Psychopharmacologic Treatment of Attention-Deficit/Hyperactivity Disorder and Disruptive Behavior Disorders

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Attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) constitute the most prevalent cluster of child and adolescent psychiatric disorders. ADHD is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that is more severe and more frequent than in youth in similar circumstances at a comparable developmental level. There are three subtypes: predominantly hyperactive-impulsive, predominantly inattentive, and combined. ODD is a recurrent pattern of negativistic, defiant, disobedient, and hostile behavior...
toward authority figures that persists for at least 6 months. CD is a repetitive and persistent pattern of violating the basic rights of others or major age-appropriate societal norms. In each of the disorders, symptoms are present in more than one setting and cause significant functional impairment — although there may be relative differences in the nature and severity of presentation across settings.

ADHD, ODD, and CD present with similar impairments, including academic underachievement and poor social skills; impulsive behavior is often (but not always) present. Furthermore, there is a high degree of mutual comorbidity; almost all children with CD also have ODD, and 60% to 70% of children with ADHD have ODD. Although there is now a consensus that ADHD and CD are separate diagnoses with distinct correlates and outcomes, the relationship of ODD to both disorders is less clear.

NEUROBIOLOGICAL BASIS OF ADHD AND CD: RELEVANCE FOR PHARMACOLOGIC TREATMENT

Neurochemical markers and family-genetic analyses have confirmed the neurobiological bases of ADHD, and to a lesser extent, CD. These data provide a compelling rationale for the growing use of pharmacotherapy for these disorders. Virtually all effective pharmacotherapeutic agents for ADHD affect dopamine and norepinephrine. In contrast, serotonin has been more specifically implicated in the impulsive-aggressive behavior characteristic of CD.

Neurobiology of ADHD

There is a substantial genetic contribution to the etiology of ADHD, with heritability estimated to be .76. However, it is now clear that multiple genes are involved. Several catecholamine regulatory genes show a positive association with ADHD, but each has a rather small effect. The strongest evidence has been for the 7 repeat allele of DRD4, which is associated with a blunted intracellular response to DA. The 10 repeat allele of DAT1, linked to elevated DA reuptake, has also been implicated in the etiology of ADHD, but with a very low effect size. Recent research has implicated different polymorphisms of DAT1 in regulating response to methylphenidate, which acts by binding to DA transporters in the striatum.

Neuroimaging studies implicate several different brain regions, including the four major cortical lobes (frontal, parietal, occipital, and temporal), the caudate, cerebellum and regions of the corpus callosum, all of which are smaller in youth with ADHD compared with controls. Several, but not all, studies using positron emission tomography (PET) in combination with radioactive ligands have found elevated density of striatal dopamine transporters in adults with ADHD. Regardless, DAT density may be associated with self-reports of inattention. Functional neuroimaging studies have provided evidence that altered frontal-striatal function in ADHD is improved by stimulants.

Neurobiology of CD

The heritability of CD has been estimated to be 30% to 70%. Family studies documenting the relationship between parental substance abuse and childhood CD have led to a “common gene” hypothesis for these disorders. However, there are clearly major environmental contributions, such as poverty, trauma and abuse, maternal depression, intrauterine exposure to substances, and various parenting practices. Diagnostic crossover (from paternal alcoholism to childhood CD) across generations, in the context of both high and low environmental risk (while genetic risk remained high), confirms that genetic factors are responsible for the alcoholism-CD association. One study reported a possible interaction between the serotonin-transporter-linked promoter region (5HTTLPR) and other genetic risk factors: increased risk for externalizing behavior in people with the long (L) variant of 5HTTLPR and antisocial biologic parentage, and increased risk for externalizing behavior in people with one or more 5HTTLPR short variants (S or SL) in conjunction with a genetic diathesis for alcoholism.

Results of imaging studies indicate that ADHD and ADHD with CD are both characterized by smaller volumes of the left and total posterior superior and inferior lobes of the cerebellar vermis. They also document the affective nature of CD. One study found that male adolescents with CD exhibit reduced activation in the right anterior cingulate cortex (ACC) in response to negative affective pictures. Another found reduced activation of the left amygdala in CD but not normal controls, when viewing pictures suggesting negative affect. These findings suggest impairments in recognition and processing of emotional stimuli in patients with CD, which may relate to propensity for aggression.

The neurochemical basis of CD has primarily focused on the role of noradrenaline (NA) and serotonin (5-HT). One study found a negative correlation between cerebrospinal fluid (CSF) concentrations of MHPG (noreadrenaline metabolite) and aggressive behavior. Low activity of the enzyme dopamine-beta-hydroxylase, which converts DA to NA, has also been associated with CD. Studies with aggressive and antisocial adults have consistently found reduced CSF levels of 5 HT metabolites and blunted responses to 5 HT challenge.

The heritability of CD has been estimated to be 30% to 70%.
# Table 1

## Food and Drug Administration Approved Medications for the Treatment of Attention-Deficit Hyperactivity Disorder

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA-Approved Dose</th>
<th>Daily Dose Ranges Used Clinically (mg/kg)</th>
<th>Dose Schedule</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate (MPH):</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Focalin</td>
<td>5 to 30 mg/day</td>
<td>0.25 to 1.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td>Short-acting stimulants may require more frequent dosing. Mean daily dose usually 0.75 to 1.5 mg/kg for d-MPH; about half of that for d-MPH</td>
</tr>
<tr>
<td>Ritalin</td>
<td>10 to 60 mg/day (average 20 to 30 mg/day)</td>
<td>0.5 to 2.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>MPH</td>
<td>0.5 to 2.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate (MPH):</td>
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<tr>
<td>Ritalin SR</td>
<td>10 to 60 mg/day (average 20 to 30 mg/day)</td>
<td>0.5 to 2.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>Metadate ER:</td>
<td>10 to 60 mg/day (average 20 to 30 mg/day)</td>
<td>0.5 to 2.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>Metadate CD</td>
<td>20 mg/day (max 60 mg/day)</td>
<td>0.5 to 2.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>Ritalin LA</td>
<td>20 mg/day (max 60 mg/day)</td>
<td>0.5 to 2.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>Concerta</td>
<td>18 to 54 mg/day (children); 18 to 72 mg/day (adolescents)</td>
<td>0.5 to 2.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>Daytrana</td>
<td>12.5 to 37.5 cm² (10 to 30 mg)</td>
<td>0.5 to 2.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>Ampheptamine (AMP):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextedrine</td>
<td>2.5 to 40 mg/day</td>
<td>0.25 to 1.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>Dextrostat</td>
<td>2.5 to 40 mg/day</td>
<td>0.25 to 1.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>Adderal</td>
<td>2.5 to 40 mg/day</td>
<td>0.25 to 1.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>Mixed amphetamine salts (G)</td>
<td>2.5 to 40 mg/day</td>
<td>0.25 to 1.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>AMP Extended Duration:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisdexamfetamine (Vyvanse)</td>
<td>30 to 70 mg/day</td>
<td>0.25 to 1.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>Dextedrine Spanseule</td>
<td>2.5 to 40 mg/day</td>
<td>0.25 to 1.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>*Adderal XR</td>
<td>Max 20 mg/day in adults; 30 mg/day in children</td>
<td>0.25 to 1.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>Atomoxetine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Strattera</td>
<td>Children: Target dose is 1.2 mg/kg/day</td>
<td>0.25 to 1.0 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
</tr>
<tr>
<td>Adults: Start at 40 mg per day, then 80 mg (target) and 100 mg (max)</td>
<td>Maximum labeled dose 1.4 mg/kg</td>
<td>Twice daily or three times daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*G = generic*

*FDA-approved for treating adult ADHD.*

*Note: Higher than approved dosing may be needed to achieve an optimum response.*
### TABLE 2.
Treatment, Safety Considerations, and Management Strategies for ADHD Medications.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Key Safety Considerations</th>
<th>Management Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate release formulations</td>
<td>Tachycardia, arrhythmia, sudden death</td>
<td>Heart rhythm/blood pressure monitoring, echocardiogram in high risk cases; baseline ECG not recommended</td>
</tr>
<tr>
<td>(d-L-MPH; d-MPH)</td>
<td>Growth suppression</td>
<td>Baseline height/weight with periodic monitoring</td>
</tr>
<tr>
<td></td>
<td>Tics</td>
<td>Decrease anxiety/weight with periodic monitoring</td>
</tr>
<tr>
<td></td>
<td>Potential for abuse and diversion</td>
<td>Counsel, non-stimulants, extended release formulations</td>
</tr>
<tr>
<td>Extended release (MPH-LA, MPH-CD, OROS MPH, d-MPH XR)</td>
<td>Presumed same as above but not studied; lower potential for abuse and diversion</td>
<td></td>
</tr>
<tr>
<td>Methylphenidate transdermal system</td>
<td>Skin erythema</td>
<td>Observation; topical creams</td>
</tr>
<tr>
<td></td>
<td>Other side effects similar to other MPH formulations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lower potential for abuse/diversion (requires extraction from patch, which is difficult)</td>
<td></td>
</tr>
<tr>
<td>Amphetamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate release (d-AMP, MAS)</td>
<td>Same as for MPH overall, but individual differences exist</td>
<td></td>
</tr>
<tr>
<td>Extended release (d-AMP spansule; MAS XR)</td>
<td>Lower potential for abuse/ diversion</td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Hepatotoxicity</td>
<td>Baseline history; follow clinically for abdominal pain/ jaundice</td>
</tr>
<tr>
<td></td>
<td>Tachycardia, arrhythmia, sudden death</td>
<td>HR/BP monitoring, echocardiogram in high-risk cases; baseline ECG not recommended</td>
</tr>
<tr>
<td></td>
<td>No abuse potential</td>
<td></td>
</tr>
<tr>
<td>Off-label Treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion, Bupropion SR or XL</td>
<td>No abuse potential; decreased seizure threshold</td>
<td>Do not exceed 150 mg in a single dose for IR or 300 mg for XL</td>
</tr>
<tr>
<td>Emerging Treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisdexamphetamine</td>
<td>Side effects generally similar to other stimulants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abuse potential limited by requirement for GI metabolism</td>
<td></td>
</tr>
<tr>
<td>Guanfacine</td>
<td>Hypotension, rebound hypertension</td>
<td>HR/BP monitoring</td>
</tr>
<tr>
<td></td>
<td>No abuse potential</td>
<td></td>
</tr>
</tbody>
</table>

agents. Reduced central 5 HT function was also associated with risk factors for persistence in aggressive children, including adverse child rearing practices and parental history of aggression.

**PHARMACOTHERAPY OF ADHD**

Pharmacotherapy of disruptive behavior dates to 1937, when Bradley reported dramatic improvement in behavior when benzedrine was given to a group of post-encephalitic children. Psychostimulants remain the medication of choice for uncomplicated ADHD and can also be used safely and effectively in many complicated presentations. Stimulants have been studied in hundreds of controlled trials in all age groups, have documented safety, and are now available in extended-release preparations. Several other medication classes have demonstrated efficacy for ADHD, but of these only atomoxetine is approved by the Food and Drug Administration (FDA; see Table 1, page 566, and Table 2). Other non-stimulants are used off-label, offering alternatives to non-responders or non-tolerators of stimulants or atomoxetine, or those with special presentations (eg, comorbidity).
Psychostimulants: Efficacy

Methylphenidate (MPH), dextroamphetamine (DEX), and mixed amphetamine salts (MAS; a mixture of several amphetamines, 75% of which is DEX) have all been shown to be effective, with effect sizes that are large to very large. There are not substantive differences in response among the different stimulant classes and formulations, dosed equivalently throughout the course of the day. However, there are important differences in mode of action that may account for selective individual response. It is therefore usually recommended that non-responders to one stimulant class be treated with the other. In addition, one or another formulation of the same medication may be preferred for a particular person because of differences in delivery, absorption, and metabolism resulting in different time-action profiles. Initiation of stimulant treatment is best determined by considering properties intrinsic to the different medications, most notably mode of delivery, relative dosing, and duration of activity. The new, long-acting stimulants, the first of which became available in 2000, have become the preferred first-line treatment for most patients. However, there are exceptions to this practice, attributable to

Results of imaging studies indicate that ADHD and ADHD + CD are both characterized by smaller volumes of the left and total posterior superior and inferior lobes of the cerebellar vermis.

Stimulants are used to treat ADHD alone or in the context of comorbidity, because comorbidity generally does not moderate stimulant response. However, there has been debate regarding the efficacy and safety of stimulants in treating certain comorbid disorders. Results of early studies found stimulants to be less effective and less well tolerated in the treatment of ADHD with comorbid anxiety disorders. However, more recent studies have not found this to be the case. Stimulant use in ADHD with comorbid bipolar disorder has been even more controversial. Some have suggested that stimulants should not be used in this population at all because of the risk of precipitating mania. Others suggest that it is essential to treat ADHD when it is comorbid with bipolar disorder, but it is necessary to treat the mania first. If some manic symptoms (e.g., affective liability or irritability) are present, but not the full bipolar syndrome, findings suggest that stimulants can be used effectively. Also, the fact that ratings of irritability often improve in children with ADHD with stimulant use complicates the approach to children who have ADHD with bipolar syndromes.

Stimulant Classes and Formulations

The currently available formulations of methylphenidate are:

- OROS-MPH (Concerta, 12-hour formulation). This is the only continuous-release oral MPH, with 22% of the medication delivered throughout the first 4 hours and the rest over the course of the day. The starting dose of 18 mg is equivalent to 5 mg IR-MPH administered three times daily.
- d,l-MPH CD (Metadate CD, 8-hour formulation), which uses a double-pulse release mechanism (10 mg is equivalent to 5 mg IR bid) formulated to deliver 30% in the first 4 hours and 70% in the second 4 hours.
- d,l-MPH LA (Ritalin LA; 8-hour duration), a double-pulse formulation that uses brand-name Ritalin delivered via a 50-50 split.
- d-MPH (Focalin) IR and XR. d-MPH is the active stereoisomer of MPH and is administered at approximately half the dosage of d,l-MPH. d-MPH IR may last for up to 6 hours, and XR may last up to 12 hours.
- MPH transdermal system (MTS; Day-
transa), approved in children 6 to 12 years old. Efficacy and tolerability are comparable to oral MPH. This formulation offers flexible duration of action because the medication lasts for approximately 3 hours after the patch is removed. Efficacy was documented up to 12 hours but may extend up to 15 hours if the patch is left on.

- MPH-SR, the original wax matrix sustained formulation, which is less often used because it has lower efficacy.
- IR-MPH, which lasts about 4 hours. Its niche increasingly is to supplement the longer-acting preparations, either to achieve more rapid onset of effect or to extend duration of action. When used as a primary agent, three times daily dosing is often necessary to provide coverage during homework and evening time. The labeled daily maximum dose of d,l-MPH is 60 mg, with the exception of OROS-MPH, which is approved for 54 mg in children and 72 mg in adolescents. The maximum labeled dose of d-MPH is 30 mg in children, and 20 mg in adults.

The available amphetamine formulations are:

- MAS-XR (ie, Adderall-XR), which uses a double-pulse delivery system, similar to several of the MPH formulations (50-50 split), acts for 12 hours, and is now the most frequently prescribed psychostimulant formulation.
- Lisdexamfetamine (LDX; Vyvanse), a pro-drug of dextroamphetamine (DEX), approved in 2007, in which DEX is covalently bound to the amino acid L-lysine, making it more difficult to abuse. LDX is inactive until metabolized by gastrointestinal enzymes, which gradually release DEX. LDX is associated with lower self-reports of euphoria than DEX, and has comparable efficacy and tolerability to MAS-XR.
- MAS IR (ie, Adderall), which lasts approximately 5 to 6 hours.
- DEX IR, which lasts approximately 4 hours.

- DEX spansule, which lasts 6 hours or longer. DEX spansule was found to be roughly equivalent to MAS.18 DEX and MAS are more potent than MPH, so the initial starting dose and upper dose limit are lower. The recommended dosage range for DEX is 2.5 to 40 mg. Although DEX has a somewhat longer half-life than MPH, there is a more prominent dissociation of pharmacokinetic/pharmacodynamic effects, and three times daily dosing of IR is often required.

**Psychostimulants remain the medication of choice for uncomplicated ADHD and can also be used safely and effectively in many complicated presentations.**

**Stimulant Adverse Effects**

The most commonly encountered adverse effects (AE) of stimulants include headache, abdominal pain, decreased appetite (with or without weight loss), and initial insomnia. There are slight increases in pulse and blood pressure, which are generally not meaningful at the group level but can take on greater significance for some people, especially those with pre-existing cardiovascular pathology. Motor or vocal tics can develop or be exacerbated. However, there has been a convergence of evidence that stimulant treatment does not necessarily exacerbate tics and some suggestion that these conditions are relatively independent. Thus, it is medically appropriate to use stimulants in people with tics when the ADHD symptoms have an impairing effect on quality of life and alternative medications are not effective. Atomoxetine and guanfacine can treat tics as well as ADHD symptoms, and these medications may offer an alternative to stimulants in ADHD with tic disorders.

The extent to which stimulant treatment may be associated with growth retardation remains controversial. Recent results from the Multimodal Treatment of ADHD (MTA) study suggest that acute use of immediate-release stimulants, administered 3 times daily, 7 days per week, produced a slowing of growth by approximately 1 cm per year throughout the first 24 months of treatment in medicated versus unmedicated patients.22 Although the decrease in growth trajectory flattened after the initial treatment period, it did not “catch up” to the curve for unmedicated patients by 36 months. Interpretation of these data are complicated by the fact that the ADHD children in this and most other clinical trials are larger than the age and gender-based norms, so it is not clear if this degree of slowing of growth is actually of clinical concern. Also, it is not clear if this finding would hold for the new extended-release stimulants or for dose regimens that give breaks on weekends or holidays. It is important to monitor weight and height before and during treatment. Decisions regarding if and when to medicate with stimulants or other medications, and when to consider alternative management strategies, should be made on an individual basis.

The issue of cardiotoxicity and stimulant treatment has received considerable attention recently. Reports of 12 cases of sudden cardiac death in children taking MAS prompted an initial review by the FDA (see FDA Web site: www.fda.gov/cder/drug/advisory/adderall.htm or www.fda.gov/cder/drug/infopage/ADHD). Of the 12 reported cases, five occurred in patients with underlying structural heart defects (abnor-
mal arteries or valves, abnormally thickened walls, etc). In several of the other cases, there were problems complicating the assessment of medication-related risk (eg, family history of ventricular tachycardia; association of death with heat exhaustion, dehydration, and near-drowning; very rigorous exercise; fatty liver; heart attack; and type 1 diabetes mellitus). The most recent information indicates that risk for sudden death in patients taking stimulants does not exceed the base rate in the general population (0.6 to 6/100,000 per year), and this outcome is often associated with pre-existing structural cardiac defects, other complicating circumstances or a positive family history. Following an extensive review, the FDA issued a warning along with a recommendation to provide information regarding the benefits and risks of stimulants.23

Likewise, there is considerable interest in stimulant misuse and diversion. Up to 11% of youth with ADHD report selling their medications, while another 22% with comorbid CD or substance use disorder reported misusing their medications.24 A survey of 1,025 college students found that 16% reported abusing or misusing stimulant medication.25 Stimulant abuse and dependence generally occur in the context of other addiction disorders and psychiatric comorbidity and are much less frequent in ADHD alone. It is commonly believed that MPH may be abused at lower rates than amphetamines (AMP), but evidence from both human and animal studies suggests that both stimulants have strong abuse potential, depending on how they are administered and dosed.26

Finally, a recent update of the labeling for AMP formulations provides a warning regarding risk for exacerbation of behavior disturbance and thought disorder in patients with pre-existing psychotic or manic symptoms. However, it is well known that these effects can occur with both stimulant classes, and any formulation, and likely occur with several non-stimulants as well.

**Atomoxetine**

Atomoxetine (ATX) is a new non-stimulant medication with highly potent and selective activity to block the noradrenergic transporter. It is structurally distinct from both the stimulants and the tricyclic antidepressants and is the first non-stimulant approved for the treatment of ADHD, in both children and adults. ATX is effective in reducing overall ADHD symptoms, as well inattentive and hyperactive/impulsive symptoms in children, adolescents, and adults. Dosing follows a weight-based schedule, starting at 0.5 mg/kg. The maximum labeled dose is 1.4 mg/kg daily, but there are good safety data up to 1.8 mg/kg. Atomoxetine can be administered either twice or once daily, despite the fact that its half-life in the overwhelming majority of people is 4 to 5 hours. Side effects can be minimized by starting with a split-dose schedule rather than once a day for the first few months. Poor metabolizers of the drug (owing to a polymorphism in the CYP 2D-6 system) have a half-life approaching 19 hours. However, blind titration data indicate that dosing is similar for extensive and poor metabolizers, and screening for metabolic status is not required. ATX is approved in both children and adults; with effect sizes that are somewhat lower than for the psychostimulants. Therapeutic effects have been described as lasting the full day, but there are clearly individual differences in response. ATX does not directly affect dopamine reward networks, presumably accounting for its low abuse potential. Also, self-reports of drug “likability” in substance abusers indicate that the medication does not produce euphoria.

ATX may be particularly effective in treating ADHD and several comorbid disorders. Results from one study27 found ATX to be highly effective in treating ADHD when there is a comorbid anxiety disorder; it also significantly improved the anxiety symptoms, although with a smaller effect. Other studies28 indicate that ATX is effective in treating ADHD symptoms in patients with chronic tic disorders and is additionally useful in treating tic symptoms in the subset with Tourette’s syndrome. Because it does not have abuse liability, ATX may be a good option in ADHD with SUD.

The most commonly occurring adverse effects of ATX are sedation, nausea and vomiting, decreased appetite, weight loss, and increase in pulse and blood pressure. Irritability and increased aggression can also be seen, particularly in people with comorbid mood or behavioral syndromes. Longitudinal data from industry-funded clinical trials suggest that the effects of ATX on growth are relatively small in comparison to national norms, particularly after accounting for the initial effects of decreased appetite.29 There were no changes in electrocardiogram (ECG) in any of the clinical trials; however, use is cautioned in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease because of potential increases in blood pressure and heart rate. There are two additional warnings in effect for ATX, for liver toxicity and suicidal ideation. In 2004, post-market surveillance identified two cases (out of approximately 2 million exposures) of acute hepatotoxicity, which resulted in the FDA warning. Both were characterized by abdominal pain, jaundice, and substantially elevated liver function tests, which resolved with medication discontinuation. A subsequent case report described two additional children with acute hepatitis after receiving ATX, but neither met the criteria for medication-induced liver toxicity in the FDA analysis. More recently, an FDA review of 2,200 children and adolescents from 12 short-term clinical trials (1,357 treated with ATX and 852 with placebo) revealed that the rate of suicidal thinking with ATX was 3.7 per 1,000 patients. Suicidal ideation alone was present
in 5 cases treated with ATX, and there was a nonlethal medication overdose in one additional case (see FDA Web site: www.fda.gov/cder/drug/advisory/atomoxetine.htm). Although this is a very small signal, a "black box" warning was issued in 2005, to advise that there is increased potential for suicidal ideation, which generally occurs in the first few months.

**Strategies for managing adverse effects of ADHD treatments**

For prophylaxis and management of the most common AEs associated with stimulants and atomoxetine, treatment should be initiated at a low dose and titrated upward to a maximally effective level. Baseline clinical evaluation should include history and/or examination for tics and other neurological conditions, as well as height, weight and vital sign measurement. Many rating scales (eg, the Conner's questionnaires) are sensitive to medication effects and can be used to monitor adequacy of dose and maintenance of medication effects. Routine liver function tests and ECG are not recommended for either stimulants or ATX, either at baseline or during treatment, unless there are suggestive symptoms. It is important to obtain a history of sudden death or structural cardiac defects in patients or their families before initiating use of either stimulants or atomoxetine. Further consultation, including ECG and echocardiogram, should be considered in high risk patients with arrhythmias, hypertension, structural cardiac defects, or a family history of untoward cardiac events. It is important to follow vital signs after dose changes and to screen for symptoms suggestive of cardiovascular AEs. Screening for suicidality is achieved by obtaining a history of mood disturbance and/or suicidal thoughts/behaviors in the patient or family before initiating treatment and monitoring for the emergence of emotional changes during treatment, including increased sadness, tearfulness, irritability, anger, or euphoria. Although the risk for suicidal behavior with ATX (and possibly other treatments) is quite low, the potential for such behavior must be discussed prior to treatment and monitored.

**NON-FDA APPROVED TREATMENTS**

**Tricyclic Antidepressants**

Until the late 1990s, the noradrenergic tricyclic antidepressants, principally imipramine and desipramine, were the most often prescribed non-stimulants for ADHD, with usage supported by controlled trials. The recommended dose of desipramine is 2.5 to 5 mg/kg/day. Cardiac side effects are of concern, and pre-medication work-up must include at least an ECG. Several sudden deaths have been reported in children taking desipramine, and although there are still arguments as to if there is cardiovascular toxicity in children, proper informed consent should be obtained.

**Other Anti-depressants**

Bupropion and venlafaxine are chemically unrelated to other known antidepressants. Bupropion has been studied in multicenter trials in both children and adults,30 separating from placebo in both cases. Effect sizes are lower than for stimulants and also ATX. Because it is both a non-stimulant and an approved anti-depressant in adults, bupropion may be particularly useful in the treatment of adolescents/adults with comorbid ADHD with depression, ADHD with substance abuse (SA), and ADHD with SA/CD. Dosing of bupropion is generally 3 to 6 mg/kg/day in youth or 300 to 400 mg/day in adults, administered in divided doses (IR and SR formulations), or once daily (XR formulation).

Venlafaxine use in ADHD is supported only by open studies or case reports. The most common side effects are nausea and sedation. An open study suggested that venlafaxine monotherapy may be useful in patients with ADD with major depression. Total daily dosing is 37.5 to 225 mg of the IR formulation in divided doses or 150 to 300 mg of the long-acting once-daily formulation.

**Alpha₂-adrenergic agonists**

The alpha₂ adrenergic agonists have been used since the mid-1980s to treat ADHD and aggression as well as ADHD with comorbid tic disorders.32 Clonidine was used fairly extensively before reports of cardiovascular toxicity and the occurrence of three sudden deaths in youth treated with the combination of clonidine with MPH; however, there were mitigating circumstances in many of these cases. Subsequent studies found that clonidine can be used safely either alone or in combination with stimulants. More recent study and clinical use has focused on guanfacine, because of its relatively more specific effects on the alpha₂a receptor, its longer half-life, and more consistent benefit on attention. An open-label study and a small placebo-controlled crossover study suggested efficacy in reducing hyperactive behaviors and improving attention control. A controlled study found guanfacine to be safe and effective for children with tic disorders and ADHD.

Clonidine dosing is generally 0.1 to 0.4 mg/day split into three or four doses, while guanfacine (which is 10 times less potent) has been used in doses of 1 to 4 mg/day split into two or three doses. Sedation is the most frequent adverse effect, more pronounced with clonidine than guanfacine. It is important to carefully evaluate and monitor cardiovascular function when using the alpha₂ agonists, especially when used in combination with stimulants. A long-acting guanfacine formulation is currently being tested in clinical trials in children and adolescents.

**Modafinil**

Modafinil is a novel cognitive enhancer and wake-promoting agent,
which is structurally and pharmacologically different from other agents used for the treatment of ADHD. Modafinil is FDA-approved for the treatment of narcolepsy, shift work sleep disorder, and adjunctive treatment of obstructive sleep apnea/hypopnea syndrome. Potential advantages include its schedule IV designation by the Drug Enforcement Administration (DEA), and its apparent minimal effect on cardiovascular parameters. Several recent clinical trials have found it to be reasonably well tolerated and effective in treating ADHD symptoms in children both at school and home. However, FDA review of premarket data in 2006 concluded that more study was required before approval could be given for ADHD because of a medication-related rash in one child, which raised the possibility of risk for Stevens-Johnson syndrome. Currently, modafinil is used off-label as an alternative treatment for adults and possibly youth with ADHD, particularly those who fail or do not tolerate other treatments or who have medical risk factors that render treatment with other agents undesirable.

PHARMACOLOGIC TREATMENT OF ODD AND CD

Stimulants and Atomoxetine

It is well established that psychostimulants are extremely effective in treating a range of disruptive behaviors, including both ODD and CD, although they are only labeled for ADHD. Several studies have examined the effects of stimulants in treating aggression in the context of ADHD, all with positive findings. In addition, stimulants were found to be effective in treating symptoms of CD in youth with ADHD with CD, even after the effects on ADHD were controlled in the analyses. The results of several studies also suggest that stimulants and atomoxetine are effective in treating ODD symptoms in the context of ADHD, although the effects of ATX in this population may be somewhat less robust.

Serotonin Reuptake Inhibitors

Clomipramine, a mixed noradrenergic and serotoninergic agonist, and fluoxetine, a selective serotonin reuptake inhibitor (SSRI), have been examined in open studies for the treatment of aggression and impulsivity in children with ADHD-disruptive behavior disorder (DBD). These medications are of interest because of findings implicating serotoninergic mechanisms in aggression and the reported utility of fluoxetine in treating adults with impulsive aggression. Currently, there are no controlled trials to support the efficacy of SSRIs for core symptoms of childhood ADHD, and there are no data to indicate that they are effective in treating ODD or CD. However, because CD is frequently comorbid with mood disorders in children, SSRI use could be entertained in children with comorbid depression and CD.

Other Agents

A variety of other pharmacotherapeutic agents have been utilized in the treatment of aggression and episodic dyscontrol in children with ADHD and comorbid behavior and mood disorders, including lithium, anti-convulsant mood stabilizers such as carbamezapine and sodium valproate, beta-adrenergic blockers such as propranolol, and neuroleptics. The best data are for risperidone and quetiapine in treating CD and/or aggression, including subjects with comorbid ADHD.

BEHAVIORAL AND MULTIMODAL TREATMENTS

This review has focused on pharmacologic management of ADHD and disruptive behavior disorders. However, there are a number of evidence-based psychosocial treatments for these disorders as well. The best studied and most effective treatment includes using parents as agents of change and teaching parents how to implement contingency-based para-

The results of several studies also suggest that stimulants and atomoxetine are effective in treating ODD symptoms in the context of ADHD, although the effects of ATX in this population may be somewhat less robust.
CONCLUSIONS

ADHD and the DBDs are disorders that together account for the majority of referrals to pediatric mental health services, show substantial risk for poor outcomes later in life, and therefore represent a significant public health problem. The past several years have seen an increase in new evidence-based pharmacotherapeutic agents, which have revolutionized clinical treatment and greatly enhanced the research literature. A byproduct of these new development programs has been the systematic collection of long-term data regarding safety and tolerability. Nevertheless, there remain people who do not fully respond to or do not tolerate current treatments. Furthermore, despite great improvements in the time-action profiles of the stimulants, treatment is hampered by on-off effects. Research over the next several years is likely to focus on the development of new non-stimulant treatments for ADHD that produce benefit throughout the day, safer long-term treatments of impulsive-aggression, and interaction of drugs with nutrition and nutrients. With an ever-expanding armamentarium of therapeutic agents, research focusing on the biological and genetic basis of treatment response promises to improve our ability to match treatments to individual patients.

REFERENCES


