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Treatment of Attention Deficit Hyperactivity Disorder in Children and Adolescents

Safety Considerations

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Contents

Abstract 17
1. Consideration of Safety 18
2. Methylphenidate 19
3. Amfetamines 22
4. Atomoxetine 23
5. Conclusions 24

Abstract

Despite a large body of evidence for both the validity of the diagnosis of attention deficit hyperactivity disorder (ADHD) and the efficacy of its treatment with medication, there is an equally long history of controversy. This article focuses on presenting safety information for medications approved by the US FDA for the treatment of individuals with ADHD.

Stimulant medications are generally safe and effective. The common adverse effects of stimulant medications, including appetite suppression and insomnia, are usually of mild severity and manageable without stopping the medication. The more severe adverse effects such as tics or bizarre behaviours occur with low frequency and usually resolve when the medication is stopped. The possible impact on growth requires careful monitoring. Several rare but potentially severe adverse effects including sudden cardiac death and cancer following long-term treatment have been reported; however, these effects have not been adequately demonstrated to be of significant concern at this time. Atomoxetine also has a mild adverse effect profile in terms of severity and frequency although the numbers of studies and years of clinical experience is considerably less with this drug than for the stimulant medications.

When the risks are juxtaposed to the clear efficacy in significantly reducing dysfunctional symptoms of ADHD, benefit-risk analyses support the continued use of these pharmacological treatments for patients with ADHD.

Despite the large body of evidence for both the validity of the diagnosis of attention deficit hyperactivity disorder (ADHD) and the efficacy of its treatment with medication, an equally long history of controversy exists.[1] Interestingly, the first report about the benefits of stimulant medication published by Bradley in 1937[2] actually predates the definition of the disorder. Bradley noted the beneficial effect of amfetamine on the behaviour of children hospitalised for disturbed behaviour when it was used to treat the headaches they developed after having pneumoencephalograms performed for diagnostic purposes. Bradley's work was not well recognised until the 1950s when clinicians rediscovered his results and began treating children with dextroamfetamine for what was then known as minimal brain damage.[3] Methylphenidate was later approved for commercial use in 1957. Early studies were some of the first examples of randomised controlled studies in children to determine efficacy.[4] By 1977, 62 double-blind, placebo-controlled studies had been reported in the literature.[5] Since that time, the number of controlled studies has increased dramatically so that a review in 1998, using rigorous research criteria and only including studies reported from 1981 forward, found 123 studies[6] and by 1993 a 'review of reviews' reported on over 3000 citations and 250 reviews.[7] A more recent meta-analytic review was completed in 2001 and supported the previous findings that stimulant medication is efficacious in treating children with ADHD.[8]

Although the initial interest was in dextroamfetamine, the adverse publicity from the use of the drug as a treatment for weight reduction and its addictive properties when used in that context diminished its popularity about the time that methylphenidate became commercially available and known to clinicians. A longer acting stimulant medication, pemoline, was approved in 1975; however, it was recently taken off the market because of its uncommon but severe liver toxicity.[9] The only other US FDA medication approved for use in patients with ADHD is the selective noradrenaline (norepinephrine) reuptake inhibitor atomoxetine, which was approved in 2003. Five randomised control trials have demonstrated its efficacy and adverse effects.[10-14]

Applications for FDA regulatory approval of other medications, such as α-adrenoceptor agonists and bupropion, have not been sought and have more limited evidence of efficacy for treating the core symptoms of ADHD.[15] Furthermore, although 18 studies[16] exist demonstrating the efficacy of the tricyclic antidepressants, approval for their use in ADHD has not been sought. The existence of severe adverse events, such as sudden cardiac death from a prolongation of the PR interval combined with a narrow margin of safety, has limited interest in treatments with these medications.[17] Modafinil is not approved for use in ADHD, and an application for approval was denied by the FDA because of a concern about a higher rate of occurrence of Stevens-Johnson syndrome. Thus, the remainder of this article will focus on presenting the safety information only for those drugs that have been FDA approved for the treatment of patients with ADHD.

1. Consideration of Safety

In considering the safety of medications, six issues should be kept in mind: (1) severity; (2) duration; (3) frequency; (4) timing; (5) margin of safety; and (6) benefit-risk ratio.

1. Severity can range from life threatening and fatal adverse events to mild adverse events that primarily cause discomfort and annoyance but do not pose any serious risk.
2. The duration of the adverse event is a second consideration and the extent to which the effects are permanent is a prime consideration.
3. Frequency refers to how many patients taking the medication report an adverse event. Although adverse effects may be only mild or annoying, if they occur in a large enough percentage of the patients taking the medication, they can make the medication less desirable.
4. Timing refers to when the adverse event occurs within the period of usage (e.g. an adverse event may occur at the onset of therapy or only at a much later time after years of treatment).

5. The margin of safety refers to the adverse events that occur when doses over the therapeutic range are taken accidentally or intentionally.

6. The benefit-risk ratio is the decision about initiating and maintaining treatment where one must balance the severity of the condition, particularly the extent of dysfunction it creates and the efficacy of the medication, against the severity of the adverse effects and the chance of adverse effects occurring.

To examine the adverse effects of stimulant medications, we used Ovid to search the literature from 1966 to June 2006 for mention of stimulant medications, adverse effects and side effects. The search identified 155 publications, of which 25% were considered pertinent (i.e. those articles that reported adverse events for specific medications or groups of medications and were either studies or reviews of studies). The reported adverse effects for the stimulant medications can be grouped according to those that have been identified during short-term, randomised, controlled studies,[18] those identified in studies that have examined adverse effects in children over more extended periods of time[19-22] and several more recently identified possible adverse effects, such as sudden cardiac death[23] and precancerous cytogenetic changes.[24]

The most common adverse effects identified in short-term studies include appetite suppression, decreases in growth, headaches/stomachaches, changes in blood pressure and pulse, changes in sleep, increases in tics, cognitive effects, rebound phenomenon and psychotic behaviours. These findings have been summarised best in several systematic reviews.[18,25] The adverse effects identified in longitudinal studies provides further clarification of the effects over time. Lastly, those adverse effects more recently reported, sudden cardiac deaths and cancer risks, will be presented in more detail but have limited evidence. A summary of the adverse effects for stimulant medications is presented in table I.

2. Methylphenidate

Methylphenidate is a piperidine derivative that is structurally and pharmacologically similar to dextroamfetamine. In the US, the use of methylphenidate has increased each year since Safer and Krager[26] began monitoring the number of prescriptions written in 1971, with the exception of the years 1987–1990 when there was an active campaign to discredit stimulant medications in the treatment of children.[27] From 1990 to 1995, there was a marked increase in the use of stimulant medications. The increase was estimated to be from 2.5-fold[28] to 6-fold.[29] This change is mostly attributable to an increased use of methylphenidate in the treatment of older children, adolescents and adults with ADHD.[30]

Within the past 5 years, a number of new formulations that allow methylphenidate to be released over an extended time have been developed. Most use a micro-bead technology and usually last approximately 8 hours (Metadate CD®,[31] Ritalin LA®[32] and Focalin XR®[33]).**1** An osmotic pump system is used in one formulation and lasts about 12 hours (Concerta®).[34] An older preparation using a wax matrix design (Ritalin SR®) does not work as well, only lasting about 6–8 hours on average and having a slower onset.[35] All of the formulations use a racemic form of methylphenidate with the exception of dex-methylphenidate (Focalin®)[36] and its extended release form (Focalin XR®).[33] Most recently, a transdermal patch (Daytrana™) has also been approved.[37] In all of the orally administered formulations of racemic methylphenidate, the levo isomer is rapidly metabolised in its first pass through the liver so that it is essentially an inactive component. The transdermal formulation initially bypasses the liver so that it has some delay until the levo-isomer is metabolised.[38] However, the initial profiles of beneficial and adverse effects of the system have been similar to the oral formulations of methylphenidate.[38] The safety and efficacy of all of the extended release formulations have been con-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Drug reactions and contraindications

Generic[a] and brand names	Common adverse effects	Less common adverse effects	Contraindications
Methylphenidate Concerta® Metadate ER® Metadate CD® Ritalin® Ritalin SR® Ritalin LA® Focalin® Focalin XR® Daytrana™	Decreased appetite Sleep problems Headaches Irritability/nervousness	Gastrointestinal: nausea; abdominal discomfort; weight loss Increased heart rate and blood pressure Dizziness Stuttering Growth suppression Extensive bruising Muscle damage Dyskinesia Behavioural rebound Hallucinations/mania Exacerbation of tics and Tourette's syndrome (rare)	MAO inhibitors within 14 days Glaucoma Concerta®: pre-existing severe gastrointestinal narrowing Metadate ER®: caution should be used when prescribing concomitantly with anticoagulants, antiepileptic drugs, phenylbutazone and tricyclic antidepressants
Mixed salts of amfetamine Adderall® Adderall XR®	Same as for methylphenidate	Same as for methylphenidate	Symptomatic or history of cardiovascular disease Hyperthyroidism Moderate-to-severe hypertension MAO inhibitors within 14 days Glaucoma
Dextroamfetamine Dexedrine® DextroStat®	Same as for methylphenidate	Same as for methylphenidate	Same as for mixed amfetamine salts
Atomoxetine Strattera®	Decreased appetite Somnolence Nausea Abdominal pain	Mood swings Dyspepsia Rare hepatotoxicity Increased suicidal ideation	MAO inhibitors within 14 days Narrow angle glaucoma

a Generic name is given in bold.

MAO = monoamine oxidase.

sistently similar to immediate release methylphenidate so that they can be described as a group.

Methylphenidate has well proven short-term efficacy for the treatment of ADHD as noted previously. There have been >170 short-term, randomised, control trials of stimulant medications (mostly methylphenidate) involving >5000 mostly male, elementary school children (aged 5–12 years).[18] Short-term improvements have been demonstrated in the core symptoms of inattention, hyperactivity and impulsivity. In many cases, the medications have also led to improved relationships with peers and parents, and better control over conduct and aggression. The studies over the years have been synthesised in four formal meta-analyses[6,39-41] and one review of reviews.[7] These all support the efficacy of methylphenidate, at least in the short-term, in reducing core symptoms of ADHD, as well as improving function in a number of domains such as peer relationships and academic performance. The most powerful effects[6] have been found on measures of observable social and classroom behaviours with effect sizes (extent of change divided by the standard deviation) ranging from 0.63 to 0.85 (average 0.81) and measures of attention, distractibility and impulsivity ranging from 0.75 to 0.84 (average 0.78). However, the effects on intelligence and achievement tests are more modest, ranging from 0.19 to 0.47 (average 0.34). More recently, the US National Institute of Mental Health-sponsored MTA (Multimodality Treatment of ADHD) study has documented long-term benefits for at least 24 months.[22,42] The researchers in the MTA study have continued to follow the children to 60 months but the results have yet to be published.

The common adverse effects of methylphenidate have been well defined, are generally mild, mainly occur early after the onset of treatment and demonstrate that the drug has a wide margin of safety.[43] The most common adverse effects of methylphenidate that show a differential in frequency from those found in placebo are decreased appetite and sleep disturbance.[8,18,25] Headaches and stomachaches also occur but in some studies occurred as frequently in children receiving placebo.[8,25] Anxiety, dizziness and drowsiness occur less frequently.[8] In addition, jitteriness, irritability and proneness to crying or whining are reported when the medication is wearing off.[44]

Mild increases in pulse or blood pressure can occur, but are rarely clinically significant, particularly in children.[8,18,25] One summary found that half of the studies showed an increase compared with the placebo group.[25] The changes in blood pressure may be of more concern in adults where hypertension is a more common issue. The presence of a history of hypertension should be elicited when considering the benefit-risk profile of stimulant medications.

Rare occurrences include psychotic symptoms and sensitivity reactions.[8,18,25] These effects usually require terminating the medication. A negative effect of 'cognitive toxicity' where over-focusing may impair cognition can occur when the dose is too high or a patient is more prone.[45] Lowering the dose can usually manage this adverse effect.[45]

The effects of the medications on growth still require further clarification. Eleven of the 22 studies examining growth effects found an attenuation of growth in children being treated with stimulant medications; two of the 11 studies showed rebound growth when the medication was stopped.[46] However, the other studies that did not find the growth suppression effects, suffered from weaker experimental designs such as inadequate power or lack of controls.[46] The MTA study,[42] the most recent and systematic examination of the growth effects, found an attenuation of growth for at least 24 months, which was strongest in those who remained on medication for the whole time. However, the children in this study started off above average as a group. It appears that continuous treatment with stimulant medications does attenuate growth, but the long-term clinical significance of the decline is not yet clear. This certainly supports the importance of the need for clinicians to closely monitor the growth of the patients they treat with stimulant medications.

The concerns about abuse potential are discussed subsequently. Drug interactions are rare, but there has been an isolated report of methylphenidate increasing the blood level of ciclosporin.[47] A concern has been raised about the combination of methylphenidate and clonidine causing sudden death by cardiac arrhythmia, but a clear association could not be established and there are differences of opinion as to whether the association exists.[48]

Tics may occur or be increased in some of the patients treated with methylphenidate. In a study of children with Tourette's disorder,[49] both amfetamine and methylphenidate significantly increased the tics only in high doses, and with methylphenidate use were observed to diminished over time. If tics significantly worsen an individual's functional abilities, that patient may need to discontinue the medication. However, many patients find it possible to continue treatment for their ADHD because the improvement in their function related to their ADHD is considerably greater than the discomfort caused by the increase in tics.

In the initial studies of methylphenidate undertaken to gain FDA approval, it was found that treatment with methylphenidate lowered the seizure threshold in patients with epilepsy. However findings subsequent to the approval have not found an increase in seizures in patients with epilepsy who are treated with methylphenidate and whose seizures are under control.[50,51] However, it is important to note that almost all of the studies regarding treatment of individuals with ADHD exclude patients who have seizure disorders, so that the information available is very limited.

Several studies have reported the long-term observation of children being treated with stimulant medications.[20,21,52] The effects of decreased appetite and sleep disturbance continue to be the most

common adverse events. These effects have persisted in many of those children who initially manifest them, but they usually are tolerable for most of the children.

Two concerns have been raised recently about possible adverse effects of methylphenidate occurring with long-term treatment. Since the treatments for individuals with ADHD are symptomatic and not curative, it is likely that many patients will remain on the medications long-term. However, the amount of objective information available about long-term effects is very limited. The first has to do with cancer risk. A recent study found that in 12 of 18 children with ADHD who were methylphenidate-treatment naive at baseline and who had completed the study, there was a significant increase in the number of white blood cell chromosomal aberrations after treatment with methylphenidate for 3 months.[24] Previously, two studies of chromosomal aberrations in rodents receiving methylphenidate did not find genotoxic effects,[53,54] and the only other study of cancer risk in humans did not find an increased cancer rate in patients receiving methylphenidate.[55] Before the risk of cancer can be fully determined, previous findings need to be replicated in a larger sample with better methods of long-term surveillance.

A second recent concern is about the possibility of sudden cardiac death in patients receiving methylphenidate. An analysis of postmarketing reports of adverse events from 1999 to 2003, reported eight cases of sudden cardiac deaths (seven children and one adult).[23] Among the patients who died, cardiac malformations were found in two and a history of syncope in one patient. Three of the individuals were on concomitant medications. An additional 19 patients (eight children and 11 adults) had nonfatal events, including palpitations/arrhythmias in eight, syncope in three, stroke in two and QT prolongation in one patient. Eleven of the individuals were taking concomitant medications.

The results are difficult to interpret without comparing them to the expected rate of sudden cardiac death in the population. The instances of sudden death in young persons range from 1.3 to 8.5 per 100 000 patient years.[56] Given the large number of patients taking products with methylphenidate, it is not possible to ascertain at this time if the rate of sudden deaths or severe adverse reactions is more than should be expected in the general population. The reported cases would suggest it is not, but the system is likely to under-report the number of cases. For these reasons, physicians are encouraged to obtain careful histories and physical exams to identify patients with significant cardiac disease or who have a significant family history of cardiac disease, particularly arrhythmias, and to use methylphenidate cautiously in those patients. If there is an increased risk, it is likely to be low.

Methylphenidate products now carry warnings about sudden death in patients with structural cardiac anomalies, long-term growth suppression, psychosis, mania, aggression, use in severe depression and normal fatigue, patients with hypertension, other cardiac disorders, visual disturbance and, as noted previously, in individuals with seizure disorders.[57] The methylphenidate transdermal patch (Daytrana™) also carries a warning about contact dermatitis and osmotically controlled-released oral system (OROS™) methylphenidate carries a warning about potential gastric obstruction. It is only indicated for children aged ≥6 years, although a recent multisite study showed its efficacy and safety in preschool-aged children.[58] There is also a boxed warning about its use in individuals with drug dependence or alcoholism. Methylphenidate is classed as a controlled substance (class II in the FDA system) because of its potential to be abused.

3. Amfetamines

Amfetamine is the other stimulant medication commonly used to treat individuals with ADHD. It is a sympathomimetic amine. Both the dextro- and levo isomers are active and although both were studied in the 1970s,[59] the dextro-form became the dominant isomer in use. In the 1990s, a compound of mixed amfetamine salts, that consisted of a fixed combination of equal amounts of dextroamfetamine saccharate, dextroamfetamine sulfate, racemic amfetamine aspartate monohydrate and racemic

amfetamine sulfate was marketed and is now the predominant amfetamine prescribed to treat patients with ADHD. It is also available in an extended release form.

Amfetamines have a similar profile of efficacy and adverse effects to methylphenidate.[60] They have a slightly longer half-life with the levo isomer lasting longer than the dextro isomer.[61] The treatment effects profile is very similar to that of methylphenidate. There are differential responses to amfetamines and methylphenidate on an individual basis so that 38% respond to either medication, 35% respond to amfetamine only and 26% respond to methylphenidate only.[62]

The safety profile is also similar between methylphenidate and amfetamines. However, a comparison study of both medications found that dextroamfetamine caused more severe insomnia, irritability, proneness to crying, anxiousness, sadness and nightmares, but caused less severe appetite suppression.[63] Rare occurrences include psychotic symptoms and sensitivity reactions. As in methylphenidate, 'cognitive toxicity' can also occur.[45] Lowering the dose can usually manage this adverse effect. The effects on growth are similar to those for methylphenidate.[22] Although dextroamfetamine was found to have a more sustained effect on increasing tic formation in patients with co-morbid Tourette's disorder than methylphenidate,[49] it was not found to reduce the seizure threshold.[57]

The concern about the possibility of sudden cardiac death risk for patients taking stimulant medications actually first started because of cases reported about mixed amfetamine salts. An analysis of postmarketing reports of adverse events,[23] from 1999 to 2003 for amfetamines reported 14 cases of sudden cardiac death (12 children and 2 adults). Hypertension was present in three, cardiac malformations in two, cardiac hypertrophy in one, dysrhythmia in one, coronary artery disease in one, a history of a heart murmur in one and a maternal history of arrhythmia in one. Six individuals were taking concomitant medications. An additional 35 patients (18 children and 17 adults) had non-fatal events including arrhythmias in eleven, increase blood pressure/hypertension in nine, dyspnea in seven, myocardial infarction in six, stroke in four, syncope in three, left ventricular hypertrophy in one and sub-arachnoid haemorrhage in one patient. Three patients were taking concomitant medications. As with methylphenidate, it is difficult to interpret the results given the large number of patients taking products with amfetamine. It is not yet possible to ascertain if the rate of sudden deaths or severe adverse reactions is more than should be expected in the general population. The reported cases would suggest it is not, but the system is likely to under report the number of cases. For these reasons, as with methylphenidate, physicians are encouraged to obtained careful histories and physical examinations to identify patients with significant cardiac disease or a significant family history of cardiac disease, particularly arrhythmias, and to use amfetamines cautiously in those patients.

Mixed amfetamine salts (Adderall®) now carry warnings about sudden death in patients with structural cardiac anomalies, long-term growth suppression, psychosis, mania, aggression, seizure, blurred vision and use in nursing mothers.[57] Although no age restriction is placed, FDA labelling does not recommend its use for children <3 years of age. However, the age restrictions for both methylphenidate and amfetamines reflect more on when they were initially approved for use than they do on specific evidence for their use or adverse effects in young children. Amfetamines have the potential to be misused and are considered to be a controlled substance (class II in the FDA system). The product information sheet of these drugs carry boxed warning about their high potential for abuse.

4. Atomoxetine

Atomoxetine (Strattera®) is the levo isomer of the ortho-methylphenoxy analog of nisoxetine,[64] and it provides selective inhibition of presynaptic noradrenaline uptake. It has demonstrated efficacy over placebo in five, multi-site, randomised control studies.[10-14] The adverse events that occurred more frequently than in placebo included decreased appe-

tite (14%), vomiting (12%) and dizziness (6%).[65] Slight increases in blood pressure also occurred. Rare events from postmarketing surveillance have been two cases of hepatotoxicity that resolved with stopping the medication and one of these cases is now thought not to be related to the medication.[57] Although liver function tests are not recommended for monitoring, patients should be encouraged to inform their physicians about symptoms suggesting hepatotoxicity such as jaundice or a flu-like illness. Seven cases of suicidal ideation occurred in adolescents on re-reviewing study data.[57] No cases resulted in suicide or suicide attempts, but physicians and parents are encouraged to monitor children closely for these manifestations. Atomoxetine carries warnings about suicidal ideation, severe liver injury, psychosis, mania, aggressive behaviours and priapism.[57]

Table II. Adverse effects and possible strategies for management

Decreased appetite
administer after meals
change diet
use drug holidays
Sleep problems
eliminate afternoon dose
reduce/sculpt dose in afternoon
Headaches/stomachaches/irritability/dysphoria
decrease dose
try another stimulant medication or atomoxetine
Behavioral rebound
decrease afternoon dose
try sustained-release stimulant medication
Growth suppression
monitor height and weight
lower dose
use drug holidays
Tics
observe
reduce dose
try atomoxetine
try another stimulant
Psychosis/euphoria/mania
stop treatment with stimulants

5. Conclusions

In summary, stimulant medications are relatively safe and effective interventions. For the more common adverse effects of the medications, the steps that can be taken to reduce the impact are listed in table II. Their common adverse effects of appetite suppression and insomnia are usually mild and manageable without stopping the medication. The more severe adverse effects of tics or bizarre behaviours are less common and resolve when the medication is stopped. Several rare but potentially severe and long-term effects, such as sudden cardiac death or cancer, have been raised, although they have yet to be demonstrated as significant concerns. Atomoxetine also has a mild profile of adverse effects, although the numbers of studies and years of clinical experience is considerably less than that for the stimulant medications.

Substance abuse can occur with either amfetamines or methylphenidate. There is no abuse potential with atomoxetine. Abuse is not usually a problem for patients with ADHD who are receiving therapeutic doses of a stimulant medication for its therapeutic effects. Findings suggest that treatment with stimulant medications may actually reduce the risk of substance abuse in individuals with ADHD although the studies are methodologically weak.[66] The greater risk is for diversion of the medication for recreation or performance enhancement purposes by care takers or, in the case of patients who are in high school or college, their co-students. Growing concern about increasing misuse of stimulant medications on college campuses exists.[67] Most of the reported abuse has been with the immediate release preparations, although the medication can be extracted from the extended-release preparations but with more difficulty.

When the risks are placed in juxtaposition to the clear efficacy in significantly reducing dysfunctional symptoms of ADHD, the benefit-risk analysis remains one that is favourable for the pharmacologic treatment of patients with ADHD.

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