

Pharmacotherapy of Attention-Deficit/Hyperactivity Disorder in Adults

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A history of childhood attention-deficit/hyperactivity disorder (ADHD) is a mandatory prerequisite for the diagnosis of adult type ADHD, for which no DSM criteria exists. Since the diagnosis must be made retroactively, tentative criteria have been designed to establish the presence of the childhood disorder. In the 1970s, I advanced the hypothesis that "minimal brain dysfunction" (as ADHD was called) might be produced by decreased catecholaminergic function. A total of over 300 ADHD patients have been included in treatment studies, including 224 patients who received stimulants in four double-blind, placebo-controlled trials: three of methylphenidate (N = 176) and one of pemoline (N = 48). An additional 79 patients have been included in open-label trials of pargyline, selegiline, bupropion, levodopa, phenylalanine, and tyrosine. Altogether, these studies have demonstrated the efficacy of methylphenidate, pemoline, and monoamine oxidase-B (MAO-B) inhibitors when administered to adult ADHD patients; a robust response was produced in 60% of the patients. Bupropion and selegiline were effective in the open-label studies and should be systematically evaluated. A long-term study is being conducted with methylphenidate maintenance; patients have been followed for as long as 5 years, and little, if any, drug tolerance has been observed. Treatment of adult patients who have ADHD is symptomatic, not curative, but the combination of medication and psychotherapy may offer life-changing opportunities to individuals who suffer from the disorder.

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Until the 1980s, attention-deficit/hyperactivity disorder (ADHD) was believed to be a childhood psychiatric syndrome in which the symptoms diminished with age. ADHD is now thought to persist into later life and may be a common psychiatric disorder in adults.¹ If symptoms of childhood ADHD persist into adulthood, drug treatment of the syndrome should be considered. Since 1976, treatment studies have been performed with patients who were thought to have adult ADHD. A summary of those studies is hereby offered.

ESTABLISHING THE DIAGNOSIS

A history of childhood ADHD, as described in the DSM-IV, is a mandatory prerequisite for the diagnosis of adult type ADHD, for which no DSM criteria exist. That being

the case, the physician must first ascertain if symptoms of ADHD were present in childhood. To that end, my colleagues and I have designed tentative criteria to establish the presence of the childhood disorder. Because adult patients had either forgotten or were hesitant to disclose disturbing childhood behavior, an attempt was made to interview the patient's mother or another adult familiar with the patient's upbringing.

The Conners 10-Item Rating Scale for "hyperactivity"² was used as a Parents' Rating Scale, which was a judgment of childhood "hyperactivity" made by the patient's mother. The scale was standardized on normal and ADHD adults so that the score could be translated into the percentile of an adult's "hyperactivity" in childhood.³

Another rating scale, the Wender Utah Rating Scale, was devised to aid the retroactive diagnosis of childhood ADHD when the parents or another knowledgeable adult were not available.⁴ Adult patients used the 61-item scale to rate their own memories of the characteristic descriptors of childhood ADHD. The test was standardized on normal adults, adults with unipolar depressive disorders, and ADHD adults.

Ultimately, the diagnosis of ADHD must be made on the basis of certain specific behaviors, not just on generalized traits. Thus, the Utah Criteria were devised to include childhood history and adult diagnostic criteria.¹ The Utah

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Table 1. The Utah Criteria*

I. Childhood Characteristics
A. Narrow Criteria (DSM-IV) - The individual must meet the DSM-IV criteria for ADHD in childhood.
B. Broad Criteria - Both characteristics #1 and #2, and at least one characteristic from items #3 through #6.
1. Hyperactivity
2. Attention deficits
3. Behavior problems in school
4. Impulsivity
5. Overexcitability
6. Temper outbursts
C. Parents' Rating Scale (Conners Abbreviated Rating Scale) - A score of ≥ 12 places the patient in the 95th percentile of childhood "hyperactivity."
II. Adult Characteristics
A. Motor hyperactivity
B. Attention deficits
C. Affective lability
D. Hot temper
E. Emotional overreactivity
F. Disorganization and inability to complete tasks
G. Impulsivity
H. Associated features

*Adapted from reference 5.

Criteria make childhood hyperactivity that continues into adulthood a mandatory diagnostic symptom. The criteria eliminate those subgroups of ADHD children and adults who are characterized by inattentiveness *without* hyperactivity or impulsivity; the criteria also exclude patients with major mood disorders, schizophrenia, antisocial personality disorder, and schizotypal or borderline personality disorders (Table 1).⁵

OVERVIEW OF TREATMENT STUDIES

In the 1970s, the hypothesis was advanced that "minimal brain dysfunction" (as ADHD was called) might be produced by decreased catecholaminergic function.^{6,7} In many of the children who survived von Economo's encephalitis in the pandemic of the early 1920s, behavioral symptoms developed similar to those of mixed ADHD and conduct disorder; recovering adults manifested symptoms of Parkinson's disease. The characteristic findings of Parkinson's disease were later ascribed to decreased dopaminergic function because CSF levels of homovanillic acid (HVA), the principal metabolite of dopamine, were decreased in these patients. Both methylphenidate and the amphetamines, which are indirect dopamine agonists, are effective in the reduction of ADHD symptoms. When my colleagues and I recognized the syndrome in adults in 1976, we initiated treatment trials of stimulant drugs and subsequent metabolic studies.

To test the dopamine hypothesis, HVA levels in the CSF were measured prior to a trial of methylphenidate in adults who had ADHD, and in non-ADHD controls.⁸ A decreased level of HVA was found in responders to methyl-

phenidate, compared with controls, and an increased level of HVA was found in nonresponders. These findings replicated two previous studies in children.^{9,10} The next approach was to administer pharmacologic doses of the dopamine precursor amines, phenylalanine,¹¹ tyrosine,¹² and levodopa.¹³ The primary finding of these studies was a moderate-to-marked improvement of ADHD symptoms in patients who took tyrosine. This makes sense since increasing levels of tyrosine should have been ineffective. This result is probably best explained by an increase in tyramine that could be directly pharmacologically active. Phenylalanine and levodopa had no such effect.

On the basis of the dopamine hypothesis, my colleagues and I administered drugs that had specific dopaminergic actions. Dopamine is metabolized by monoamine oxidase B (MAO-B) in the brain; serotonin and norepinephrine are metabolized by MAO-A. Two MAO-B inhibitors, pargyline (no longer marketed) and selegiline, were administered in low doses to adults who had ADHD. Both drugs produced moderate-to-marked improvement in about 60% of the patients, presumably by increasing the availability of dopamine without increasing levels of serotonin and norepinephrine.^{14,15}

A total of over 300 ADHD patients have been included in these treatment studies, including 224 patients who received stimulants in four double-blind, placebo-controlled trials: three of methylphenidate (N = 176; references 16, 17, and Wender PW 1997. Unpublished data), and one of pemoline (N = 48).³ An additional 79 patients have been included in open-label trials of the following drugs: pargyline (N = 16),¹⁴ selegiline (N = 11),¹⁵ bupropion (N = 19),¹⁸ levodopa (N = 8),¹³ phenylalanine (N = 13),¹¹ and tyrosine (N = 12).¹²

The degree of patient response to different drugs was measured by the Global Assessment of Functioning (GAF). The average pretreatment GAF score in the ADHD patients we studied was 55, which represented moderate symptoms. In both crossover and parallel design studies, about 60% of the patients who received the stimulants methylphenidate and pemoline showed a moderate-to-marked improvement compared with 10% of the patients who received placebo. The average posttreatment GAF score in those patients with a moderate-to-marked response was 75. Patients who were entered in the bupropion trial had previously received either stimulants or MAOIs as maintenance medications for a mean of 3.7 years prior to the study. A total of 14 patients experienced moderate-to-marked benefit from bupropion, and 10 patients chose to continue taking bupropion instead of reverting to their previous medication.

Two double-blind, crossover studies have attempted to replicate these treatment studies. Mattes et al.,¹⁹ who used different diagnostic criteria, failed to demonstrate a favorable response to methylphenidate in 61 patients. Spencer et al.²⁰ replicated a favorable response to methylphenidate

in 23 patients. Altogether, these studies have demonstrated the efficacy of methylphenidate, pemoline, and MAO-B inhibitors when administered to adult ADHD patients, and the therapeutic response is robust in at least 60% of the patients.

In general, tricyclic antidepressants (TCAs) have not been useful in the treatment of childhood or adult ADHD.¹ After an immediate response, patients become tolerant to the drug in 6 to 8 weeks, despite increased dosages. ADHD patients also seem to be less tolerant of TCA side effects and complain about anticholinergic effects, weight gain, and impaired sexual function. Serotonin selective reuptake inhibitors may benefit ADHD patients with comorbid major depressive disorder or dysthymia, but they seem to be of little value in ADHD patients without these disorders.

A long-term study is presently being conducted of 123 patients who have been treated with methylphenidate. The purpose of the study is to determine if patients who take stimulant medication for long periods of time will continue to show a beneficial therapeutic response. We are also interested in the long-term social and vocational improvement of these patients over time. Pharmacotherapy may enable ADHD patients to concentrate in a matter of minutes but it may take years for patients to rebuild personal relationships.

MEDICATION EFFECTS ON TARGET SYMPTOMS

Effects of medications on the seven target symptoms of ADHD can be measured by use of the Targeted Attention Deficit Disorder Rating Scale (TADDS).¹ The TADDS is designed for outpatients and does not include the full range of psychopathologic items that are assessed on the GAF. The following changes have been noted in patients who have participated in these treatment studies⁵:

Hyperactivity: Fidgeting and restlessness decrease. Subjects are better able to stay in one place and focus on tasks, whether work-related or recreational.

Inattention: Patients report an increased ability and more conscious control over concentration; i.e., they can concentrate when they want to. In some instances, the increased attention to spousal conversation has improved marital relations.

Mood lability: Both high and low mood swings decrease; patients describe their overall mood as being more stable.

Temper: The threshold for outbursts is raised; angry outbursts are less frequent, less extreme, and may disappear altogether.

Disorganization: Patients are less disorganized and may initiate orderly strategies to complete tasks.

Stress sensitivity: Patients are better able to tolerate stress and to cope with problems on a daily basis.

Impulsivity: Impulsivity decreases. Patients are less likely to interrupt speakers. They try to think before speaking, which

serves to improve communication skills and enrich personal relationships.

DOSAGES

Although stimulant medications are the treatment of choice for adults who have ADHD, the duration of action is extremely short. Therefore, multiple daily doses must be administered, which may be a difficult task for a disorganized ADHD patient. An important accessory that helps to organize a dosage schedule is an electronic alarm system such as a multiple-alarm watch or pill container.

The dose of methylphenidate is 10 to 15 mg every 2 to 3 hours, or 40 to 90 mg/day. A sustained release preparation of methylphenidate is available, but some patients report that their symptoms are not controlled with its once-a-day dosing. The dose range of dextroamphetamine is 5 to 15 mg every 3 to 4 hours, or 20 to 45 mg/day. Dextroamphetamine is also available in long-acting formulation, but patients report that their symptoms are not suppressed for the claimed 6 to 8 hours. Methamphetamine is marketed as an effective (but expensive) long-acting formulation; the dose is 20 to 45 mg/day and patients report symptom suppression for 8 to 10 hours. The amphetamines and methylphenidate appear to be equally effective for the treatment of ADHD, but patients may respond better to one rather than the other. If an individual is a partial responder to one stimulant, a trial of the other stimulant should be offered. Pulse and blood pressure should be carefully monitored in all patients who take stimulant medications. The best time to check for elevation of these parameters is 1 hour after administration of the drug; adjunct medications may be required to control the effects of stimulants on the cardiovascular system.

Pemoline, in doses of 75 to 150 mg/day, is usually administered once daily, although some patients require a dose twice daily. Liver function tests should be monitored indefinitely since hepatic toxicity may occur and may be lethal. Even when administered in a long-acting preparation, pemoline does not seem to be as effective as methylphenidate or the amphetamines. Bupropion and selegiline were efficacious in the open-label studies and should be systematically evaluated; compared with the stimulants, the two drugs are long-acting and are not likely to be abused.

CONCLUSION

Ongoing education is vital for patients who have adult ADHD, and pharmacotherapy should be combined with psychotherapeutic approaches in the management of the disorder. The patient should be informed of the life-long features of ADHD and the possible implications for long-term medication treatment. Patients should also be assisted in discarding adaptive techniques that were devel-

oped for dealing with the symptoms of ADHD and are no longer necessary. Different psychological problems may surface when ADHD symptoms remit, and psychotherapeutic intervention should be available to assist the patients in managing other issues. Treatment of adult patients who have ADHD is symptomatic not curative, but the combination of medication and psychotherapy may offer life-changing opportunities to individuals who suffer from the disorder.

Drug names: bupropion (Wellbutrin), dextroamphetamine (Dexedrine and others), levodopa (Larodopa), methamphetamine (Desoxyn), methylphenidate (Ritalin), pargyline (Eutonyl), pemoline (Cylert), selegiline (Eldepryl).

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