Psychopharmacology of ADHD: Children and Adolescents

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Medications can provide significant salutary effects for children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Due to their well-established safety and efficacy, psychostimulants are generally considered first-line pharmacotherapy for most young patients with ADHD. Since psychostimulant treatment often requires frequent dosing and may be associated with unacceptable side effects and risks, other classes of medication have been studied as possible treatment alternatives. The most extensively researched nonstimulant medications are the tricyclic antidepressants. In addition, α_2 agonists have also been shown to reduce symptoms of ADHD. However, concerns regarding potential cardiotoxicity have tempered the enthusiasm for both of these classes of medication. Newer antidepressants such as bupropion and venlafaxine may hold promise as treatments for ADHD.

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Although modern psychopharmacology is sometimes considered to have begun with the use of chlorpromazine as an antipsychotic in the 1950s,[1] it may be asserted that modern psychopharmacology actually began almost 15 years earlier with Bradley's report that described the efficacy of racemic amphetamine sulfate in the treatment of children with disruptive behaviors.[2] Since that time, numerous pharmacologic studies[3–5] have been undertaken in attempts to ameliorate the symptoms of restlessness, impulsivity, and inattention, which characterize attention-deficit/hyperactivity disorder (ADHD).[6] The purpose of this paper is to briefly review the available data about the pharmacotherapy of ADHD in order to provide the clinician with rational, empirically based strategies.

DIAGNOSIS/ASSESSMENT

One of the cornerstones upon which the pharmacologic treatment of ADHD is based is a careful, thorough clinical evaluation. Parents of children and adolescents often wish to have their child "tested" for ADHD. This implies that there is a specific test that is available to either confirm or refute the presence of this disorder. Although clinically relevant information may be obtained from cognitive testing or the administration of a continuous performance test,[7] it is generally recommended that an evaluation process which incorporates data obtained from parents, schools, and the patient is the most reliable way to accurately diagnose ADHD.[8,9]

Although symptoms of restlessness, distractibility, and inattention can be symptoms leading to psychiatric evaluation in a young patient, it should be recalled that these symptoms may occur with almost any psychiatric disorder, some medical disorders, and in nonsyndromal circumstances. For this reason, the possibility that other disorders may be present is essential before a diagnosis of ADHD is made.[7,9] Conversely, since ADHD may be found comorbidly with other disruptive behavior disorders, mood disorders, and anxiety disorders,[10–14] it is also important to consider that the presence of another psychiatric disorder does not necessarily exclude a diagnosis of ADHD.

Once a diagnosis of ADHD is confirmed, pharmacotherapies are available that can provide robust salutary effects to these patients.[5] Although this paper describes pharmacotherapy for ADHD, it is generally recommended that a multimodal treatment approach, which incorporates nonpharmacologic interventions, be considered in the treatment of pediatric patients with ADHD.[8,15] The American Academy of Child and Adolescent Psychiatry has developed practice parameters that outline such a multimodal approach.[8]

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Table 1. Commonly Prescribed Psychostimulants for the Treatment of ADHD in Pediatric Patients: Available Formulations and Recommended Dosing Strategies*

Medication	Tablet Strengths (mg)	Starting Dose	Between-Dose Interval (h)	Titration Rate (mg/wk)	Usual Therapeutic Doses[a]
Methylphenidate	5, 10, 20	5 mg bid	3–4	5–10	0.3–0.8 mg/kg/dose[b]
Dextroamphetamine	5, 10, 15	5 mg qd or bid	4–6	5	0.2–0.5 mg/kg/dose[c]
Adderall[d]	10, 20	5 mg qd or bid	4–6	5	0.15–0.4 mg/kg/dose[c]
Pemoline	18.75, 37.5[e], 75	37.5 mg qam		18.75	1–2 mg/kg/day[f]

*Data from references 15, 17, 28, and 34.
[a]Adolescents may require lower mg/kg dosing than school-age patients.
[b]Total daily dose of more than 60 mg not recommended.
[c]Only rarely should more than 40 mg/day be considered.
[d]Consists of equal parts amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate.
[e]Pemoline is available in chewable form.
[f]Maximum daily dose = 112.5 mg/day.

STIMULANTS

General Considerations

The psychostimulants have a unique place in pediatric psychopharmacology. Whereas most other classes of psychotropic medication have not been extensively studied in the young,[16] there are numerous studies that have documented the safety, efficacy, and tolerability of these agents in young patients with ADHD.[4,5,17] Although most research studies have examined the psychostimulants in school-age children, the stimulants have also been shown to be effective in ameliorating symptoms of ADHD in both preschoolers[18] and adolescents.[19,20] Because of their overall documented safety and efficacy, stimulants should generally be considered first when initiating pharmacotherapy for most patients with ADHD.[8]

The most commonly prescribed and studied psychostimulants include methylphenidate, dextroamphetamine, and magnesium pemoline.[21] Recently, the medication Adderall, which had been previously available as Obetrol, has been remarketed and advertised as a treatment for ADHD.[22] Adderall consists of equal parts of four amphetamines: amphetamine sulfate, amphetamine aspartate, dextroamphetamine sulfate, and dextroamphetamine saccharate. At present, Adderall has not received the same extensive empiric study as a treatment for ADHD that the other stimulants have had.[22]

Dosing

Since most side effects of psychostimulants appear to be dose related,[4] determining the lowest effective dose, which allows maximal therapeutic benefit while minimizing adverse effects, is the goal of safe, effective pharmacotherapy. In order to determine optimal therapeutic dosing, it is important to address target symptoms that are identified prior to the initiation of treatment in different settings. This is often best accomplished by gathering information from several sources.[17,23] Although weight-dependent medication dosing strategies can be used as guidelines for most patients, optimal treatment regimens do vary from patient to patient.[23,24] Plasma levels of methylphenidate have not been shown to be helpful for determining optimal therapeutic doses.[25,26]

For school-age children, it is recommended that treatment with methylphenidate be initiated at 5 mg b.i.d. Since each standard preparation dose of methylphenidate is generally effective for 3 to 4 hours, it is generally administered before breakfast and lunch.[27] If higher doses than this are to be administered, gradual increments of 5–10 mg/week are recommended.[28] School-age patients generally respond to a dose 0.3–0.8 mg/kg of methylphenidate.[29–31] Higher doses may have adverse effects on concentration and learning.[32,33]

Standard preparations of dextroamphetamine are given at approximately one half to two thirds the dose of methylphenidate with a similar timing of doses.[15,28] In school-age children, Adderall is usually initiated as a 5-mg dose given either once in the morning or b.i.d. with 4 to 6 hours between doses. It is recommended that Adderall be increased in 5-mg/week aliquots.[28]

For pemoline, the recommended starting daily dose is 37.5 mg and may be increased by 18.75 mg/week as necessary.[34] Pemoline's effects have been shown to last at least 7 hours after administration.[27] Only pemoline has an explicitly stated maximum daily dose, which is 112.5 mg.[34] Most patients respond to a single 1–2 mg/kg dose of pemoline given in the morning.[15,35] A summary of recommended dosing strategies for the psychostimulants in school-age children is found in Table 1.

Although concerns about insomnia have made clinicians wary about giving afternoon doses of stimulants in order to assist patients with homework or disruptive behavior during the after-school hours, recent studies have shown that an afternoon dose of standard methylphenidate does not typically lead to insomnia and is associated with salutary effects during the late afternoon hours.[36,37]

Sustained-Release Preparations of Methylphenidate and Dextroamphetamine

An important problem that may be associated with standard preparations of methylphenidate and dextroamphetamine is that of in-school dosing. Patients who are

prescribed these shorter acting stimulants on a b.i.d. schedule typically receive their medicines before breakfast and lunch.[23,27] This generally means that medications must be administered by school personnel. For this reason, patients can often be readily identified by their peers and others as being the recipient of a medication for their behavior. For some youngsters, this can be a most embarrassing and unpleasant experience and can lead to difficulties with compliance.[38–40]

There are sustained-release preparations of methylphenidate and dextroamphetamine which are typically effective for up to 8 hours after ingestion that are meant to serve as equivalents to a similar total dose of each standard preparation divided b.i.d. Prescribing a patient a longer acting psychostimulant may obviate the need for a patient to receive an in-school dose of medicine. In addition, the convenience of administering medications less frequently to young patients may improve compliance and acceptability from both the patients and their families. However, administering slow-release methylphenidate or dextroamphetamine is not without potential difficulties.

Although sustained-release methylphenidate and sustained release dextroamphetamine have been described as being at least equally effective as both standard methylphenidate and pemoline in some controlled trials,[41–43] this has not been a universal finding.[44,45] For these reasons, concerns have been raised about whether slow-release preparations of methylphenidate and dextroamphetamine are equally as effective as their standard preparation counterparts for individual patients.[23,46]

The sustained-release methylphenidate preparation is available only in 20-mg tablets. This does not allow for smaller aliquots in titrating doses that may be helpful for some patients. In addition, the sustained-release preparation of methylphenidate derives its increased duration of action by gradual release from a wax-matrix resin vehicle.[4] For this reason, the tablets of this medication should not be chewed; this is an important consideration for youngsters who cannot swallow tablets. If the sustained-release tablet of methylphenidate is chewed, the time-release properties of the agent may be lost, leading to release of the entire dose of medication at administration and possible adverse events.[47] Longer acting preparations of dextroamphetamine are available as 5-, 10-, and 15-mg capsules containing small coated particles of the agent. As with sustained-release preparations of methylphenidate, dextroamphetamine capsules should not be chewed so that the extended release properties of the medication may be maintained.

Substance Abuse

Methylphenidate, dextroamphetamine, and Adderall are all classified as schedule II agents and are therefore considered to be associated with a significant abuse potential. Since pemoline is related to the psychostimulants, it is labeled as a schedule IV medication, which suggests that it does not have the same risk for abuse as the other stimulants.[28] Although it has not been documented that treatment with any of these schedule II medications leads to substance abuse, prescribing these medicines to youngsters carries the risk that these medications may be abused or sold by patients or their family members. For this reason, careful consideration of this possibility must be given before prescribing any schedule II psychostimulant to a patient.

Side Effects/Therapeutic Monitoring

The short-term side effects of the psychostimulants are well described and appear to be dose related.[4,23] Recent studies have considered side effects associated only with methylphenidate. The most common of the adverse events reported with methylphenidate treatment include anorexia, stomachaches, initial insomnia, headaches, and irritability.[48–50] Due to these anorectic effects, patients' weight should be followed prior to and during the course of stimulant therapy. Somewhat reassuring are the results of a recent study which has reported that a child's height-adjusted weight may predict which children will experience greater degrees of stimulant-induced weight loss, with heavier children likely to lose more weight than thinner ones.[51]

Other possible side effects from the stimulants include increased blood pressure and pulse due to the sympathomimetic properties of the psychostimulants.[4,33,52] For this reason, blood pressure and pulse should be monitored in patients who receive psychostimulants.[8] Children generally have minimal changes in blood pressure and pulse associated with a 0.3-mg/kg dose of methylphenidate.[53,54] However, black adolescents may be particularly at high risk for developing increases in diastolic blood pressure with methylphenidate treatment.[19]

Rare cases of leukopenia and psychosis have also been reported associated with psychostimulant therapy. For this reason, baseline and yearly complete blood counts are recommended with stimulant therapy.[4]

Concerns have been raised that methylphenidate may retard growth in children. The initial report that described this phenomenon was published in 1972.[55] Subsequent studies have demonstrated that treatment with methylphenidate generally does not affect the ultimate stature of school-age patients treated with this drug[56,57] and that reduction in growth velocity is not present in adolescents.[58] In addition, it has recently been reported that ADHD itself may lead to a temporary reduction in growth velocity that may be manifest through mid-adolescence and is not related to psychostimulant therapy.[59] Nonetheless, since some patients will experience significant reduction in growth rate when treated with methylphenidate,[17] careful monitoring of stature is also recommended during stimulant pharmacotherapy.

Another concern associated with psychostimulant treatment is that these medications may induce irreversible tics or exacerbate tics in patients already suffering from tic disorders.[4] In fact, the presence of motor tics or a family history of Tourette's syndrome has been recommended by some as a contraindication to the use of psychostimulants in children with ADHD.[28,60,61] This is an important issue because 20% to 50% of patients with Tourette's syndrome also manifest symptoms of ADHD.[4] However, recent work has shown that stimulants may be safe and effective in ameliorating the symptoms of ADHD in young patients with tic disorders.[62] In addition, tics have been reported to occur in about 9% of youngsters treated with psychostimulants. Although this may be somewhat disconcerting, these tics are almost always transient, and in only rare instances (less than 1%) does a chronic tic disorder develop.[63]

Other than these stimulant-induced side effects, there are two other treatment-related adverse events that may also occur with pemoline. Choreiform movements have been reported to occur with administration of this medicine.[64] In addition, treatment with pemoline may lead to hepatocellular injury.[65] Increases in serum transaminases occur in approximately 3% of patients treated with pemoline.[23] Although most pemoline-induced hepatotoxicity is mild and reversible,[65] three fatalities due to liver failure have been described as being caused by pemoline.[66] It has been estimated that treatment with pemoline increases the relative risk of a youngster developing fulminant liver failure.[66] The mechanism that leads to pemoline-induced hepatocellular injury is not known.[65] For this reason, baseline and every-6-month monitoring of transaminase levels have been recommended.[23] As a result, pemoline has not become a medication of first choice for most patients.[46]

Psychostimulant Metabolism

Although the pharmacokinetics of the psychostimulants have been described,[44,67–72] more needs to be learned about the metabolism of the psychostimulants. For example, the cytochrome P450 system is a series of hepatic enzymes responsible for the metabolism of a wide variety of medications, including numerous psychotropic agents.[73–75] Recent studies have attempted to delineate the clinical roles these enzymes play in drug metabolism and the potential contribution to drug-drug interactions with psychotropics.[76,77]

Although the cytochrome P450 isoenzymes associated with the oxidative metabolism of antidepressants, antipsychotics, and anxiolytics have received extensive study, little work has been done with the psychostimulants. As preliminary papers consider that combination pharmacotherapy may have a role in the treatment of young patients with comorbid psychiatric disorders,[78–83] it may be of clinical importance to examine whether possible drug-drug interactions between stimulants and other agents are mediated through this enzyme system.

There is in vitro evidence that methylphenidate inhibits the cytochrome P450 2C9-mediated metabolism of tolbutamide.[84,85] In addition, there are data describing that the oxidation of amphetamine is mediated by the cytochrome P450 2D6 isoenzyme.[86–88] The clinical significance of these findings to the treatment of young patients with ADHD has not been explored. There are no published data regarding the role of the cytochrome P450 system in the metabolism of pemoline.

Treatment Failures

Although it is generally accepted that approximately 70% of patients who are initially treated with one psychostimulant will derive therapeutic benefit from it,[9,46] the question of what to do in treatment failures is an important one. Patients who fail a therapeutic trial with methylphenidate may do quite well with dextroamphetamine. Similarly, patients who do not do well with dextroamphetamine can have robust salutary effects with methylphenidate. In fact, since patients may respond differently to these stimulants,[89–91] it has been advocated that both agents be prescribed before determining which agent should be employed in ongoing treatment.[92] Therefore, it is important to remember that failure with one stimulant does not necessarily predict failure with another.

Overview

The psychostimulants are the most frequently prescribed agents in pediatric psychopharmacology. They are generally safe and effective for ameliorating the symptoms of ADHD. However, the psychostimulants are imperfect medications. Although stimulants' side effects are predictable and often well tolerated, adverse events can cause significant difficulties and may lead to medication discontinuation.

OTHER AGENTS

Since stimulants often need to be dosed frequently, may be abused, and may be associated with side effects that are unacceptable to patients and their families, investigators have examined whether nonstimulant medications have a place in the pharmacotherapy of ADHD. The nonstimulant agents that have been most extensively studied include antidepressants (Table 2), α_2 agonists, and neuroleptics.

Antidepressants

The class of antidepressant medication that has been most extensively studied for the treatment of ADHD is the tricyclic antidepressants. The most commonly studied of these are desipramine and imipramine.[3,5] Controlled studies of imipramine generally described therapeutic efficacy. Studies that have compared imipramine with a psycho-

Table 2. Antidepressants With Potential Benefit for Pediatric Patients With ADHD*

Tricyclic antidepressants
Amitriptyline
Desipramine
Imipramine
Nortriptyline[a]
Monoamine oxidase inhibitors
Bupropion
Fluoxetine[a]
Venlafaxine[a]

*Adapted from references 3 and 112.
[a]Controlled studies have not been performed.

stimulant indicate mixed results, with reports describing similar, fewer, or greater benefits from imipramine.[5,93–95] However, side effects and tolerance were commonly described with imipramine treatment.[93–97]

Desipramine was subsequently reported to be effective for the treatment of ADHD in pediatric patients in both open and placebo-controlled trials.[98,99] Unfortunately, reports of inexplicable sudden death in children prescribed this medication[100] have lead to concerns about its use in this population.[101,102] Although less extensively studied, amitriptyline and nortriptyline have also been described as being helpful in ameliorating symptoms of ADHD.[103–105]

Other antidepressants have also been studied in young patients with ADHD. The monoamine oxidase inhibitors clorgyline and tranylcypromine sulfate have been reported to be effective in one controlled study.[106] Dietary restrictions associated with tranylcypromine sulfate and the unavailability of clorgyline have precluded their use from becoming widespread.

Some of the newer antidepressants may hold promise as treatments for ADHD. Of these agents, bupropion has received the most rigorous scrutiny and has been consistently shown to reduce symptoms of ADHD in young patients in controlled clinical trials.[107–110] In one open study, fluoxetine has also been described to be of benefit in children with ADHD.[111] However, a recent report has questioned whether fluoxetine monotherapy is truly effective for ADHD.[80]

Lastly, one open trial of venlafaxine in the young has reported that venlafaxine may ameliorate the symptoms of ADHD in pediatric patients.[112] Similar findings have been described in several open studies in adults with ADHD.[113–115] There has also been one open study that has examined venlafaxine in 25 youths between the ages of 6 and 15 years with conduct disorder. Some of these subjects also met criteria for ADHD or major depression. The investigators reported that venlafaxine treatment was well tolerated and led to "significant clinical improvement" in these patients.[116]

α_2 Agonists

Clonidine has been described as being effective in the treatment of ADHD in open and controlled studies.[117–120] It has been recommended that clonidine be titrated gradually and dosed frequently in order to minimize both the cardiovascular effects and sedation which may accompany its use. Clonidine may also induce dysphoria, which can often lead to significant difficulties. Patients and their families also need to be warned about abrupt discontinuation of clonidine in order to avoid the possibility of rebound hypertension.[121] An open trial describing salutary effects from guanfacine in children with ADHD has also been reported.[122]

Although controlled and open studies have been performed with α_2 agonist monotherapy in ADHD, the popular practice of coadministering an α_2 agonist and a psychostimulant has not received a similar degree of scientific scrutiny. Adjunctive clonidine has been described as being of putative use for children with ADHD who have sleep difficulties[123,124] or for those youths who obtain only a partial therapeutic response from either agent.[121] With electrocardiographic changes being described with clonidine,[125] and because of recent reports of unexplained sudden death occurring in children treated with clonidine/methylphenidate combination therapy,[126] careful cardiovascular monitoring is recommended for all patients prior to and during α_2 agonist pharmacotherapy.

Neuroleptics

Controlled studies with neuroleptics have been performed that have described reductions in disruptive behavior in patients treated with the low-potency antipsychotics thioridazine[127] and chlorpromazine,[128] as well as the high-potency neuroleptic haloperidol.[129] Due to concerns about the plethora of side effects possible from these medicines,[130,131] and the fact that stimulants are generally more effective than antipsychotics for the treatment of ADHD,[3] neuroleptics are generally not recommended as a treatment for uncomplicated ADHD[8] and are considered a treatment of "last resort" for pediatric patients with ADHD.[5]

SUMMARY

The psychostimulants have been repeatedly demonstrated as being both safe and effective pharmacologic treatments for ADHD. Yet, the psychostimulants remain an imperfect treatment for this syndrome due to their side effect profile, need for frequent dosing, and abuse potential. Several antidepressants and two α_2 agonists have been reported as being safe and effective alternatives in clinical trials.

At present, due to the relative paucity of empirically based data available for nonstimulant medications, the psychostimulants remain the pharmacologic choice for the pharmacotherapy of most patients with ADHD. Further psychopharmacology research in ADHD is needed to define the roles of nonstimulant treatments.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), chlorpromazine (Thorazine and others), clonidine (Catapres), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), fluoxetine (Prozac), guanfacine (Tenex), haloperidol (Haldol and others), imipramine (Tofranil and others), methylphenidate (Ritalin), nortriptyline (Pamelor and others), pemoline (Cylert), thioridazine (Mellaril and others), tranylcypromine (Parnate), venlafaxine (Effexor).

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