Antidepressants in the Treatment of Attention-Deficit/Hyperactivity Disorder

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Antidepressants differ in their effectiveness for treating attention-deficit/hyperactivity disorder (ADHD) in adults and children. None are as effective as psychostimulants for treating the attentional and cognitive symptoms, but they can help reduce impulsive and hyperactive behavior. Tricyclic antidepressants have well-demonstrated efficacy in treating behavioral symptoms, but desipramine should be avoided, at least in youths and adolescents (and perhaps adults), because safer tricyclics are available. Bupropion was effective in its few controlled trials, but tics and (especially in youth) skin rash limit its value. Venlafaxine appears effective, but controlled studies are needed. Serotonin selective reuptake inhibitors have not been tested in controlled trials, but they cause inconsistent changes, often aggravate ADHD symptoms, and can cause frontal apathy and disinhibition. Clonidine has not been adequately examined but seems to have small or uncertain effects. Psychostimulants remain the treatment of choice because of their unique effect on attention. Multimodal treatments (medications plus psychosocial) might not be more effective than medications alone.

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CHANGING VIEWS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Attention-deficit/hyperactivity disorder (ADHD) is recognized to have some validity as a clinical entity,[1,2] yet it is a behaviorally and cognitively defined neuropsychiatric disorder with mixed underlying biologies that can respond to a wide variety of pharmacologic interventions.

ADHD typically presents in combination with other neuropsychiatric disorders. In clinical samples of youth with ADHD, comorbid conduct disorder is present in 40% to 70% of the children, at least according to the older definitions of conduct disorder described in nosologic predecessors of DSM-IV.[3] After discounting ADHD children with comorbid conduct disorder, oppositional-defiant disorder, mood disorders, posttraumatic stress disorder (PTSD) and other anxiety disorders,[4,5] language and specific learning disorders,[6] Tourette's disorder,[7] schizophrenia,[8] and other medical conditions, it appears that the subset of ADHD children with no comorbidity may be quite small. Some specialists are not convinced that any such pure cases exist, or if they do, they are unusual and not necessarily representative of the general ADHD population. This comorbidity can easily confound the clean assessment of pharmacologic effects on ADHD.

Comorbidity presents additional problems as well. It is easy for ADHD to be overdiagnosed because its symptoms are closely mimicked by other psychiatric diagnoses, especially in children and adolescents, and it is not unusual for ADHD to be misdiagnosed as other psychiatric disorders, especially in adults. ADHD "look-alike" disorders are many of the same disorders with which it can present comorbidly, e.g., bipolar disorder, a variety of anxiety disorders (including posttraumatic stress disorder), schizophrenia, and occasionally even depressive disorders. Not only can disorders be mimicked by the symptoms of ADHD, misdiagnosed as ADHD, or present comorbidly with ADHD, but also ADHD aggravates the course of a variety of neuropsychiatric and general medical conditions. In reviewing pharmacologic effects on ADHD, it is crucial to bear in mind that clinical and research samples of "ADHD" usually represent a considerable heterogeneity of diagnoses.

There are other barriers to interpreting drug effects on ADHD. Even in the absence of psychiatric comorbidity, various neuromedical conditions can cause syndromes that fulfill DSM-IV criteria for ADHD. Certain kinds of brain damage can produce such symptoms, and they need not be, in the old language, *minimal* brain dysfunction. Major brain injury, particularly but not exclusively in the frontal lobes,[9] can also produce ADHD-like symptoms as a result of disease, trauma, or unusual brain development. Early severe malnutrition is the most common cause of ADHD internationally.[10] Chemical neurotoxicity

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can produce ADHD symptoms in people who ingest leaden paint or who excessively inhale lead-containing gasoline fumes while living near highways.[11] An ADHD-like presentation is associated with fetal alcohol syndrome and possibly with prenatal cocaine exposure. Medications that treat ADHD can help most of these patients, even though numerous etiologic factors can lead to this presentation.

Genetic forms of ADHD are also numerous. An ADHD syndrome tends to run in families, especially among males.[12] ADHD has been associated with polymorphisms at the dopamine (reuptake) transporter gene[13] and at the dopamine D_4 receptor gene,[14] suggesting possible mechanisms of hereditary transmission. It is likely that many genes will be found to predispose to the development of ADHD. Some genetically based versions of ADHD are due to general medical disorders, such as hyperthyroidism or, rarely, to generalized resistance to thyroid hormone.[15] Interestingly, anti-ADHD medications can treat virtually all of these types of ADHD, too.

Not all etiologic types of ADHD are drug-responsive. For example, another genetic form of ADHD is *right hemisphere syndrome*, a nonverbal learning disorder (not recognized by DSM) in which there is a functional imbalance between left and right hemispheric functioning.[6,16] Although often viewed as a disorder, it actually reflects a *difference* in brain organization: performance IQ is markedly below verbal IQ, even if both IQs are far above or far below normal. This difference presents with major problems in idea organization, information processing, and some aspects of affective control in an individual with relatively strong verbal skills. A distinctive clinical feature of right hemisphere syndrome which can be useful in diagnosis is "social dyslexia," a difficulty in reading or feeling social cues that can result in "off" responses, social clumsiness or oddity, and an inability to understand the humor of others (though perhaps being quite witty themselves). These people often have difficulty in arithmetic and school mathematics, but they might be quite able to function in a sophisticated way in computer specialties. Remarkably, of children with right hemisphere syndrome, 93% have been shown to fulfill criteria for ADHD.[16] Yet children and adults with this relatively common form of ADHD are notoriously difficult to help with medications (unless there is drug-treatable comorbidity): Most anti-ADHD medications have little or no effect on ADHD associated with right hemisphere syndrome, though psychostimulants might be helpful for certain features of the inattention. Specifically, psychostimulants (but not antidepressants) may produce improvement in right hemisphere disordered inattention as demonstrated by response inhibition or letter cancelation tasks, whereas classical use of continuous performance tests and Wisconsin card sort tasks will not demonstrate changes in the inattention of right hemisphere disorder (K. Voeller, M.D., University of Florida, personal communication, 1996).

To find that a patient fulfills criteria for ADHD does not, by strict DSM-IV criteria, require that the diagnosis be conferred if the symptoms can be better explained by another psychiatric disorder.[3] Nonetheless, much treatment and some research are based on the assumption that fulfillment of DSM criteria is sufficient to arrive at the diagnosis, without consideration of comorbidity or other potential causes of the symptoms. Numerous estimates over the years suggest that 50% to 95% of youth who fulfill criteria for ADHD actually have a different psychiatric disorder. Given the large variety of psychiatric conditions that can mimic it, ADHD has become a "diagnosis of exclusion." This means that a variety of different disorders must be considered and ruled out before the diagnosis of ADHD is made.

There has been some speculation that ADHD in the absence of other psychiatric disorders does not exist. In this line of thinking, ADHD symptoms are viewed as resulting directly from another disorder or from the aggravating effects of comorbid disorders in a person with a "very active" temperament. If ADHD is itself a relatively benign constitutional feature that interacts with various forms of psychopathology, a patient might only come to clinical attention if the interaction of the comorbid disorder and the highly active temperament is sufficiently disruptive. A patient with "pure" (non-comorbid) ADHD might merely appear to be very active and quick. The theory that ADHD is a temperament raises interesting questions about the use of pharmacologic treatments. However, it is likely that only 5 to 7% of children and adults with ADHD have no identifiable comorbidity.[1,17]

Recent imaging studies have been somewhat inconsistent in their findings in ADHD, but, combining studies in children and adults, there is general agreement on hypofunctioning in the frontal cortex and structural changes in the corpus callosum. The frontal hypometabolism especially involves the premotor and dorsolateral frontal regions.[18–20] Decreases in size of the corpus callosum have been reported in both anterior and posterior regions.[21–23] In addition, changes in functional activity have been found in the visual cortex,[18] right temporal cortex,[20] cingulate cortex,[20] the caudate,[18] and posterior putamen,[20] among many other regions.[19,24] There have also been data showing a loss of the normal (right larger than left) asymmetry of the caudate nucleus.[25]

Both the frontal hypometabolism and the sensory cortex hypermetabolism appear to normalize during psychostimulant treatment.[18] The increased activity in the visual cortex suggests that individuals with ADHD are being overstimulated by sensory stimulation. The findings in the frontal cortex and corpus callosum are associated with a variety of brain functions, including sustained attention. These findings are consistent with a host of neuropsychological studies over the years that have generated findings consistent with frontal dysfunction,

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sensory overstimulation, and problems with hemispheric transfer and coordination of information.

In reviewing current literature about ADHD, it is essential to remember that "ADHD" represents (1) a mixture of comorbidities, without the proper use of psychiatric comorbidity as appropriate exclusion criteria, (2) a variety of etiologies, (3) polygenic contributions, and (4) considerable diversity in neuropsychological functioning. Furthermore, most studies of ADHD have been based on samples consisting of (5) boys, (6) in preadolescence and more recently adulthood (very few in adolescence or preschool years), (7) with concurrent conduct disorder or oppositional-defiant disorder, and (8) in short-term treatment. The research samples are predominantly of Caucasian race and Western ethnicity.

It currently appears that the phenomenology of ADHD itself is not very age-dependent, but the clinical picture might vary with gender. As defined in DSM-IV, ADHD appears predominantly in males, but the prevalence in females might be higher if alternative criteria were used that were more suitable for identifying females with ADHD. The usual prevalence estimates range from 3% to 10% in both adults and youth, although cross-cultural variations are still being determined. In an average American first grade classroom of 20 students, one child (on average) would be expected to have ADHD. In old-time classes of 40 children, two of these youngsters in the classroom would probably take up about one third of the teacher's disciplinary time, so the impact of ADHD enormously exceeds its prevalence.

Perhaps the most important conceptual change about ADHD over the last 25 years is the new belief that it is a significant and serious disorder. Ample data have demonstrated that youths do not routinely "outgrow" their symptoms as they enter adolescence or adulthood.[26–32] In general, the symptoms that persist into adulthood tend to be largely cognitive, reflecting some degree of developmental improvement in behavioral impulsivity and motor hyperactivity. According to the two longitudinal studies that have followed ADHD children into their adulthood, 30% to 50% of ADHD children retain significant symptoms at age 25,[27,28,32] and 8% still fulfill diagnostic criteria at age 25. ADHD is no longer viewed as a trivial and vaguely amusing problem of childhood.

ADHD has long been viewed as a risk factor for the development of a large variety of psychiatric disorders. The major longitudinal studies have concurred that 18% to 32% of ADHD children grow up to have antisocial personality disorder and that 10% to 16% develop substance use disorders.[28,29,33] However, those samples were heavily laced with patients with comorbid conduct disorder, so it is not clear whether the high rate of antisocial outcome also applies to children with ADHD in the absence of conduct disorder. Speculatively, it seems likely that ADHD children with healthy ego functions and strong family support may have a lower rate of antisocial outcome than average ADHD children in the average environment, who might be pulled toward antisocial coping mechanisms as a means of dealing with the ADHD symptoms.

DSM-IV acknowledges two main symptom sets in subtyping ADHD, based on research that has firmly separated the inattention dimension from the hyperactivity/impulsivity dimension. Although there is considerable debate about this issue, future research may yet show that the hyperactivity and impulsivity dimensions are distinct from each other. In conceptualizing individual patients, I also consider two additional dimensions—motivational deficits and organizational deficits, meaning "disorganization" in cognitively grasping and handling ideas in all realms (that is, executive dysfunction). Cognitive "disorganization" in youth can involve doing homework for the wrong day, not remembering to bring a coat home, or being unable to write a coherent series of paragraphs. Adults might not readily be able to string various pieces of reality together, use a conceptual map for planning, manage parallel tasks, or keep themselves from repeatedly running out of pills. Motivational problems in ADHD children have been historically attributed to psychological causes, such as chronic failure, discouragement and demoralization, and defensive cognitive rigidity. A more current view is to conceive of motivational deficits in anatomical and chemical terms, for example, in terms of serotonin in the frontal cortex.[9,34,35]

In a very rough and simplistic way, inattention can be conceptualized as related to mesolimbic system (norepinephrine) and dorsolateral frontal cortex (norepinephrine and dopamine) dysfunction, hyperactivity to mesolimbic dysfunction (norepinephrine), impulsivity to behavioral activating system (norepinephrine, serotonin) and frontal cortex (serotonin, norepinephrine, dopamine), motivation to frontal cortex (serotonin in the dorsolateral regions), and disorganization to the corpus callosum. However, more sophisticated models have been proposed.[5,36]

Whether using neuropsychiatric, anatomical, chemical, psychosocial, environmental, or temperament models of ADHD, it is interesting to note that ADHD presents "democratically" in the population. It appears across a wide variety of individuals, in all races and ethnicities, in all socioeconomic groups, in "geniuses" and people with mental retardation, and in those with high and low ego functioning.

PSYCHOSOCIAL TREATMENT OF ADHD

There has been a long line of attempts to treat ADHD with measures that do not entail pharmacotherapy. These methods differ widely in their apparent clinical effectiveness and in the quality and extent of documentation of their efficacy.

Various environmental manipulations can help reduce the severity of symptoms in specific settings: reducing sen-

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sory stimulation to minimize distractions, establishing quiet places to play or study, decorating with simple furniture and subdued colors, keeping toys away in the closet and work materials out of sight, allowing one or two friends to visit at a time, passing up parties, and avoiding supermarkets and malls. These modifications in the home, job site, or classroom can sometimes provide significant relief of symptoms in those settings, although the changes do not generalize to other situations. Children are often dependent on parents and teachers to make these environmental accommodations,[37] whereas adults with ADHD can learn how to change their environment to enhance their functioning.

Parent counseling for youth (and perhaps family counseling for adults) is extremely valuable in promoting such environmental changes, increasing the understanding of people close to the patient, and altering some counterproductive or nonadaptive responses of family members. Both adults and children with ADHD are typically unable to accurately or fully perceive their ADHD symptoms, so it is helpful for the prescribing clinician to establish routine contact with a family member to supplement the patient's self-reports. Family contact may also be useful to identify family members who might genetically share the ADHD disposition or might share an independent psychiatric disorder whose presence is relevant to understanding the ADHD-like symptoms.

Parents and family members can also derive support from the national lay organizations and advocacy groups, such as ChADD (Children and Adults With ADD; 305–587–3700, www.chadd.org). These groups offer support, education, and referrals as well as legal and lobbying services.

School consultation, parents' reports, and phone calls are routine in evaluating ADHD treatment in children, but adults with ADHD are often treated with little or no attempt by clinicians to contact even key figures at home. Although possibly not feasible in many work settings, the use of non-patient observers is generally advisable, even for adults. In schools and jobs, it is not unusual to find teachers or colleagues who "do not believe in" this medical condition. Unfortunately, insufficient diagnostic evaluations and indiscriminate drug treatments have sometimes contributed to this impression.

Cognitive-behavioral interventions have been employed with notable success. A variety of forms of cognitive-behavioral therapy have been employed, and several have demonstrable efficacy in well-controlled studies.[37] Whether as individuals or in groups, patients can learn strategies for slowing down impulsive responses, focusing attention, scanning and selecting detail, learning to not gloss over errors, double-checking for correctness, managing strong feelings or aggressive impulses, handling oneself through a temper tantrum, making changes to create a stabilizing environment, arranging for additional time for completion of tasks, and enhancing social skills without impulsive escapes, among many others.

Psychodynamic psychotherapy has no direct therapeutic effect on ADHD, but it often can be helpful in managing comorbid psychopathology, reducing anxiety, and improving coping responses, and thereby exert a therapeutic influence on ADHD symptoms.

A variety of attentional training programs and products are being promoted as treatments, but so far their effectiveness has not been rigorously demonstrated in most cases. These interventions would not be expected to have much impact on other ADHD symptoms, unless it is assumed that the behavioral symptoms of ADHD are a consequence of inattention.

A large number of pseudo-pharmacologic treatments (caffeine, herbs, antibiotics) and dietary approaches (avoiding salicylates, food dyes, sugar) have been offered, but their effectiveness either has never been tested or has been proven clinically insignificant or nonexistent.

Multimodal treatment of ADHD is the standard of practice, especially in youths,[38,39] often entailing pharmacotherapy, parent work, cognitive-behavioral therapy, school support, and sometimes group-based social skills training. Although the multimodal approach is the current dogma, at least for children with ADHD, two rigorously controlled studies have raised questions regarding its effectiveness.[40,41] These recent studies examined the interactions of pharmacotherapy with cognitive-behavioral treatment in one case and parent behavioral guidance in the other. These studies found that both pharmacologic and psychosocial approaches are effective, that psychostimulant treatment is more effective than the psychosocial treatment studied, that the combined psychosocial and psychostimulant treatments are more therapeutically effective than psychosocial treatment alone, and that combined treatment does not contribute more to measured outcome than psychostimulant therapy alone. In short, multimodal treatment may add little beyond what psychostimulant treatment alone will do.

Although these studies were well conducted, it remains possible that other psychosocial treatments might be more effective or that these psychosocial treatments might have appeared more effective if other outcome measures or if longer treatment durations were examined. There has also been some serious questioning of the effectiveness of cognitive training therapy for children with ADHD.[42] Needless to say, combined psychosocial and pharmacologic treatment is still appropriate,[43] especially for individuals who need psychosocial treatment for their comorbid disorders, but it is interesting that such data-based doubts are emerging about the effectiveness of standard treatment. The two studies on multimodal treatment challenge the traditional assumption that multimodal treatment is always preferable and raise the possibility that psychostimulants alone might be sufficient treatment for at least some children with

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ADHD. Similar studies are unavailable in adults. The findings that medication treatment alone is generally sufficient to treat ADHD and that commonly employed multimodal treatments yield no better outcome, even acutely, could be viewed as supporting the minimalist concepts sometimes associated with financial "management" of medical care.

The current medications for treating ADHD are next reviewed, highlighting newer concepts, to give some background for the discussion of the place of antidepressant therapy of ADHD.

PSYCHOPHARMACOLOGIC TREATMENT OF ADHD

Psychostimulants

Psychostimulants remain the first line of pharmacologic treatment of ADHD. Their established position is based on more than 170 double-blind placebo-controlled studies that demonstrate efficacy in children, a track record of 60 years of clinical use,[44] their general familiarity to physicians, their ease of use, and their relative freedom from serious adverse effects when used as prescribed in physically healthy patients. Few controlled studies of the psychostimulants in adults with ADHD are available,[45–50] but they demonstrate substantive benefits in symptoms of attention, impulsivity, and hyperactivity with an overall response rate of 70%.[50] Of the five placebo-controlled studies,[46–50] though, only three showed clear drug-placebo differences.[46,49,50]

Clinically, the most compelling reason to begin with psychostimulants is that they are uniquely effective in treating the attentional components of ADHD. All other drug treatments are primarily effective for managing the behavioral features (impulsivity and hyperactivity) and, only to a lesser degree, the cognitive symptoms, but the psychostimulants alone can consistently produce clinically significant improvement in attention in children with ADHD. No controlled studies in adults have carefully evaluated the effects of stimulants on cognitive and attentional symptoms of ADHD.

The mechanisms of psychostimulant action in ADHD remain speculative. It is easy to generate hypotheses but difficult to demonstrate that a specific neurochemical change is responsible for ameliorating a particular symptom. Stimulants act at multiple locations in the brain, on various neurotransmitter systems, and with several different sites of action at the level of individual neurons. Administration of a psychostimulant induces an enormous number of neurochemical changes throughout the brain, so simplistic theories of mechanism cannot go very far.

D-Amphetamine (Dexedrine and generics) and methylphenidate (Ritalin and generics) have a short duration of clinical action, generally 3 to 6 hours, that typically produces an on-off effect after each dosage. There are usually two or three "bumps" each day during ordinary treatment. Furthermore, as the short-acting effects are subsiding, symptom rebound (exceeding baseline levels of dysfunction) appears; in effect, the short-acting psychostimulants can aggravate exactly the symptoms that they are intended to treat. Sustained-release formulations of D-amphetamine and methylphenidate are available on the market, but they do not actually deliver a sustained effect in most youths and are often less effective than regular-release preparations.[51–53] The pharmacologic effects of these psychostimulants are by and large identical, except that D-amphetamine has a somewhat longer elimination half-life than methylphenidate, but its duration of clinical action is only slightly longer and is rarely clinically significant. There has been an unverified suggestion that D-amphetamine might be more inclined to induce occasional involuntary movements. The most salient difference between these agents is that D-amphetamine is less expensive than methylphenidate, both in generic and trade forms, so D-amphetamine can be considered preferable as the first choice agent in ADHD. If one stimulant fails, as they will in about 25% of patients, it is reasonable to try another stimulant before going on to alternative drugs.

Methamphetamine (Desoxyn®) is a longer acting psychostimulant that actually works quite well in providing a 4- to 12-hour duration of clinical action.[54,55] It often can be taken on a once-daily basis, but it is extremely expensive, and many physicians and families have a variety of reservations about the use of "speed" in patients, especially youths. It does not offer any particular advantages relative to two other long-acting stimulants, pemoline and Adderall.

Pemoline also has a longer action (4–10 hours) than the short-acting psychostimulants, which often allows fewer daily dosings and avoids administration at work or school. Additionally, pemoline provides a more evenly sustained clinical effect than the short-acting agents. Although formerly believed to require 3 to 4 weeks of treatment before beneficial effects emerge, pemoline has demonstrated substantive therapeutic effects without a delay in a recent study.[56,57] An open-label study of ADHD and conduct disorder showed that pemoline treatment reduced conduct symptoms as well as ADHD in 4 of 10 youths.[58] The hepatic toxicity of pemoline can be a significant clinical problem and requires ongoing monitoring of liver function, at least every 6 months throughout the duration of treatment. Typically, the hepatic changes involve mild elevations in the activity of the liver transaminases (up to 100 U/L), but clinically significant hepatitis appears in 3% of children, and acute hepatic failure can develop. The recent warning from the Food and Drug Administration (FDA) about pemoline-related deaths contains the recommendation that it not be considered a first-line drug for ADHD.[59] There have been 11 deaths among the 13 cases of acute hepatic failure reported to the FDA in the 20 years since pemoline was commercially released in 1975. The

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FDA estimates that this represents a 4- to 17-fold increase over the "spontaneous" death rate (medically unexplained, even after autopsy) among children and adolescents in the United States, which is usually estimated at 2–12 per million annually.

Another longer acting alternative is a product called Adderall, which consists of four different amphetamine salts, including both D- and L-amphetamine. For reasons that are unclear, this combination appears to produce a longer duration of clinical effect (4–10 hours), comparable to that of pemoline, without the risk of hepatotoxicity. However, the therapeutic and adverse effects of this salt combination have not been adequately examined.[60]

A major drawback of the psychostimulants is their unauthorized use. The risk of recreational abuse is significant. As street drugs, they pose a danger to drug abusers, the drug dealers, and to any patient known by colleagues to be carrying stimulant pills. There are also the problems of medical abuse, especially prescription for diet control. Theft and abuse by staff members have led some pharmacies to be reluctant to stock stimulant products.

Even when these agents are used as prescribed, a drawback shared by all psychostimulants is lack of adequate clinical effectiveness in a significant portion of the ADHD population. Again, about 25% of patients with ADHD do not respond to their first psychostimulant trial,[37] and 2% to 15% of patients do not show a significant clinical response despite multiple stimulant trials.[61]

Another drawback is that all stimulants are tricky to use in treating ADHD with comorbid Tourette's disorder, because of the risk of aggravating the tic symptoms. Even in children who do not have baseline tics, a study of 122 children found that 9% developed tics or dyskinesia during stimulant treatment, and that 1 child (0.8%) developed Tourette's disorder.[62] Although the degree of risk has been questioned,[63,64] it is likely that the stimulants present a clinically significant problem with tic aggravation, especially when used in chronic treatment.[65]

The psychostimulants offer many advantages and many disadvantages in treating ADHD. Their short duration of action, on-off effects, symptom rebound, risk of drug abuse, unavailability in some pharmacies, risks in treating Tourette's disorder, and sizable proportion of nonresponsive patients leave much room for better treatments of ADHD. The antidepressants offer significant improvements for all of these problems, except the last.

Heterocyclic Antidepressants

In many respects, heterocyclic antidepressants function as longer acting stimulants. Their efficacy in children has been demonstrated using double-blind placebo-controlled methods by 13 different investigative groups over the last 30 years.[66–82] There are no controlled studies in adults, but a retrospective chart review found that 20 of 37 adults, of whom 31 were taking other medications (mainly stimulants), showed clinically significant improvements with desipramine or nortriptyline.[83]

The effects of heterocyclic antidepressants on ADHD, unlike on depression, are apparent within 2 or 3 days. They can often be used at doses well below the range used for treating depression. Because of their longer duration of action, they do not produce symptom rebound between doses. Various heterocyclic agents appear to be effective. However, their effects on cognition and attention do not appear to be as strong as their behavioral effects, although this has not been convincingly demonstrated.

Current data suggest that heterocyclic antidepressants can be used to treat ADHD in children with Tourette's disorders without aggravating the tics,[82,84–87] but this too needs more study. Maprotiline would theoretically be the best of the heterocyclic agents for treating ADHD with a comorbid tic disorder, because of its relatively low dopaminergic activity compared to its noradrenergic activity.

The safety of the heterocyclic agents is generally viewed as well understood in adults, but some questions have arisen in youth. Anticholinergic effects, induction of seizure or psychosis, and cardiotoxicity, especially conduction slowing, have been amply described in adults and youths on heterocyclic antidepressants, and it is unclear whether either group is at greater risk for such effects. Unlike adults, who tend to have hypotensive reactions to heterocyclic agents, adolescents and probably children appear to be at greater risk for the development of hypertension on these medications.[88]

Medically unexplained sudden deaths have been reported in five children (8 to 15 years old) during the course of routine treatment with desipramine.[89–93] Although a causal link with desipramine has not been established, the risk appears to be predominantly or exclusively related to this one tricyclic agent. Furthermore, the risk of fatality following an overdose is a serious problem with each of the heterocyclic agents,[94] but the risk is higher with desipramine than other heterocyclic agents.[95,96] Death rates following desipramine overdose are high (1%) and comparably high in both adults and children.[97] All heterocyclic antidepressants appear to be equally effective in treating the behavioral symptoms of ADHD, so desipramine appears to be an unwise choice for youth and perhaps for adults too.

Apart from desipramine, the heterocyclic antidepressants offer many advantages over the psychostimulants, but their (probably) weaker benefits for attention deficits leave the psychostimulants as the first choice treatment.

Serotonin Selective Reuptake Inhibitors

Controlled data are not yet available regarding the serotonin selective reuptake inhibitors (SSRIs). A case series of 19 children and adolescents treated with fluoxetine in an open design reported positive findings,[98] and there is a case report on open-label sertraline in an adult.[99]

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Most clinicians I have encountered, however, do not find the SSRI-induced changes to be particularly impressive, at least in youth, even for behavioral symptoms. Further, clinical reports have noted a high rate of behavioral aggravation in children with ADHD during SSRI treatment.[100] In my experience, these treatments typically do more harm than good for ADHD patients, but paroxetine seems more likely than other SSRIs to produce a useful clinical change in ADHD patients.

Various forms of behavioral deterioration have been described during treatment with fluoxetine, even with gradual dose increases. Riddle and colleagues[100] initially described "behavioral activation" including motor restlessness, sleep symptoms, disinhibition, and a subjective feeling of excitement. SSRI-induced behavioral deterioration may be due to manic switch, akathisia, insomnia and sleep inadequacy, "wired" feelings, agitation, or disinhibition. The SSRI-induced disinhibition is phenomenologically similar to the type classically associated with frontal lobe dysfunction.[9] In light of these deleterious "activating" effects,[101–103] any beneficial effects of the SSRIs in children with ADHD may be difficult to perceive. Especially in patients with ADHD, the SSRI-induced restlessness, disinhibition, subjective excitement, agitation, or manic switch can give the appearance that the SSRI is intensifying the ADHD symptoms.[100]

Even more important than the acute behavioral effects, there appears to be an amotivational syndrome that can emerge after several months of SSRI treatment.[34,35] This apathy, which is also suggestive of frontal lobe dysfunction ("la belle indifference"), may be quite subtle and is usually apparent only with careful questioning. Even if not dramatic, it can be deeply disabling. Patients may "change" their interests, shift allegiance to a passive set of peers, lose their enthusiasm for even best-loved activities, or quietly avoid chores, homework, or work requiring effort or ambition. When SSRIs are used to treat depressed children,[104,105] the patient and family members are sometimes so relieved by the improvement in mood symptoms that they are inclined to view the drug as helpful even after the patient has stopped striving for goals, has let grades or productivity drop below even the level of depressive performance, and has started to hang out with "druggies." This syndrome is not an anhedonic loss of interest. The interests can remain intact, but patients just do not feel like doing anything effortful and are usually not troubled by their lack of initiative. Dose reductions produce only temporary improvement in the apathy, which usually returns later at the lower dose. When I surveyed all of my patients for drug-induced apathy, it was surprising to find that the SSRIs appeared to produce an amotivational syndrome in the majority of the children and adults who were treated with SSRIs for several months, regardless of diagnosis. Patients treated with tricyclic antidepressants did not show this amotivational syndrome.

SSRI-induced frontal apathy and frontal disinhibition are significant impediments in themselves, and they also raise concerns about other frontal deficits that SSRIs might speculatively produce. The current treatments that I am using for dealing with SSRI-induced apathy or disinhibition involve the addition of a noradrenergic agent to the SSRI regimen. Combining an SSRI with either a psychostimulant or an antidepressant that has significant noradrenergic properties appears to provide sufficient improvement in frontal symptoms to allow continued SSRI treatment.

Overall, based on the currently available data, the SSRI agents have received a mixed response from clinicians in treating ADHD. They do not appear to be reliably helpful in ADHD in children and adolescents. However, the effects of SSRIs are yet to be systematically assessed in adults or children with ADHD, so that current observations on both their therapeutic and adverse effects must be considered preliminary.

Venlafaxine

This phenylethylamine is similar in structure to amphetamine, although it is better known for its antidepressant activity and its relatively clean blockade of both norepinephrine and serotonin reuptake transporters. A double-blind placebo-controlled study found that venlafaxine improved attention and concentration in normal adult volunteers, even in the absence of ADHD, at doses of 12.5–50 mg daily.[106] Another study found that venlafaxine produced a calming and soothing effect in adults, reflected by an increase in ratings of introversion and a decrease in "high-spiritedness."[107]

Therapeutic effects of venlafaxine on ADHD in adults were described in open-label series in adults.[108–112] Adler and colleagues[108] reported that 4 of 16 patients (mean age = 35 years) dropped out due to sedation during the first week of treatment. Over the course of 8 weeks, the remaining 12 patients showed a mean decrease of 50% in the Utah ADD Rating Scale[46] scores, with 10 of 12 showing a 25% improvement or better. The mean daily dose was 110 mg (range, 50–225 mg). All 12 adults elected to continue venlafaxine treatment following the study. Hedges,[111] Reimherr,[110] and coworkers found that 8 of 20 adults (mean age = 35 years) dropped out because of drug intolerance, but 8 of the remaining 12 showed excellent responses at a mean daily dose of 109 mg (range, 50–150 mg). Hornig-Rohan and Amsterdam[109] described 15 ADHD adults (mean age = 38 years) who also had chronic depression or dysthymia and who were treated with venlafaxine and/or psychostimulants; 80% of the venlafaxine-treated and 25% of the stimulant-treated adults were described as showing a trend toward improvement in ADHD (and mood) symptoms ($p = .10$). Findling and colleagues[112] found that 7 of 10 adults responded to doses of 37.5–75 mg b.i.d., with only minor adverse effects.

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Venlafaxine has also been reported useful for ADHD children, including a case series[113] and two case reports in children.[114,115] The open-label series described 14 patients (age range, 8–17 years) with ADHD (without mood disorder) and showed that treatment with venlafaxine (mean = 60 mg/day) was associated with significant improvement on Conners' ratings of impulsivity and hyperactivity but not on a continuous performance test of cognition and attention.[113] Four of the youths discontinued treatment because of adverse effects, which included behavioral deterioration similar to SSRI-induced behavioral activation in three patients. Of the drug-naive youth, 75% responded well, a response rate that is comparable to figures repeatedly reported for psychostimulants. Therapeutic responses were noted in 20% of the children who had not responded to prior drug treatments.

In one of the few studies of antidepressants in conduct disorder, an open-label study of venlafaxine was conducted in youth (age range, 6–15 years) with conduct disorder. Venlafaxine appeared helpful in a sample of 13 children and 12 adolescents, and clinical improvement was reported in the patients both with and without ADHD.[116]

The currently available data are uncontrolled, but all of the open-label case series have suggested that venlafaxine may be an effective agent for treating ADHD in adults and children. Venlafaxine does not appear to share the frequent problems with behavioral activation that have been observed with the SSRIs in treating youth with ADHD. Furthermore, in my opinion, venlafaxine appears to have a much lower risk of inducing frontal apathy than the SSRIs, probably because of its adrenergic or stimulant-like properties. Speculatively, these properties might also imply that venlafaxine could be effective in treating the cognitive symptoms of ADHD, and more effective than other antidepressants. This agent needs controlled studies in both adults and children.

Bupropion

This structurally novel antidepressant has been found to be effective in most of the well-conducted placebo-controlled studies in children with ADHD, including two multicenter, double-blind, placebo-controlled studies[117–120] and a single-blind placebo-controlled trial.[121] The largest investigation was a multisite, randomized, double-blind, placebo-controlled study involving 109 children (age range, 6–12 years), with 72 children receiving bupropion 3–6 mg/kg daily and 37 taking placebo.[120] Significant clinical improvements in hyperactivity, impulsivity, and cognition (continuous performance test of attention, memory retrieval) were noted, with some changes noted within 3 days. One randomized double-blind placebo-controlled study[122] did not find bupropion to be effective.

In a direct comparison, bupropion (mean daily dose = 3.3 mg/kg) and methylphenidate (0.7 mg/kg) were found to be equally effective in a well-conducted randomized double-blind crossover study conducted in youth who were drug-naive or stimulant-responsive; none of the subjects in this sample were treatment-resistant.[123] Both this comparison study and the large placebo-controlled study concluded that the overall effects of bupropion in children appeared to be clinically significant, but not as much as psychostimulants.[120,123] In adults, open-label bupropion appeared useful in 14 of 19 adults with ADHD.[124]

Bupropion has been reported to induce or aggravate tics,[125] probably due to its relatively strong dopaminergic effects, making it a poor choice for treating ADHD with comorbid tic disorders. Bupropion has also been found to induce a rash in about 17% of youths (vs. 8% in placebo group) in the large controlled study[119,120] and in 3% of the 106 youths examined in small controlled studies.[117,118,121,122] The problem of bupropion-induced rash, including maculopapular, urticarial, and pruritic sites, is much more common than with other antidepressants. No clinical seizures were reported, but, in the large study in youth,[120] EEG findings became abnormal in 6 of the 72 patients during bupropion treatment, including 3 with new spike-and-wave discharges. Otherwise, it seemed relatively free of troublesome adverse effects.

In my experience, bupropion does not typically add more than a minor improvement in ADHD children or adults who have previously responded to psychostimulants, but it can be useful for patients who do not tolerate adverse psychostimulant effects. For ADHD patients with a comorbid mood disorder, the clinical benefit of bupropion can be substantial over time, although this may not result from its anti-ADHD properties.

It is unclear whether bupropion will be found to have beneficial effects on the cognitive symptoms of ADHD. If it does, this feature would boost its clinical value. The problem of bupropion-induced skin rash appears to be real, at least in children, but may be a lesser problem in adults. With several controlled studies demonstrating therapeutic effects, albeit not uniformly, bupropion seems to have some potential for treating adults and many youths, except for patients with comorbid tic disorders.

Monoamine Oxidase Inhibitors

Tranylcypromine and clorgyline have been demonstrated to be effective in treating ADHD in children.[126] These well-established antidepressants are rarely if ever clinically employed in youth with ADHD because of the dietary restrictions and risks. These agents might be considered in highly treatment-resistant or drug-intolerant adults, but they may still be inadvisable in those patients with prominent impulsivity, because of an increased risk of potential dietary violations. The finding that traditional MAOIs have anti-ADHD effects is theoretically interesting, but the practical implications are few.

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Moclobemide is a newer, more selective, and reversible inhibitor of MAO-A whose dietary risks are much lower than with the traditional MAOIs and whose adverse effects are reportedly quite minimal.[127] At this time, it has not received FDA approval for commercial release in the United States, but it is available in Canada and Europe. Substantial clinical effects of moclobemide were noted in an open-label trial in 12 children (age range, 6–13 years) who could not tolerate the adverse effects of psychostimulants,[128–130] and a double-blind placebo-controlled trial in youth is proceeding.

Selegiline (L-deprenyl) produced equivocally positive effects on ADHD and tic symptoms in a double-blind placebo-controlled crossover study in 24 youths with ADHD and Tourette's disorder.[131] In open trials, selegiline appeared to produce clinically significant improvements in ADHD symptoms in 26 of 29 children and adolescents with comorbid ADHD and Tourette's disorder, but 2 patients experienced an aggravation of their tic symptoms.[132] One study, reported only in abstract form, describes selegiline effects in adults.[133]

I am unaware of any attempts to use other MAOIs to treat ADHD in adults, but it remains unclear whether any MAOI would have more to offer in treating ADHD than the heterocyclic antidepressants, venlafaxine, or bupropion.

Carbamazepine

Although recognized for its anticonvulsant and mood-stabilizing properties, carbamazepine has a tricyclic structure, so it is unsurprising that it is effective in treating ADHD. Although carbamazepine has not been rigorously evaluated for this purpose, it has enjoyed widespread use for treating ADHD in England and elsewhere. A recent review of available studies noted three double-blind placebo-controlled studies and seven open-label studies conducted in children, which were adequately described for meta-analysis.[134] The three controlled studies were conducted during the early 1970s in Mexico, Spain, and Austria.[135–137] Overall, significant therapeutic effects were reported in 70% of the youths in both the controlled and the open studies. There are no recent controlled studies of carbamazepine for ADHD in adults or children.

A possible advantage of carbamazepine relative to heterocyclic antidepressants has not been demonstrated, and its hematological toxicity, although rare, seems to make it less desirable than the tricyclic alternatives. No studies have systematically examined the effects of valproic acid or phenytoin in treating ADHD.

Clonidine and Guanfacine

Clonidine, an α_2-adrenergic agonist marketed as an antihypertensive, has become widely used for treating ADHD in children, despite a paucity of well-controlled studies of its effects. Beneficial effects were reported in small double-blind placebo-controlled studies.[138–140] However, in a randomized double-blind placebo-controlled crossover study of 37 children (age range, 7–13 years) with both ADHD and Tourette's disorder, clonidine (0.05 mg four times daily) was not different from placebo in treating the symptoms of ADHD or tics.[83] Also, in a double-blind placebo-controlled crossover study of 8 children (age range, 5–13 years) with autistic disorder and symptoms of impulsivity and hyperactivity, clonidine produced only a minor and transient improvement in the ADHD-like symptoms, and its usefulness was limited by sedation and hypotension.[141] Several open-label studies have reported some usefulness of clonidine in treating ADHD-like symptoms in a variety of situations, including conduct disorder, aggressive behavior, and HIV-1 encephalopathy.[142–145]

Overall, only one sizable well-controlled study supports the use of clonidine in treating ADHD, with or without tics. The effects of clonidine on the behavioral features of ADHD are said to be stronger than its relatively weak effects on cognition.[146]

To see whether clonidine is more effective in treating ADHD when it presents with comorbid tic disorders, a chart review was conducted and found that clonidine helped 95% of children with comorbid ADHD and tic disorders but only 53% of children with ADHD without tic disorders.[147] Although clonidine seemed primarily useful for ADHD with comorbid tic disorders (or ADHD presenting as part of a tic disorder), the best-controlled study of children with both ADHD and tic disorders found that clonidine was no different from placebo in treating impulsivity/hyperactivity, inattention, and tics.[82] These discrepancies might be explained by the findings of another retrospective review, involving 53 youths with comorbid ADHD and Tourette's disorder, which suggested that improvement in ADHD symptoms was associated with a longer length of time between the onset of vocal tics and the treatment with clonidine.[148]

Adverse effects include sedation and also a symptom rebound that appears during the offset phase of drug action (clinical duration, 3–6 hours). The symptom rebound can make it look as though the drug aggravates the ADHD behavior at doses that are excessively sedating. Potentially more serious, however, are the hypotension and bradycardia that can emerge during the first 6 hours after a dose is administered, which is then followed by a rebound hypertension and tachycardia during drug offset. Both the hypotensive and hypertensive phases can be problematic. Clonidine has been reported to cause syncope during routine treatment in adults and children, and abrupt discontinuation can be dangerous because of the rebound hypertension. Furthermore, ECG abnormalities appeared in 3 of 60 children during clonidine treatment.[149]

The transdermal administration of clonidine, by a patch, can avoid the on-off effects and the symptom rebound associated with multiple daily oral administration.[140] However,

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the skin patch is often not effective, either because of skin irritation (in about 50% of users), because sweating prevents good adhesion, or because it falls or is taken off.[140]

Combined treatment with clonidine and methylphenidate has been widely used to target both the behavioral and the attentional components of ADHD, since it was first described in 1989 by Hunt.[150] The FDA has received reports of three cases of sudden death during treatment with this drug combination. These cases were determined by the FDA to be not attributable to the drug combination because of confounding medical factors in each case.[151,152] Nonetheless, a "leak" from the FDA resulted in considerable concern among parents and physicians. New cases may yet come to light that raise more substantive concerns about the clonidine-methylphenidate combination,[153] but the current data do not point to any significant problem specific to this drug combination beyond those cardiovascular problems known to be associated with clonidine alone.

Clonidine has been commonly used to treat stimulant-induced insomnia and insomnia associated with ADHD,[154] but a potential hazard could arise when administered at nighttime in combination with daytime psychostimulants. In the morning, as the prior night's dose of clonidine is wearing off (potentially causing some mild hypertension and tachycardia) and the morning dose of psychostimulant might itself induce some mild hypertension and tachycardia, these mild effects might be additive and conceivably cause some cardiovascular symptoms in some individuals. Similarly, if clonidine were administered during the offset phase of stimulant action, the hypotensive and bradycardic effects of both drugs might be additive. Whether such additive effects produce any clinically significant problem is speculative.

Clonidine treatment of ADHD, although widely used, has had its efficacy brought into question by the best controlled study to date. Clinicians should be aware of the weak scientific basis for using this drug to treat ADHD.

Guanfacine is also an α_2-agonist, but it is longer-acting, more receptor-specific, and less sedating than clonidine.[155] Due to its receptor specificity, guanfacine has fewer adverse effects than clonidine and causes less trouble with sedation, changes in blood pressure, and altered heart rate. Several open-label series have suggested some effectiveness in treating youths with ADHD,[155,156] including those with comorbid Tourette's disorder.[157] If the fewer adverse effects of guanfacine allow higher drug concentrations to be attained, it is imaginable that the therapeutic effects of guanfacine might be more apparent than with clonidine. There are no systematic examinations of guanfacine for treating adults with ADHD, and no controlled trials in youth.

Other Medication Options

β-Adrenergic blocking agents. There are no controlled studies of β-blockers in adults with ADHD. Open trials of propranolol have been reported to be useful in treating ADHD in 13 adults, but only after 9 weeks at enormous doses (mean daily dose = 528 mg).[158] A report described three adults with ADHD who were successfully treated with open-label propranolol when the drug was used in combination with methylphenidate.[159] In youth, a double-blind placebo-controlled study comparing pindolol and methylphenidate in 32 ADHD children (age range, 7–13 years) found certain behavioral effects of pindolol 20 mg twice daily that were comparable to methylphenidate 10 mg twice daily, but generally only modest effects were observed with pindolol.[160] However, pindolol caused adverse effects (paresthesias, nightmares, hallucinations) sufficiently troublesome to cause early discontinuation of the study. In my experience, with individuals for whom propranolol appears to be helpful, the use of nadolol is just as effective, requires only once-daily administration, and causes minimal adverse effects.

Neuroleptic agents are still used as a treatment of last resort for children with ADHD. In retrospect, it seems likely that those children had a psychotic disorder that mimicked ADHD, such as bipolar disorder or schizophrenia. A review of the early studies of neuroleptics concluded that fewer than half of ADHD youths (aged 4–14 years) showed behavioral gains, that no cognitive improvement was evident, and that stimulants were clinically preferable on the basis of effectiveness, independent of the neurotoxicity of the conventional neuroleptics.[161] Conventional neuroleptics are routinely used to treat Tourette's disorder and may thereby treat comorbid ADHD.[162] Among the newer atypical neuroleptics, clozapine is too hematotoxic to be suitable for ongoing treatment of ADHD in itself, but the safer agents such as risperidone or olanzapine might be useful in treating some patients with ADHD, especially those with comorbid Tourette's disorder.

Fenfluramine was compared to methylphenidate in 28 children with ADHD and mental retardation in a double-blind placebo-controlled crossover study.[163,164] Both drugs improved hyperactivity, behavioral symptoms, and mood. Methylphenidate improved performance on a continuous performance test, whereas fenfluramine improved performance on a memory task. Methylphenidate reduced and fenfluramine slowed reaction times. Fenfluramine was found to induce more weight loss than methylphenidate in these 4-week trials. The authors inferred that both drugs were effective but had different mechanisms and target symptoms. However, another report found little benefit of fenfluramine in ADHD children.[165] No reports on fenfluramine in ADHD adults are available.

Combined or concurrent drug therapies are often used to manage treatment-resistant cases of ADHD, although no combination has been adequately examined in controlled trials. The primary risks in combining most anti-ADHD agents are cardiovascular changes (blood pressure and heart rate), but gradual dose titration and careful monitor-

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ing have allowed all anti-ADHD agents to be used in combination, including stimulants with tricyclic antidepressants,[79–81] SSRIs,[55,166,167] clonidine,[150] and others.

Lithium is not a treatment for ADHD, and it has been shown to produce negative behavioral effects in the two studies that have examined this question.[168,169] However, when ADHD and bipolar disorder present concurrently, lithium can be useful for treating the bipolar component without problematic effects on the ADHD symptoms. In these cases, if prominent symptoms of ADHD remain after the bipolar symptoms are well controlled, it is usually safe to add an anti-ADHD drug, including carefully titrated doses of psychostimulants or antidepressants.

A variety of other agents have been shown to be ineffective, including benzodiazepines, hydroxyzine, phenylalanine, tyrosine, L-dopa, and amantadine. Although folklore supported the use of caffeine as a "stimulant" to treat ADHD, caffeine has been repeatedly demonstrated to be ineffective.

CLINICAL IMPLICATIONS

Psychostimulants remain the treatment of choice for adults and children with ADHD, if only because of their distinctive impact on the cognitive symptoms. Tricyclic antidepressants have also been demonstrated in numerous well-controlled studies to have efficacy in treating the hyperactivity and impulsivity of ADHD in children, and there is a single good study demonstrating efficacy in adults, but these agents seem less useful for treating inattention and other cognitive symptoms. Desipramine should be avoided, at least in children and adolescents (and perhaps in adults), because of the ample choice of safer alternative tricyclic agents. Bupropion has been found effective in most of its controlled trials and may have effects that are comparable in magnitude to the psychostimulants; but problems with skin rash and tics can limit its usefulness. SSRIs seem to be helpful at times but are less reliable, because of their tendency to aggravate ADHD behaviors and to cause frontal symptoms; controlled trials are needed. Venlafaxine appears to be more useful in treating ADHD, because of its seemingly better side effect profile, but again controlled trials are needed. Other medications have not been adequately examined in controlled studies despite their widespread use, but they appear to have generally small, uncertain, or deleterious effects.

Heterocyclic antidepressants, bupropion, venlafaxine, or SSRIs may be preferable to psychostimulants for treating patients who have a personal history of substance abuse or who are living with someone at risk for substance abuse. Heterocyclic antidepressants, venlafaxine, and SSRIs, but not bupropion, may be less likely than stimulants to aggravate tics in patients with comorbid ADHD and Tourette's disorder. For patients with ADHD and seizure disorders, psychostimulants, venlafaxine, or SSRIs would be better options than heterocyclic antidepressants or bupropion. Finally, heterocyclic antidepressants, bupropion, venlafaxine, and SSRIs are preferable to psychostimulants for treating adults with comorbid ADHD and a depressive disorder.

Pending the demonstration of drug efficacy in treating depression in children or adolescents,[170] judgment must be reserved concerning the value of any antidepressant in treating youths with ADHD and a comorbid depressive disorder. An unpublished report of a large controlled trial suggests possible efficacy of fluoxetine,[171] but the only other controlled fluoxetine trial in youth found no antidepressant effects.[172] It is my clinical impression, however, that venlafaxine is better tolerated and more effective in depressed youth than the heterocyclic antidepressants or bupropion, and that venlafaxine is better tolerated and possibly more effective than the SSRIs in treating youth with depression. I have used venlafaxine as my first choice of antidepressant for treating depressed children and adolescents, starting long before the manufacturers of venlafaxine contributed to the financial support of this symposium.

DRUGS FOR THE FUTURE

Although a variety of different physiologic and neurochemical mechanisms operate in different individuals with ADHD, it is likely that most ADHD patients would be well treated by agents with pro-norepinephrine, pro-dopamine, and pro-serotonin properties. Patients with comorbid Tourette's disorder would be expected to do best with pro-norepinephrine/pro-serotonin agents. Medications with relatively selective neuropharmacologic effects on these neurotransmitter systems are likely to have fewer unwanted clinical effects.

It is obviously desirable to develop anti-ADHD medications whose therapeutic effects, unlike those of the psychostimulants, endure for more than 6 hours after drug administration. The availability of longer acting medications could alleviate problems of midday dosing, which are often particularly difficult to manage for ADHD patients with attentional or organizational deficits. Long-acting drugs could reduce the intensity of daily on-off effects and symptom rebound. For sustained effectiveness, pemoline and perhaps Adderall seem to be the best current options among the psychostimulants. It would be sensible to continue the trend toward the development of longer and "smoother" medications for ADHD patients.

A particularly important focus for the development of new anti-ADHD drugs is to improve their effectiveness in treating attention deficits. Except for the psychostimulants, none of the anti-ADHD agents have strong effects on attention, although this is an obviously critical feature of ADHD. At present, there is no nonabusable medication with substantial and reliable effects on atten-

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tion and cognition, although additional investigation of the newer antidepressants might change this situation considerably. Pharmacologic and pharmaceutical research could make important gains by paying more attention to the attentional symptoms of ADHD.

In addition to targeting the ADHD symptoms recognized by DSM-IV, agents that target motivational deficits and organizational deficits would be valuable to develop. These symptoms, though commonly seen in ADHD patients, are rarely evaluated in pharmacologic studies. It certainly seems plausible that motivational symptoms might be drug-treatable. It is less clear whether organizational deficits could be helped by medications, but they ought to be examined. Both motivational and organizational symptoms might be more easily examined in ADHD patients who do not have major comorbidity. Psychopharmacologic studies are generally much easier to conduct in adults than in adolescents or children. If adults with ADHD have less psychiatric comorbidity than ADHD children, it might speculatively be easier to initially assess drug effects on motivational and organizational deficits in an adult population. However, current and future medications should be tested separately in adults, adolescents, and children with ADHD.

Although studies of ADHD patients who do not have neuropsychiatric comorbidity might appear helpful for isolating drug effects on attention, impulsivity, and hyperactivity, the generalizability of findings in "pure" ADHD patients needs to be determined. An alternative strategy might be to study drug effects in ADHD patients with biopsychiatric comorbidity but who nonetheless have a high level of ego functioning. This approach might allow identification of drug effects without the confounding effects of the developmental complications of ADHD. No matter how well designed the study, though, the generalizability of findings in research populations will always be in question, especially when clinicians apply anti-ADHD treatments in a variety of different patient populations, in association with other neuropsychiatric abnormalities, in combination with general medical disorders, and in conjunction with anti-ADHD and other medications.

During the course of the life history of a medication, progressively more and diverse uses are uncovered. Antidepressants serve as a clear example of this principle and can be expected to go still further. Little pharmacologic research has yet been directed at conduct disorder and oppositional defiant disorder, two disruptive behavior disorders that often appear along with ADHD in the child and adolescent population. Some early research on these disorders has been encouraging. In a similar vein, posttraumatic stress disorder is a common problem for which there are insufficient pharmacologic treatments or investigations. The extension of antidepressant studies into these areas can be anticipated.

The expansion of pharmacologic research is difficult to predict, but a new area of clinical interest is likely to develop in the future. Recent studies have suggested that psychostimulant effects on ADHD might be different, in a variety of ways, in patients with clinically significant anxiety.[173–176] Speculatively, a different baseline state in some neurotransmitter systems (such as norepinephrine) might alter the effectiveness of or change the mechanism by which antidepressants or psychostimulants act to provide symptomatic improvement. Livingston and colleagues[173] examined the psychostimulant treatments of 182 children with ADHD and comorbid disorders and produced a surprising finding: although ADHD children with oppositional or conduct disorder and ADHD children with a mood or anxiety disorder responded to stimulant treatment at ordinary doses, those ADHD children who had both an externalizing disorder (either conduct or oppositional defiant disorder) and an internalizing disorder (either a mood or anxiety disorder) required higher stimulant doses in order to achieve an adequate clinical response. This finding suggests the possibility that psychostimulant dosages might vary with comorbidity. Conceivably, stimulant doses might also vary with nonpathologic characteristics, such as anxiety (in the absence of anxiety disorder) or other psychological states that are subject to environmental and physiologic influences. Such possible developments might greatly complicate and greatly improve the effectiveness of treatment for children and adults with ADHD.

Drug names: amantadine (Symmetrel), bupropion (Wellbutrin), carbamazepine (Tegretol and others), clonidine (Catapres), clozapine (Clozaril), desipramine (Norpramin and others), dextroamphetamine (Dexedrine, Adderall), fenfluramine (Pondimin), fluoxetine (Prozac), guanfacine (Tenex and others), hydroxyzine (Atarax and others), levodopa (Larodopa), maprotiline (Ludiomil), methamphetamine (Desoxyn), methylphenidate (Ritalin), nadolol (Corgard), nortriptyline (Pamelor and others), paroxetine (Paxil), pemoline (Cylert), phenytoin (Dilantin and others), pindolol (Visken), propranolol (Inderal and others), risperidone (Risperdal), selegiline (Eldepryl), sertraline (Zoloft), tranylcypromine (Parnate), valproic acid (Depakene and others), venlafaxine (Effexor).

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Disclosure of Off-Label Usage

The following agents mentioned in this article are *not* indicated for attention-deficit/hyperactivity disorder: bupropion, carbamazepine, clonidine, clorgiline, desipramine, fluoxetine, heterocyclics, moclobemide, MAOIs, maprotiline, nortriptyline, paroxetine, guanfacine, selegiline, sertraline, tranylcypromine.
The following agent mentioned in this article is *not* indicated for ADHD conduct disorder: venlafaxine.

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Discussion

Dr. Weinreb: Do children who take psychostimulants generally develop tolerance to the medication?

Dr. Popper: A physician may occasionally find a child who appears to respond to psychostimulants for several months or years but who then shows a sudden change in drug responsiveness, long after hepatic tolerance mechanisms would be expected to surface. Usually, I find psychosocial or comorbidity factors that explain the loss of effectiveness. Rarely, patients appear to develop genuine tolerance, with dose adjustments failing to correct the problem. Typically, I periodically switch these patients between methylphenidate and amphetamine. If the patient seems to be persistently intolerant, I switch back and forth on a weekly basis.

Tolerance appears to be a rare but more common problem in patients who take tricyclic antidepressants than with other anti-ADHD agents.

Dr. Hirschfeld: Have studies compared classes of drugs, particularly stimulants compared with the tricyclics or venlafaxine?

Dr. Popper: No study has compared stimulants with venlafaxine, and amazingly few studies have compared stimulants and tricyclics. By and large, these studies support the notion that tricyclics help behavioral symptoms but not attentional symptoms, whereas stimulants help both. We don't know yet about venlafaxine. However, since none of the available comparative studies have entailed adequate dose-response curves, even those claims are without scientific foundation.

Dr. Hirschfeld: Has clonidine been studied?

Dr. Popper: I don't know of any study that has compared clonidine with antidepressants. In a comparison of stimulants with clonidine, Hunt believes that the attentional properties of clonidine are weaker than those of stimulants. Some skeptics wonder whether the behavioral effects of clonidine might be explained purely by sedation. I find clonidine to be an extremely effective drug for some patients. The main risk in the population we treat, of course, is that clonidine causes depression. Guanfacine, which has many of the properties of clonidine, may not cause depressive episodes or not as frequently.

Dr. Keck: Is there a relationship between prematurity, low birth weight, or prenatal maternal drug and alcohol exposure in attention-deficit/hyperactivity disorder (ADHD)?

Dr. Popper: Yes. The prenatal maternal use of alcohol or cocaine, lead exposure, and maybe abuse of other drugs seem to be risk factors. Fetal alcohol syndrome is typically associated with behavioral symptoms that are indistinguishable from ADHD, and it seems that we can fully treat the behavioral symptoms of fetal alcohol syndrome with stimulants or antidepressants. Clinically, fetal alcohol syndrome and ADHD appear to be the same.

The relationship to low birth weight, prematurity, or other perinatal parameters is complicated. We used to think that prenatal or perinatal problems could cause ADHD, for example, anoxia at birth. Nelson and Ellenberg [N Engl J Med 1986;315:81–86; Pediatrics 1991;87(suppl):761–766] collected data 10 or 15 years ago that changed that model. The current model for ADHD suggests that early prenatal problems function as risk factors for the subsequent development of both perinatal problems and ADHD. Only the most extreme cases of birth anoxia, where children maintain Apgar scores of one and two, cause ADHD. Certainly, ADHD does not occur in the vast majority of low birth-weight infants. Thus, there is a correlation between ADHD, birth weight, prematurity, and anoxia, but the causal model that connects ADHD and the other factors is more complicated than we used to believe.

Dr. Yonkers: Is there any phenomenological or biological difference between the group that has persistent ADHD into adulthood and the children who remit in adulthood?

Dr. Popper: Good question. I do not think the question has been asked in a research study.

Dr. Yonkers: If, as you suggest, ADHD is a forme fruste of multiple psychiatric disorders because of the comorbidity, it may be that the hard wiring is different in the persistent group.

Dr. Popper: That's an interesting hypothesis.

Dr. Leonard: We're somewhat disadvantaged as child psychiatrists. Children are the last to be enrolled in controlled treatment trials for almost every disorder. Clearly, though, we have finally seen controlled trials of stimulants and tricyclics for ADHD.

The issue has now become, "What is the role of serotonin reuptake inhibitors (SRIs) in the treatment of ADHD?" We won't know until controlled trials are reported, but because of anecdotal reports, I feel positive about the role of SRIs for children who have ADHD. Those who study ADHD debate about whether ADHD is a primary deficit in attention or in inhibition of impulses. As you discussed, the SRIs may have a role in the behavioral manifestations of ADHD. I see the disorder as a poor modulation of affect and impulse, and that's how I ask parents about ADHD. The frontal apathy that you discussed, Dr. Popper, in my experience, has been rare. In some ways, each physician's knowledge of this disorder is derived from personal clinical experience. We need a controlled study of the different SRIs to examine their

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relative potencies and balance of effects between the serotonergic and noradrenergic systems.

One other point I want to bring up is that bright girls who have attention deficit disorder without hyperactivity remain undiagnosed for years. We're talking mostly about the disorganization component of ADHD, which Martha Denckla, M.D., calls "executive dysfunction." While ADHD is reported in the media to be overdiagnosed, I think it is underdiagnosed. ADHD is a complex, heterogeneous disorder in terms of etiology and treatments, and that is why subsets of children respond to one type of treatment, and another subset responds to a different treatment.

Dr. Popper: It's fascinating that such a heterogenous clinical entity makes sense clinically. All of these diverse presentations are pictured as a gestalt by both professionals and the public. ADHD certainly is underdiagnosed and overdiagnosed. You probably know of data regarding teachers who describe over 50% of children in their classroom as hyperactive.

Dr. Leonard: ADHD is also underdiagnosed.

Dr. Popper: I agree, so diagnosis of ADHD is tricky. ADHD is both underdiagnosed and overdiagnosed, depending on the population, especially age of the population. As far as the issue of SRIs and the frequency of frontal apathy, I also believed frontal apathy was a rare phenomenon until I informally but systematically began asking all of my patients about their symptoms. I was completely surprised that frontal apathy wasn't as rare as it had originally seemed. Depressed children and adults may have frontal symptoms that we typically don't recognize and have to learn how to inquire about. I have been unable to find this kind of apathy in children who are treated with tricyclics. I think that frontal apathy, whether it is common or uncommon, is a genuine clinical phenomenon that requires attention and treatment we don't normally provide. For now, though, we must consider all findings on SRIs in ADHD as preliminary.

Dr. Hirschfeld: One more comment. Dr. Popper, you said the oases of action of the tricyclics is 1 to 3 days, which would clearly suggest a different mechanism of action from the antidepressant effects.

Dr. Popper: Yes, the onset of action and the response to lower doses do seem to imply a different process.

Dr. Keller: As a closing comment I would suggest that we build on Dr. Leonard's point, and Dr. Popper's last comment, in terms of the clinical observation of the amotivational syndrome. We should take advantage of those clinical discoveries and test them in a randomized trial, because observer bias is compelling in most areas of medicine or discovery. I think we should take these comments as clinical suggestions and subject them to tests, so we don't miss something or take too strongly to a negative position, which might foreclose the opportunity of demonstrating the efficacy of new treatments.

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