

# A Comparative Analysis of Antidepressants and Stimulants for the Treatment of Adults with Attention-Deficit Hyperactivity Disorder

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**BACKGROUND.** Adults who identify themselves as having problems with attention and concentration will often make an office visit to request treatment with a stimulant medication, rather than an antidepressant. The uncertainty of the diagnosis and the prospect of a long-term prescription with a stimulant medication can create a dilemma for physicians.

**METHODS.** We searched MEDLINE for any English-language studies of antidepressant or stimulant treatment of adults with attention deficits. References from relevant articles were reviewed to supplement the MEDLINE search.

**RESULTS.** Antidepressants and stimulants seem to be

equally effective for adults with attention-deficit hyperactivity disorder (ADHD). Recent controlled studies suggest that desipramine (an antidepressant) may be as effective as methylphenidate (a stimulant) for improving symptoms of adult ADHD.

**CONCLUSIONS.** Although few good controlled studies exist, the available research suggests that certain antidepressants and stimulants are equally effective for adults with ADHD. Antidepressants may offer a safe first-line treatment for adults with ADHD.

**KEY WORDS.** Attention-deficit hyperactivity disorder; antidepressants; stimulants; desipramine; methylphenidate. (*J Fam Pract* 1999; 48:15-20)

## CLINICAL QUESTION Are antidepressants as effective as stimulants in the treatment of adults with ADHD?

The popular media have recently shown interest in adult manifestations of attention-deficit hyperactivity disorder (ADHD). This topic has appeared on the cover of *Time* and on the front pages of *The New York Times* and the *Wall Street Journal*.<sup>1,3</sup> Popular women's magazines have carried articles offering adult ADHD as an explanation for feeling "nuts" or having marital problems.<sup>4,5</sup> A self-help book on the topic has remained a national bestseller.<sup>6</sup> These publications seem to be striking a familiar chord with their readership. It is likely that many people experience problems with attention, concentration, and procrastination and see themselves in the symptom profiles or case examples presented in these articles. Media interest coincides with a sevenfold increase in office visits to primary care physicians that included a prescription for a stimulant medication from 1985 to 1994.<sup>7</sup> The heightened public awareness of adult ADHD has led to primary care patients who come to the office with a self-diagnosis and request treatment with a stimulant medication such as methylphenidate.<sup>8</sup>

Contrary to accepted medical belief, the popular press

has suggested that many children fail to grow out of their ADHD. Good follow-up studies do not support this viewpoint.<sup>9</sup> Hill and Schoener<sup>10</sup> reviewed all of the existing longitudinal studies and concluded that there is an exponential decline in the prevalence of the disorder with age. The rate of ADHD in a given age group appears to decline by 50% every 5 years. Hill and Schoener observed that only 8% of children with ADHD will have the disorder at the age of 25 years. A more recent follow-up study by Mannuzza and colleagues<sup>11</sup> found that only 4% of adults still had ADHD at the age of 24 years. However, Weiss and Hechtman<sup>12</sup> examined 25-year-old patients who had been hyperactive children and found that two thirds of those adults had at least one symptom of ADHD. These studies suggest that few children with ADHD will meet full criteria for the disorder as an adult, but many will have some residual symptoms in adulthood.

It is extremely difficult to accurately diagnose ADHD in adults because of the vague nature of the criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV).<sup>13</sup> Inattention and distractibility are common everyday experiences. Two recent studies<sup>14</sup> of adults who requested an evaluation for ADHD found that the majority did not have the disorder. Johnson-Green,<sup>14</sup> in a study of 33 consecutive adults seeking an evaluation for ADHD through their health maintenance organizations, found that 4 (12%) were ultimately given a diagnosis of ADHD. Roy-Byrne and coworkers<sup>8</sup> studied 143 adults with complaints of poor concentration, disorganization, distractibility, or procrastination who visited a specialty clinic for an ADHD evaluation; they concluded that 46 (32%) met the criteria for ADHD.

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There have been many studies of pharmacologic treatment of children with ADHD,<sup>15,16</sup> but there have been few studies of adults. The general consensus for treating children with ADHD is to start with a stimulant medication and proceed to an antidepressant as a second-line agent. However, physicians are often reluctant to initiate long-term prescriptions of stimulants for adults. If antidepressants are effective in the treatment of adult ADHD, physicians could treat these patients without using a controlled substance.

## METHODS

We searched MEDLINE for English-language articles that reported treatment of adults with attention deficits using either stimulant medication or antidepressants. Additionally, the references from other pertinent articles were reviewed for studies that were missed in the MEDLINE search.<sup>16-20</sup> Articles were excluded if they presented a single case study or if the study combined pharmacologic treatments (eg, an antidepressant and a stimulant). Twenty-seven treatment studies of adults with ADHD were located. Seven were excluded because they did not fit the desired profile (2 were case studies, 2 were in a language other than English, 1 included combined treatments, and 2 were of other agents [eg, propranolol]).

## RESULTS

Twenty treatment studies that used either stimulant medication or antidepressants as a single pharmacologic agent for adults with ADHD were published between 1976 and 1998. Nine of the studies used a stimulant medication (Table 1) and eleven used antidepressant (Table 2).

Of the studies testing stimulant medications for adults with ADHD, 5 were double-blind, 3 were open label, and 1 involved retrospective chart reviews of college students. The range of positive responders was 25% to 100%. The results were mixed in the 5 placebo-controlled studies; 2 reported stimulant medication was no better than placebo, and 3 demonstrated a significant response for the stimulant compared with those treated with placebo. Wender and colleagues<sup>21</sup> found that adults with a more severe childhood history of ADHD were more likely to respond to pemoline, and Mattes and coworkers<sup>22</sup> found that adults responded equally well to methylphenidate regardless of childhood history of ADHD. The stimulant medications tested (pemoline [Cylert] and methylphenidate [Ritalin]) appear to be equally effective in the studies reviewed.

Eight of the studies that used antidepressants to treat adults with ADHD were open label, and only 3 were placebo controlled. One of the controlled studies used deprenyl (Eldepryl), a monoamine oxidase inhibitor (a type of med-

**TABLE 1**

### Studies of Stimulant Treatment in Adults with Attention-Deficit Hyperactivity Disorder

First Author	Year Published	Design	N	Medication	Responders (%)
Wood <sup>37</sup>	1976	Open	15	MPH	10 (66)
Wood <sup>37</sup>	1976	Open	15	Pemoline	5 (33)
Wender <sup>21</sup>	1981	Double-blind	48	Pemoline	10/26 (39) pemoline 7/22 (32) placebo
Mattes <sup>22</sup>	1984	Double-blind	61	MPH	15 (25) MPH Placebo response not significantly different
Gualtieri <sup>38</sup>	1985	Double-blind	8	MPH	8 (100) Placebo response not reported
Wender <sup>39</sup>	1985	Double-blind crossover	37	MPH	21 (57) MPH 5 (14) placebo
Shekim <sup>21</sup>	1990	Open	33	MPH	23 (70)
Spencer <sup>21</sup>	1995	Double-blind crossover	23	MPH	18 (78) MPH 1 (4) placebo
Heiligenstein <sup>40</sup>	1996	Chart review	40	Pemoline	28 (70)

MPH denotes methylphenidate (Ritalin); N, number of patients in study.

ication difficult to use in primary care because of dietary restrictions), and found the placebo response equal to the active treatment response. The other 2 controlled studies were with desipramine (an older tricyclic antidepressant) and tomoxetine (a new selective noradrenergic reuptake inhibitor). Both studies reported a good response to the active agent and almost no response to the placebo.

For adults with ADHD, the range of positive responders to antidepressants is 0% to 75%. Three studies used a monoamine oxidase inhibitor (deprenyl and pargyline [Eutonyl]), and the others tested more commonly used antidepressants, including desipramine (Norpramin), bupropion (Wellbutrin), venlafaxine (Effexor), fluoxetine (Prozac), and sertraline (Zoloft). Tomoxetine is not currently available in any country, but agents like it are used in Europe and are under investigation in this country. Although the study groups were small, desipramine, bupropion, venlafaxine, and tomoxetine appeared to be equally effective, and fluoxetine and sertraline produced no response.

These 20 studies were primarily of people who were not identified as having ADHD until adulthood. All of the studies included patients who met the criteria for adult attention deficit; however, the criteria changed over the 22-

year span of the articles. It is not clear what effect the change in ADHD criteria had on the comparative value of the studies, but no marked change in responsiveness is discernible over the years. All of the studies were conducted in specialty clinics, and no study included patients with attention problems who did not meet full criteria for a disorder.

There are no studies that have directly compared the effectiveness of stimulants and antidepressants. The best comparative analysis from the research is between the 2 placebo-controlled studies conducted by the same research group using the same measurement of response; 1 tested desipramine and the other methylphenidate (Tables 3 and 4).<sup>23,24</sup> While the design of the 2 studies was different (1 was a placebo-crossover study and the other had a separate placebo control group), the response was determined using the same self-reported 5-point answer scale for questions on the 18 symptoms of ADHD. Both studies used robust doses of medication: on average, 1.0 mg/kg per day methylphenidate and 200 mg per day desipramine. At week 4 in the desipramine study and week 3 in the methylphenidate study the 2 groups had similar responses as measured by the ADHD scale.

TABLE 2

## Studies of Antidepressant Treatment in Adults with Attention-Deficit Hyperactivity Disorder

First Author	Year Published	Design	N	Medication	Responders (%)
Wender <sup>41</sup>	1983	Open	22	Pargyline	13 (59)
Wender <sup>42</sup>	1985	Open	11	Deprenyl	6 (55)
Wender <sup>43</sup>	1990	Open	19	Bupropion	14 (74)
Ratey <sup>44</sup>	1992	Open	30	Desipramine	19 (63)
Hedges <sup>45</sup>	1995	Open	18	Venlafaxine	8 (44)
Adler <sup>46</sup>	1995	Open	16	Venlafaxine	12 (75)
Ernst <sup>47</sup>	1996	Double-blind	24	Deprenyl	Placebo response same as intervention response
Findling <sup>48</sup>	1996	Open	4	Fluoxetine or sertraline	0 (0)
Findling <sup>49</sup>	1996	Open	10	Venlafaxine	7 (70)
Wilens <sup>24</sup>	1996	Double-blind	41	Desipramine	13/19 (68) desipramine 0/22 (0) placebo
Spencer <sup>50</sup>	1998	Double-blind crossover	21	Tomoxetine	11 (52) tomoxetine 2 (10) placebo

N denotes number of patients in study.

**TABLE 3**

**Double-Blind, Crossover Comparison of Methylphenidate and Placebo in Adults with ADHD by Spencer et al<sup>23</sup>**

Treatment	Baseline	Week 1	Week 2	Week 3
MPH	30.2	21.9	15.3	12.5
Placebo	30.2	29	29	28.6

ADHD denotes attention-deficit hyperactivity disorder; MPH, methylphenidate (Ritalin).  
 Note: The numbers reflect average scores on a self-report ADHD scale. Higher numbers reflect greater symptoms.

**TABLE 4**

**Double-Blind, Placebo-Controlled Study of Desipramine for Adults with ADHD by Wilens et al<sup>24</sup>**

Treatment	Baseline	Week 2	Week 4	Week 6
Desipramine	28	17	13	12
Placebo	27	24	23	25

ADHD denotes attention-deficit hyperactivity disorder; MPH, methylphenidate (Ritalin).  
 Note: The numbers reflect average scores on a self-report ADHD scale. Higher numbers reflect greater symptoms.

**DISCUSSION**

The available studies of monotherapy for adults with ADHD suggest that stimulant medications and certain antidepressants are both effective treatments. However, these studies have several limitations. The study groups were small, and most of the studies were uncontrolled. All but one of the studies reported the number of patients who responded to the treatment, but the criteria for being a responder was not the same in all studies. Therefore, the ability to accurately compare the results is called into question. All of the studies are set in specialty mental health clinics, even though primary care physicians have 3 times as many office visits that include a prescription for stimulant medication as psychiatrists.<sup>7</sup> Specialty clinics see a population that is severely ill, and results from these patients cannot always be applied to primary care patients.<sup>25</sup>

Despite these limitations, the available research suggests that patients will benefit equally from treatment with one of the tested stimulants or antidepressants. Unfortunately, the important question of whether to initiate treatment with a stimulant or an antidepressant has not been adequately answered.

This analysis suggests that adults with ADHD can be safely and effectively treated with certain antidepressants, and physicians need not worry about problems with long-term prescriptions for stimulant medication. Kleber<sup>26</sup> stated in an editorial on our current approach to the drug

problem in the United States, "Drug abuse remains one of the nation's critical domestic problems, linked to crime, neglect of children, family violence, incomplete education, homelessness, AIDS, high health care costs, urban decay, and diminished economic competitiveness." Methylphenidate is classified as a schedule II controlled substance because of its similarity to cocaine, its ability to induce euphoria, and its propensity to be self-administered by animals.<sup>27,28</sup> Media reports have documented the recreational use of methylphenidate; however, the exact extent of misuse remains unknown.<sup>29-32</sup> The potential for abuse is increased in adults with ADHD because of the high co-occurrence of other substance abuse disorders (range: 27% to 46% of patients) or antisocial personality disorder (range: 12% to 27%).<sup>33-35</sup> While stimulants are the recommended first-line treatment for children,<sup>15</sup> the increased use of stimulants by adults may not be the best social policy. Antidepressants have the advantage of treating the depression that may be the true cause of inattention in most adults

presenting with self-diagnosed ADHD.<sup>8,14</sup>

Unfortunately, the tricyclic antidepressants, such as desipramine, can cause many side effects. The newer antidepressants, such as bupropion and venlafaxine, seem to be effective for adults with ADHD and are usually better tolerated by patients. However, more research that directly compares these agents with desipramine and stimulant medications is needed. It is important to note that the most popular antidepressants (the selective serotonin reuptake inhibitors) showed no benefit, unlike the antidepressants with noradrenergic effects (desipramine, venlafaxine, and tomoxetine). These results are consistent with the belief that the serotonin receptor is minimally involved in ADHD.<sup>10</sup>

The finding that antidepressants provide benefit for adults with ADHD is consistent with our understanding of antidepressants and ADHD. First, antidepressants are an effective, well-used, second-line agent for the treatment of ADHD in children.<sup>16</sup> Second, the symptoms of ADHD decrease with age.<sup>10</sup> Third, mood disorders increase with age.<sup>36</sup> Finally, problems with attention and concentration are common complaints in patients with major and minor depression.

**IMPLICATIONS FOR FURTHER RESEARCH**

The proper treatment for adults who have some symptoms of ADHD but fail to meet the full criteria for it cannot be established from the available data. This is particularly troublesome for primary care physicians, because patients

with partial symptoms may represent the largest percentage of adults requesting treatment for ADHD symptoms.<sup>8,14</sup> Future research should focus on treatment options for this population. In particular, would antidepressants help problems with concentration and attention in patients who have a subthreshold ADHD?

The studies we reviewed were small, but more research is currently being conducted that should further our understanding of the effective treatments available for adults with ADHD. Unfortunately, all of the studies we analyzed and most of those pending are from specialty clinics. Future research needs to be conducted in primary care settings.

**RECOMMENDATIONS FOR CLINICAL PRACTICE**

It is a relatively new development in clinical care that adults self-diagnose ADHD and request treatment. Some physicians have been reluctant to treat these patients because of concerns about the long-term use of stimulant medication.

This review suggests that certain antidepressants are as effective as stimulants for treating adults with ADHD. This increases the number of treatment options for physicians and allows them to treat adults without having to worry about the misuse of controlled medications. Although the study groups were small, the 4 most effective antidepressants were desipramine, bupropion, venlafaxine, and tomoxetine. It is reasonable to classify the noradrenergic agents (desipramine, venlafaxine, and tomoxetine) into one class, and the dopaminergic agent (bupropion) into another. A good approach is to start with an agent from one class and switch to an agent from another class if the patient fails to respond or has intolerable side effects. It is important to use an adequate dose of an antidepressant (a dose similar to that used to treat depression) before switching to another agent.

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