar to other MPH formulations in both children and adults.65,77 Effect sizes of d-MPH-ER have been reported as 0.7965 for children and adolescents and up to 0.83 for adults.65

Prodrug Formulations

The concept of using prodrugs (inactive precursors of active pharmacological agents) was developed several decades ago in response to a variety of issues involving physiochemical and pharmacokinetic characteristics, targeting of drug effects by time and location, duration of action and limiting drug toxicity.104 Lisdamfetamine dimesylate (LDX) is the only long-acting prodrug stimulant to be used in the treatment of ADHD. It has now been indicated in the US for the treatment of ADHD in children between six and 12 years of age and in adults. LDX is a therapeutically inactive molecule. After oral ingestion, LDX is converted to l-lysine, a naturally occurring essential amino acid that is inactive with respect to ADHD, and active dAMP, which is responsible for the therapeutic effect.104 Since LDX is an inactive prodrug that requires hydrolysis to dAMP to have stimulant-class pharmacological effects, it may have less potential for diversion and abuse.104 Preliminary evidence indicates that LDX has reduced abuse-related drug-liking effects. In a placebo- and active-controlled trial of 36 adult stimulant abusers, orally administered LDX (50 and 100mg) was associated with lower abuse-related liking compared with orally administered dAMP sulphate (40mg, which is equivalent to LDX 100mg in dAMP base content).106 Abuse-related liking was similar between dAMP 40mg sulphate and LDX 150mg (50% higher amphetamine content than dAMP). In an abuse-liability trial that evaluated intravenous LDX, LDX 50mg did not produce significantly different abuse-related drug-liking compared with placebo, whereas immediate-release dAMP 20mg with the same amphetamine base content had significant drug-liking effects compared with placebo.65

LDX is a well-tolerated and effective treatment for children with ADHD. In a multicentre, double-blind, placebo-controlled, parallel-group, forced dose-escalation study of LDX given at 30, 50 or 70mg/day, improvements were reported in subjects receiving LDX at all three doses compared with placebo. LDX effect size ranged from 1.2 to 1.6 at 30, 50 and 70mg/day. The long-term efficacy and tolerability of LDX in children with ADHD has recently been shown in an open-label, dose-optimisation continuation study over a 12-month period. AEs were generally mild to moderate and were consistent with those observed for other stimulant medications.64,71,76,104 Similarly to MAS XR and long-acting MPH formulations, psychiatric AEs (particularly those related to emotionality) do not appear to occur with increased incidence or severity compared with IR stimulants. In a recent clinical trial of LDX in adults with ADHD, improvements in ADHD-RS were significantly greater at end-point for all LDX doses compared with placebo. AEs were generally mild or moderate and included dry mouth, decreased appetite and insomnia.

Comparative Patterns and Duration of Effect

The laboratory school study design has been used extensively over recent years to examine day-to-day impairments of ADHD in a structured and controlled setting that allows assessment of aspects of deportment, attention and academic productivity over the course of the day. This study design is very useful in assessing overall and comparative patterns and duration of effect over the day. A study of the effects of MAS at increasing single doses in children with ADHD (n=30) showed improvements at higher doses at early time-points (1.5 hours) that dissipated over the course of the day (7.5 hours). A single dose of OROS-MPH produced a similar pattern of effects across the day to IR MPH given three times a
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day. OROS-MPH has also been examined in comparative studies with other ER MPH formulations.

In a five-way randomised, placebo-controlled study comparing OROS-MPH with ER MPH, efficacy was similar at lower doses over the course of daily assessments, while at higher doses ER MPH demonstrated greater efficacy than OROS-MPH at early time-points up to eight hours but similar efficacy from eight to 12 hours. In a comparative study of OROS-MPH and another ER MPH formulation (Metadate ER), while both agents demonstrated efficacy compared with placebo throughout the day, assessments were better for the ER MPH at earlier time-points and for OROS-MPH at later time-points. Studies that examined the duration of effect of dMHP have demonstrated efficacy from 0.5 to 12 hours.

A novel delivery system for MPH, the MPH transdermal system, may provide an option for clinicians when patients are unable to regularly take oral medications or to tailor treatment to the heterogeneous needs of particular patients. In a study of the MPH transdermal system worn for nine hours, assessments of deportment, attention and academic performance were improved seen from two to 12 hours for MAS XR compared with placebo, in randomised, placebo-controlled, cross-over studies. Efficacy was demonstrated from 0.5 to 12 hours. In two higher doses of ATX (1.2 and 1.8mg/kg/day) compared with placebo. Kelsey et al. found that at average doses similar to the middle dose in the previously mentioned study, ATX demonstrated efficacy compared with placebo. Gibson et al. analysed the results of five studies that compared ATX with stimulants and found no differences between ATX and IR stimulants but significantly greater improvements with either MAS XR or LDX compared with placebo two hours, the first measured time-point, to 12 hours. Effects of both MAS XR and LDX were examined in randomised, placebo-controlled, cross-over studies. Efficacy was seen from two to 12 hours for MAS XR compared with placebo, while LDX demonstrated efficacy 1.5–13 hours after dosing.

Non-stimulants

ATX is a potent inhibitor of the presynaptic norepinephrine transporter, with minimal affinities for either adrenergic receptors or other neurotransmitter transporters and receptors. Several studies in Europe and the US have shown that ATX is effective in treating children and adolescents and adults with ADHD. An eight-week study of children and adolescents (n=297) with ADHD found improvements in parent and investigator rating scales in subjects on the two higher doses of ATX (1.2 and 1.8mg/kg/day) compared with placebo. found that at average doses similar to the middle dose in the previously mentioned study, ATX demonstrated efficacy compared with placebo. Gibson et al. analysed the results of five studies that compared ATX with stimulants and found no differences between ATX and IR stimulants but significantly greater improvements with either MAS XR or OROS-MPH compared with ATX. The effect size of ATX has been reported as 0.71. ATX has been proposed as a first-line alternative to stimulants when AEs associated with stimulant use are unacceptable and for treating ADHD co-morbid with substance abuse based on a lower abuse potential than that of traditional stimulants. A recent report showed beneficial effects of ATX on both ADHD and anxiety symptoms, and ATX may be preferred in this situation.

ATX is generally well tolerated, with most AEs being mild to moderate in severity. Its AE profile has some similarities to that of stimulants that in decreased appetite and weight loss are commonly reported, as are insomnia and dry mouth. Other commonly reported AEs include dizziness, nausea and rhinitis. Rarely, hepatotoxicity and serious psychiatric AEs such as hypomania and mania have been reported. In a review of clinical trials, the cardiovascular effects of ATX were reported as small but significant increases in heart rate and blood pressure but no electrocardiogram (ECG) changes. A trial in 197 children with ADHD found small but significant increases in pulse rate and PR interval but no increases in blood pressure.

Although the α2A-adrenoceptor agonist clonidine has been used to treat ADHD for many years, only limited data are available on its efficacy and safety. A meta-analysis of studies of clonidine use in ADHD over a 10-year period found a moderate effect size of 0.6 for ADHD symptoms. Beneficial effects are generally confined to hyperkinetic and impulsive symptoms, with limited benefit for cognitive and inattentive symptoms. The most common AEs seen with clonidine are sedation, drowsiness and depression. A 16-week randomised, placebo-controlled trial in children with ADHD that compared clonidine versus placebo versus added MPH found that clonidine offered some limited benefit compared with placebo, with MPH performing significantly better. Sedation with clonidine was considered to be the most problematic AE.

Guanfacine is a selective α2A-adrenoceptor agonist. Open-label and small placebo-controlled trials have shown that guanfacine 0.5–4.0mg/day tablets in divided doses is safe and effective in treating children, adolescents and adults with ADHD. An ER formulation guanfacine extended-release (GXRI) is an investigational product in the US. In children with ADHD, GXRI demonstrated significant improvements from baseline to end-point compared with placebo on the ADHD RS-IV scale, as well as the hyperactivity, impulsivity and inattentiveness subscales of the ADHD rating scale. The most commonly reported treatment-emergent AEs were headache, somnolence, fatigue, upper abdominal pain and sedation. Small to modest changes in blood pressure, pulse rate and ECG parameters were observed but were not considered by the authors to be clinically meaningful.

Before the introduction of ATX, tricyclic antidepressants (TCAs) were considered the next most useful option for pharmacotherapy of ADHD, after stimulants. Although TCAs have numerous effects on various neurotransmitter systems, their therapeutic actions in treating ADHD are thought to be due to their effects on norepinephrine and dopamine re-uptake. The two TCAs most commonly used in treating ADHD are desipramine and imipramine. Biederman et al. summarised efficacy data for these agents. As a prototype for the class, desipramine was found to be efficacious in children and adults with ADHD who had failed treatment with stimulants or were not able to take stimulants for other reasons. The use of TCAs in the treatment of ADHD has decreased in recent years based on the availability of ATX and safety concerns associated with risk of cardiotoxicity.

Bupropion has been shown to be efficacious in a randomised placebo-controlled trial and a cross-over trial with MPH. AEs associated with bupropion included headache, dry mouth, nausea, insomnia, constipation and dizziness. Seizures may occur with bupropion, with incidence rates of 0.1–0.4%.

Multimodal Treatment of Attention-deficit–Hyperactivity Disorder

In recent years, pharmacotherapy has been used in conjunction with other modes of therapy for ADHD, particularly with behavioural therapies. The Multimodal Treatment Study in Children with ADHD (MTA) was a large, randomised study undertaken to assess the relative efficacy of pharmacotherapy (MPH), behavioural treatments...
and the combination of the two. In this study, children enrolled with ADHD (n=579) were randomly assigned to receive medication, behavioural therapy, combination treatment or standard community care over 14 months. While all four groups showed improvements in ADHD symptoms, subjects in the combined and pharmacotherapy groups showed greater improvements than those in the other two groups. The combined group showed improvement over the behavioural and community care groups. The medication and combined treatment groups did not show a difference.

Another key finding was that the medication group showed improvement over the community care group even though subjects in the latter group were often treated with medication. This latter finding suggests that the more aggressive treatment of study investigators (e.g. higher doses) led to better outcomes.

**Differences in Treatment of Attention-deficit–Hyperactivity Disorder Between Europe and North America**

In considering the differences and similarities between the approaches to treating ADHD in Europe and North America, the relative role of pharmacotherapy versus other treatment options is an important defining characteristic, along with differences in the availability of agents and the perceptions and attitudes of clinicians.

Barriers to diagnosing and treating ADHD in the EU and North America include country, state and regional variations in treatment algorithms and product availability. Table 1 lists stimulant agents available in the US and Europe. Clearly, medication options differ considerably, with many more being available in the US. The limited number of options in Europe is to some degree related to regulatory barriers that mitigate against the approval of some agents, such as MAS. Under current regulations, MAS and MAS XR would be required to gain approval for each chemical entity in the mixture of amphetamine salts. Other issues that affect the use of medications throughout Europe are the varying mechanisms and regulations that determine public financing of healthcare and medication costs in various countries and the requirement for staged treatment protocols that specify the use of IR stimulants as initial pharmacotherapy. It is also the case that differing patenting situations reduce the incentive for certain products developed in the US to be licensed in Europe.

Treatment paradigms and algorithms also differ between Europe and North America. Treatment consensus guidelines from North American professional medical associations have concluded that stimulant medications have the most evidence supporting efficacy and safety in treating ADHD in children and remain the first choice for pharmaceutical-based intervention. In Europe, guidelines for the diagnosis and treatment of ADHD differ from those in North America. Historically, in the EU the International Classification of Diseases Tenth Revision (ICD-10) is most commonly used to diagnose ADHD, whereas the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) is most commonly used in the US. These diagnostic criteria differ in three substantive ways. First, the ICD-10 requires pervasive symptoms as defined by presence of the full syndrome in two independent settings, whereas the DSM-IV-TR defines pervasiveness as “impairment in social, academic, or occupational functioning from ADHD symptoms” in two or more situations. Second, the ICD-10 defines one syndrome encompassing all three core symptoms (i.e. inattention, hyperactivity and impulsivity), and the DSM-IV-TR requires either inattention or hyperactivity/impulsivity or all three symptoms. When all three core symptoms are present, combined-type ADHD is diagnosed. Third, whereas the ICD-10 does not support diagnosis of multiple co-morbid conditions with ADHD in favour of a primary diagnosis of the other condition, the DSM-IV-TR allows multiple co-morbid diagnoses.

As a result of these differences, prevalence estimates and response to treatment choices may vary depending on the criteria applied. Recent European and UK guidelines based on the health technological assessments of the UK National Institute of Health and Clinical Excellence (NICE) make a number of recommendations regarding the diagnosis and treatment of ADHD. These guidelines recommend that both the ICD-10 and the DSM-IV-TR definitions of ADHD should be used for diagnosis and acknowledge that, although they differ in terms of the breadth of symptoms that are defined, groups of patients who defined by either set of criteria suffer from similar levels of impairment.

Concerning overall scope and prioritisation of pharmacological and non-pharmacological treatments, current US practice guidelines for treatment of ADHD (as detailed above) differ from both European and NICE recommendations in important ways. In the current NICE technological assessment, pharmacotherapy as a first-line treatment should be reserved for patients with severe symptoms or those refusing or not responding to first-line group psychological and parent training interventions. Additionally, when pharmacotherapy is indicated, long-acting pharmacological treatments, including stimulants and non-stimulants, should be available but should not replace short-acting agents as initial pharmacological treatment for reasons of cost and flexibility and for assessment of optimal dose. These decisions appear to have been based on an assumption that if all else was even, non-pharmacological approaches would be inherently preferable to pharmacological approaches; however, no attempt is made to support these assumptions with evidence. It should also be noted that consensus throughout Europe has not been attempted with the NICE guidelines.

A recent European guideline that represented a broader perspective recommends a balanced appraisal of all treatment modalities for the mildly and moderately affected patient on a case-by-case basis, with non-pharmacological and pharmacological interventions having equal footing as potential first-line choices. This guideline still differs from US guidelines with respect to the primacy of stimulant medications and the use of long-acting agents as first-line treatment in childhood ADHD (except for very small children) in the US, related to the issues of availability and regulatory treatment protocols mentioned earlier.

Additionally, European and American regulators, physicians, politicians and the general public may differ in how they weigh the costs and benefits of stimulant treatment and in their perceptions of the characteristics and role of stimulant agents. Opinions regarding the place of stimulants in the treatment of ADHD vary, in part related to concerns by regulators, clinicians and politicians in some parts of Europe about using stimulant medications in children because of their potential for adverse effects on growth, fear of...
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tolerance and addiction and fear of abuse liability.19,20 The clinical use of stimulants has been limited in several regions for decades because of epidemics of illicit drug abuse peaking in the last quarter of the 20th century.20 There may continue to be some confusion regarding the similarities and differences between therapeutic AMP/MPH and illicit substances such as methamphetamine. The resultant limited clinical experience with the safe and effective use of stimulants may contribute to their use by some European physicians. Treatment options with lower abuse liability than that associated with short-acting stimulants include ER and prodrug formulations of AMP and MPH, as well as the non-stimulants, including ATX.77,117,152

Conclusions

The goal of therapy for ADHD is to make the optimal treatment choices for each patient based on his or her individual needs. Available evidence establishes the important role of pharmacotherapy, especially for the most severely affected patients. Whether pharmacotherapy is considered first-line, supplementary or secondary treatment varies, as described above. While all agree that pharmacotherapeutic treatment can be an effective treatment modality if used appropriately. When choosing among pharmacotherapy options, balancing factors of higher efficacy versus tolerability issues will determine the available choices for each patient. The goals of pharmacotherapy are clinical efficacy, satisfactory duration of action and safety/tolerance. Historically, stimulants have been regarded as first-line treatment for ADHD; however, non-stimulants such as ATX have been shown to be effective, and may be especially useful in patients who experience unacceptable side effects with stimulant medications.21,22 ER formulations of stimulant medications were developed to address the inconvenience of multiple daily dosing, the impact of peak/trough fluctuations on efficacy and tolerability and the substantial abuse liability of the IR formulations.23 There is considerable evidence that ER stimulants are safe and effective in the treatment of children, adolescents and adults with ADHD. As a class, they display relatively rapid onset of action, extended duration and acceptable tolerability and AE profiles.


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