Low-Dose Amphetamine Salts and Adult Attention-Deficit/Hyperactivity Disorder

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Background: Effective treatments for attention-deficit/hyperactivity disorder (ADHD) in adults are still being defined. Pediatric studies have suggested that a mixed amphetamine salt product (Adderall) is safe and effective in the treatment of childhood forms of ADHD. Presently, there are no reports in the scientific literature concerning the safety and efficacy of Adderall in adults with ADHD, which is the focus of this study.

Method: Twenty-four outpatients (mean age = 33.3 years) with DSM-IV ADHD were administered Adderall in an open-label fashion, starting at 5 mg p.o. b.i.d., with titration according to clinical response, across a 16-week period. Relatives or spouses of each patient completed serial checklists (including the Copeland Symptom Checklist and the Brown Attention-Deficit Disorder Scales). Prospectively collected data were analyzed retrospectively.

Results: Thirteen patients (54%) responded in a positive manner to Adderall, based on Clinical Global Impressions-Improvement scale scores. The mean end dose for responders was 10.77 mg/day (0.14 mg/kg/day). An intent-to-treat analysis revealed a decrease in the mean Copeland score from 99.05 to 63.3 ($p < .001$), while the mean Brown score dropped from 76.75 to 50.85 ($p < .0001$). Nine patients (38%) were poor responders or nonresponders to Adderall. Acute anxiety symptoms occurred in 4 of 7 patients with a comorbid anxiety diagnosis.

Conclusion: Adderall may be an effective agent for the treatment of adult forms of ADHD, with positive responses occurring at relatively low doses, at least for some individuals. However, Adderall may precipitate anxiety in vulnerable individuals. Further study is required.

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Attention-deficit/hyperactivity disorder (ADHD) can involve impairment across a variety of domains, with presenting signs and symptoms including hyperactivity, impulsivity, inattention, distractibility, and low frustration tolerance. The prevalence of ADHD in childhood may be over 10%, and symptoms persist into adulthood (to a degree that causes continuing impairment) in as many as 65% of these individuals.[1–8] While efforts have been made to develop sensitive and specific diagnostic inventories for ADHD in adulthood,[9–15] the diagnostic process itself often presents the most challenging aspect of the clinical management of adults with this disorder.[16,17] However, substantial evidence suggests that adult forms of ADHD can be reliably diagnosed and effectively treated.[18,19] Despite this progress, the range of effective treatments for adults with ADHD has yet to be defined, particularly with regard to possible pharmacotherapeutic approaches.

Childhood treatment studies have been more extensive. For instance, psychostimulants represent the mainstay of pharmacotherapeutic treatment for childhood forms of ADHD.[20,21] The first controlled trial involving the use of amphetamines in children with ADHD (or at least a phenotypic equivalent of this disorder) was published in 1937.[22] In subsequent years, the findings of numerous clinical trials have been published involving psychostimulants in children and adolescents with ADHD, including 22 studies involving amphetamines.[23]

In March 1996, a mixed amphetamine salt product (Adderall, a psychostimulant that contains *d*-amphetamine and *l*-amphetamine) received U.S. Food and Drug Administration approval for unrestricted use in the treatment of ADHD.[24] Clinical reports have emerged concerning the efficacy of this mixed amphetamine salt product in childhood forms of ADHD.[25–27] In these childhood studies, Adderall appeared to be both effective and well tolerated. In addition, Adderall seemed to have a unique clinical profile, at least when compared with the standard preparation of methylphenidate. More specifically, these studies demonstrated both a unique time-course effect (the time of peak effect and the duration of action increased as the dose of Adderall was increased) as well as a marked preference for Adderall on the part of caretakers and teachers. In conjunction, no unusual or serious side effects were noted with Adderall treatments.

Empirical studies have suggested that psychostimulants are effective in the treatment of adult ADHD.[28–34] Given the encouraging findings concerning Adderall in childhood ADHD, an exploration of the potential applications of Adderall in the adult population appears to be warranted.

METHOD

Twenty-four adult outpatients with ADHD (DSM-IV 314.01, combined type) were diagnosed and treated with Adderall during a 12-month period at a university-based neuropsychiatric clinic. Demographic, medical, psychiatric, and outcome data were collected on these patients in a prospective manner, as they are for all patients at the clinic, and the data were analyzed retrospectively via a chart review.

The ADHD diagnosis was rendered following a structured and semistructured interview of both the patient and at least one first-degree relative or the patient's spouse (if he or she was married). Standardized checklists (including the Wender Utah Rating Scale,[9,10] the Copeland Symptom Checklist for Adult Attention Deficit Disorders,[12] and the Brown Attention-Deficit Disorder Scales[15]) were completed as part of the diagnostic process, and the commonly accepted threshold scores described by the authors of these checklists were applied prior to formal rendering of the ADHD diagnosis.

The diagnostic process included a complete review of all medical and psychiatric records, a complete physical examination, and baseline laboratory work (including a complete blood count with differential, serum electrolyte levels, liver function tests, thyrotropin levels, thyroid panel, urinalysis, a urine toxicology screen, and in select cases, an electrocardiogram). The clinical algorithms for the use of psychostimulant medications in this clinic considered hypertension (resting systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg) and a myocardial infarction in the preceding 12 months to be contraindications to psychostimulant therapy. Additional exclusion criteria included any of the following: mental retardation, any active substance use disorder, schizophrenia or a psychotic disorder, bipolar disorder, a current episode of major depression, and a cluster B personality disorder. The diagnosticians were the authors, who are dually board-certified in general as well as child and adolescent psychiatry.

Each patient was administered Adderall in an open-label fashion following written, informed consent. The form of Adderall utilized was the scored 10-mg tablet, which contains 2.5 mg each of *d*-amphetamine sulfate; *d,l*-amphetamine sulfate; *d,l*-amphetamine aspartate; and *d*-amphetamine saccharate. At the time of initiation of Adderall therapy, 4 of the patients were also taking a fixed dose of a selective serotonin reuptake inhibitor (sertraline or venlafaxine), with no change in dose throughout the Adderall trial.

Table 1. Comorbid Diagnoses

Diagnosis	N	%
Reading disorder	10	42
Mathematics disorder	9	38
Disorder of written expression	5	21
Dysthymia	5	21
Depressive disorder NOS	5	21
Social phobia	3	12
Anxiety disorder NOS	3	12
Panic disorder	2	8
Eating disorder NOS	1	4
Developmental coordination disorder	1	4

The Adderall was initiated at a dose of 5 mg p.o. b.i.d. (breakfast and lunch), and the dose was titrated according to clinical response over the next 16 weeks, employing a twice-daily dosing schedule throughout the study. Serial checklists (including the Copeland Symptom Checklist[12] and the Brown Attention-Deficit Disorder Scales[15]) were completed every 2 weeks by the patient along with his/her spouse or a first-degree relative. Structured side effect checklists were completed on a weekly basis. Telephone contacts occurred every 2 weeks, while clinic visits were conducted on a monthly basis (at which time Clinical Global Impressions scales[35] were also completed by the physician). The clinical endpoint of dosage adjustment occurred when intolerable side effects intervened or the patient and his/her family member, in conjunction with the prescribing physician, determined that maximum clinical benefits had occurred. It should be noted that no specific target end dose was established a priori, and dosage adjustments were typically conducted every 2 weeks as needed in 5-mg increments. Treatment-related changes were evaluated in a within-subjects manner, using paired t tests at the $\alpha = .01$ level.

RESULTS

In this study, there were 12 men (mean ± SD age = 33.25 ± 9.73 years) and 12 women (mean ± SD age = 33.42 ± 11.89 years). The mean number of years of postsecondary schooling was 2.94 ± 1.84 years, corresponding to a mean Hollingshead-Redlich Education Code[36] of 2.61 ± 0.78. The mean Hollingshead-Redlich Highest Occupation Code[36] was 3.46 ± 0.83. The comorbid diagnoses at the time of initiation of Adderall treatment are detailed in Table 1.

Utilizing the criterion of a score of 1 ("very much improved") or 2 ("much improved") on the Clinical Global Impressions-Improvement scale (CGI-I) as a marker for positive response, 13 (54%) of the patients were positive responders to Adderall after 16 weeks. The specific CGI-I scores included 10 (42%) who were "very much improved" and 3 (12%) who were "much improved." An

Table 2. Side Effects (all patients)

	N	%
Anxiety (generalized)	5	21
Acute anxiety (panic)	4	17
Decreased appetite	3	12
Irritability	3	12
Stomachache	2	8
Dysphoria	2	8
Insomnia	2	8
Tremor	2	8
Sedation	2	8
Headache	1	4
Motor tic	1	4
Dizziness	1	4

additional 2 (8%) were "minimally improved." In this group of 15 (positive or minimal responders), few side effects were noted: 2 patients experienced a mild decrease in appetite, 1 experienced initial insomnia, and 1 experienced mild sedation 4 to 5 hours after a given dose (Table 2 includes all side effects observed). In addition, in this group, the mean ± SD effective dose was 10.33 ± 4.10 mg/day or 0.14 ± 0.06 mg/kg/day, while the modal dose remained at 5 mg p.o. b.i.d. For the 13 that obtained a CGI-I score of 1 or 2, the mean effective dose was 0.14 ± 0.06 mg/kg/day, corresponding to 10.77 ± 4.3 mg/day.

In the above-described cohort of 15 individuals, the Copeland dimensions of inattention/distractibility, impulsivity, noncompliance, and underactivity were most noticeably affected by the Adderall treatment. In terms of mean percent change for these various dimensions, inattention/distractibility decreased by 41%, impulsivity by 33%, noncompliance by 30%, underactivity by 27%, emotional difficulties by 26%, underachievement/disorganization by 24%, overactivity by 22%, "impaired family relationships" by 18%, and "poor peer relations" by 15%.

In the poor or nonresponder group of 9 patients (38%), all experienced side effects (including a more substantial decrease in appetite, gastrointestinal upset, migraine headache, and heart palpitations; see Table 2), prompting each one to discontinue the Adderall within the first 3 weeks of the trial. Of note, 4 of 7 patients in the study with a comorbid anxiety diagnosis experienced near-immediate symptoms of acute anxiety (including diaphoresis, tremor, shortness of breath, and an impending sense of doom) at the start of Adderall therapy. This adverse response led to discontinuation of Adderall in each case within the first 24 hours. Accordingly, these 4 patients did not provide checklist scores subsequent to the initiation of Adderall, although they did complete side effect checklists.

Intent-to-treat data analyses (utilizing a last-observation-carried-forward approach) were conducted on the outcome measures from the 20 patients that continued taking Adderall for more than 2 weeks. Utilizing this approach, Adderall continued to manifest a favorable response. In this cohort of 20, the mean ± SD Copeland score dropped from 99.05 ± 27.02 to 63.3 ± 35.19 ($t = 4.83$, 2-tailed, $p < .001$), while the mean Brown score dropped from 76.75 ± 17.77 to 50.85 ± 27.66 ($t = 5.20$, 2-tailed, $p < .0001$). For this intent-to-treat analysis, the mean CGI-I score at the end of 16 weeks was 2.30 ± 1.66. In addition, the mean Adderall dose was 10.50 ± 4.34 mg/day, corresponding to 0.13 ± 0.06 mg/kg/day.

DISCUSSION

This study has a variety of weaknesses. The design was open-label, which allowed for variable titration (dose adjustment) of the Adderall. The sample size was relatively small, which diminishes the generalizability of the findings. The exclusion criteria may have diluted the generalizability even further, given that the majority of patients with adult ADHD frequently have more complicated patterns of comorbidity.[37] The outcome measures have not been well standardized, outside of the CGI scale. In this study, no control group was included, and there were no blind raters. Finally, 3 of the positive responders were taking fixed doses of either sertraline or venlafaxine during the course of this study. This may have been a confounding variable, since there is preliminary evidence that venlafaxine may be mildly helpful with some dimensions of ADHD.[23]

Despite these shortcomings, the results of this pilot study suggest that, in select cases, Adderall may be an effective treatment for the adult form of ADHD. This apparent efficacy is in agreement with the preceding studies involving methylphenidate and adult ADHD.[29,31–33] One interesting finding in this study is that a small majority of the patients (15/24, 62%) achieved maximum clinical benefit on a relatively low dose of Adderall (0.14 mg/kg/day). This finding is in contrast to those of the more recent studies involving methylphenidate, which have suggested that more substantial dosing (in the range of 1 mg/kg/day) is required before consistent positive responses are observed.[31,32] One possible explanation may be that the dose of Adderall was not adequately advanced in the nonresponders in this study (although all of these individuals experienced side effects at low doses and would not tolerate further dose increases).

Further studies addressing the potential efficacy of Adderall in adult ADHD would be worthwhile. One particularly interesting avenue of exploration may involve the specific time course of response to Adderall in this population. In addition, it may ultimately be helpful to perform more systematic comparison studies between the various psychostimulants, not only to determine relative efficacy, but also to discern if there are preferential patterns of response. If the latter proves true, this may ultimately assist with appropriate medication choice at the start of drug therapy. Equally informative would be an analysis of the impact of the various psychostimulants on the different dimensions of adult ADHD.

An example of the idiosyncratic response to psychostimulant treatment from this study would be that 7 of 9 nonresponders to Adderall were successfully crossed over to an alternative psychostimulant, with essentially no side effects noted. Four of these patients proved to be positive responders to dextroamphetamine sulfate, while the remaining 3 responded positively to methylphenidate. The key difference between Adderall and dextroamphetamine sulfate is the *l*-amphetamine component of Adderall. Given the side effects observed in this study, it is possible that the levo (*l*-) isomer of amphetamine is relatively more anxiogenic compared with the dextro (*d*-) isomer, at least in individuals vulnerable to anxiety.[38]

None of the patients reported (or appeared to experience) euphoria or tolerance. However, Adderall did not prove to be free of side effects, as discussed above. While the findings of this pilot study are promising, further studies will be required to determine the potential utility of Adderall in the management of individuals with adult ADHD.

Drug names: dextroamphetamine (Dexedrine and others), methylphenidate (Ritalin and others), sertraline (Zoloft), venlafaxine (Effexor).

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