A Randomized Double-Blind Trial of Paroxetine and/or Dextroamphetamine and Problem-Focused Therapy for Attention-Deficit/Hyperactivity Disorder in Adults

Margaret Weiss, M.D., Ph.D.; Lily Hechtman, M.D.; and The Adult ADHD Research Group

Objective: To determine the effect of psychotherapy, dextroamphetamine, and/or paroxetine on attention-deficit/hyperactivity-disorder (ADHD) in adults.

Method: Ninety-eight adults with DSM-IV ADHD were randomly assigned to receive psychotherapy and dextroamphetamine, paroxetine, both, or placebo for 20 weeks. A 2 × 2 factorial design compared patients who received dextroamphetamine versus no dextroamphetamine with patients who received paroxetine versus no paroxetine. Data were collected from August 2000 until May 2002.

Results: One half of the 98 enrolled subjects were found to have at least 1 lifetime mood or anxiety disorder on the Structured Clinical Interview for DSM-IV. Sixty percent of patients who received medication and 80% of those who received placebo completed the 5-month trial. ADHD symptoms were significantly ($p = .012$) lower in patients in the completer group who received dextroamphetamine. Paroxetine had no effect on ADHD. Hamilton Rating Scales for Anxiety (HAM-A) and Depression (HAM-D) scores were low to start, and no treatment differences were evident at endpoint. Significantly ($p < .001$) more patients in the completer group were rated by clinicians as ADHD responders if they received dextroamphetamine (85.7%) or combined treatment (66.7%) versus paroxetine (20.0%) or placebo (21.1%). Significantly ($p = .003$) more patients in the completer group were rated by clinicians as mood/anxiety responders if they received paroxetine (100%) or combined treatment (73.3%) versus those receiving dextroamphetamine (57.15%) or placebo (47.4%). Clinicians rated any patient who received medication and psychological therapy as significantly more improved overall than those who received placebo and psychological therapy (intent to treat: $p = .033$; completers: $p = .001$).

Conclusion: ADHD symptoms improved with dextroamphetamine. Mood and internalizing symptoms were seen as improved with paroxetine by clinicians, despite absence of response on the HAM-A and HAM-D. The presence of a lifetime internalizing disorder attenuated the response to dextroamphetamine. Patients who received both dextroamphetamine and paroxetine had more severe adverse events but did not show greater improvement overall than patients treated with 1 medication. Clinical Trials Registry #GSK707.

(J Clin Psychiatry 2006;67:611–619)

Received May 12, 2005; accepted Nov. 8, 2005. From the Department of Psychiatry, University of British Columbia, Vancouver, British Columbia (Dr. Weiss); and the Department of Psychiatry, McGill University, Montreal, Quebec (Dr. Hechtman), Canada.

This investigator-initiated trial was funded by GlaxoSmithKline, Research Triangle Park, N.C.

Individual financial disclosure appears at the end of this article.

Members of the Adult ADHD Research Group appear at the end of this article.

Corresponding author and reprints: Margaret Weiss, M.D., Ph.D., Division of Child Psychiatry, University of British Columbia, Children's and Women's Health Centre, Box #178, B430-4500 Oak St., Vancouver, British Columbia, Canada V6H 3N1 (e-mail: mweiss@cw.bc.ca).

The prevalence of attention-deficit/hyperactivity disorder (ADHD) in adults is estimated at 4.7%.[1–3] Clinicians working with adults with ADHD describe this population as having significant difficulty with dysphoria and/or anxiety.[4–6] Studies examining comorbid disorders in adults with ADHD support clinicians' reports indicating that approximately 46% of adults with ADHD have a lifetime history of comorbid anxiety disorders and that 59% have a lifetime history of depression.[2,7] More recently, the National Comorbidity Study-Revised confirmed that more than a third of subjects who met diagnostic criteria for ADHD also had a current mood and/or anxiety disorder.[1,8] Conversely, 1 in 5 patients currently in treatment for mood and anxiety disorders meets diagnostic criteria for ADHD.[9,10] If one third or more of patients with either ADHD or a mood and anxiety disorder is comorbid for both conditions, it is also possible that many of the remaining patients have clinically significant but subthreshold symptoms. Given that lifetime rates of comorbid internalizing disorders are much higher than current rates of mood and/or anxiety disorders, it is possible that these patients may carry clinically impairing residual internalizing symptoms.

Patients who have lived with untreated ADHD symptoms often complain of associated symptoms of low self-esteem, temper outbursts, mood dysregulation, reactivity, anxiety, poor motivation, and other symptoms that fall within the spectrum of internalizing disorders.[5] In some patients, these associated symptoms may even be the presenting complaint, although the patient will not meet the diagnostic criteria for a current mood or anxiety disorder.

© Copyright 2006 Physicians Postgraduate Press, Inc.

Although awareness of adult ADHD has increased among clinicians, there remains a lack of empirical data on effective pharmacologic treatments for adult patients with ADHD and a comorbid mood or anxiety disorder or ADHD with associated mood and anxiety symptoms.

Practice guidelines differ on whether ADHD or anxiety/depression should be treated first.[11,12] Common treatment approaches have included the use of single agents for either disorder or combination pharmacotherapy for both disorders.[13] While selective serotonin reuptake inhibitor (SSRI) and stimulant treatments are often combined in clinical practice, there are no published data on the safety and efficacy of this practice.

Spencer et al.[14] report that 74% of adults with ADHD respond to stimulants in short-term trials. The efficacy of SSRIs for the treatment of ADHD in adults is unknown. A limited number of studies have suggested that SSRIs may have some utility among ADHD patients with comorbid internalizing symptoms.[13] This exploratory research suggests that serotonergic medication may impact symptoms associated with ADHD such as irritability, aggression, oppositional behavior, rages, anxiety, or dysphoria.

The neurobiology of ADHD clearly identifies both norepinephrine and dopamine neurotransmitters to be important. Recent evidence, however, has also suggested the involvement of the serotonin system in ADHD. It is known that serotonin receptors have a modulatory effect on lower dopamine pathways,[15] and a variety of imaging,[16,17] genetic,[18,19] and animal studies[20] have indicated the involvement of the serotonin system in ADHD. It is commonly assumed that SSRI medication has no effect on ADHD in adults, but this has never been empirically demonstrated.

An informal chart review of patients presenting to the 5 adult ADHD clinics represented in this study indicated that up to three quarters of them had received or were receiving SSRI medication. Given the comorbidity of ADHD and internalizing disorders, as well as a variety of subthreshold associated mood and anxiety symptoms in patients with ADHD, empirical data are needed to determine the effect of SSRI medication and/or stimulant medication on patients with a primary diagnosis of ADHD.

Comorbid internalizing symptoms are generally much more familiar to physicians than ADHD. As a result, many adults with ADHD may be misdiagnosed as having an atypical mood or anxiety disorder and then inappropriately treated with an SSRI. It has been found that 1 in 5 patients in mood or anxiety clinics have undiagnosed ADHD.[9,10] This finding demands systematic evaluation of the efficacy of stimulant and/or SSRI medication in reducing ADHD and/or internalizing symptoms in adult patients with ADHD and the safety of using these medications in combination.

This was an investigator-initiated, industry-funded study to look at the efficacy and safety of stimulant, SSRI, and their combined use in patients with a primary diagnosis of ADHD and a range of secondary mood and anxiety symptoms that are seen in ADHD patients. Clinical trials of adults with ADHD have focused on ADHD symptoms to the exclusion of associated mood and anxiety symptoms, and we wish to determine the impact of stimulants and/or SSRIs on both sets of symptoms over the intermediate term. All patients in this study received problem-focused therapy at each visit to optimize their understanding of the disorder, assist with development of skills not learned in childhood, and assure that patients taking placebo received treatment.

METHOD

The current study examined the relative efficacy and safety of paroxetine (PAR), dextroamphetamine (DEX), paroxetine and dextroamphetamine combined (PAR/DEX), and placebo in adults with a primary diagnosis of ADHD. Since this study employed a randomized placebo treatment arm, an intermediate outcome timeline, and a medication (paroxetine) without demonstrated efficacy in the past for ADHD, we felt it would be ethically necessary to also provide all patients with problem-focused therapy. The study was done at 2 U.S. sites (Yale University and Duke University) and 3 Canadian sites (McGill University, University of Toronto, and University of British Columbia). The study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from site institutional review boards, and written informed consent was obtained from all participants.

Participants

Participants were patients, 18 to 66 years of age, recruited from clinical outpatient psychiatric services, who met DSM-IV[21] diagnostic criteria for ADHD. Adults with eating disorders, substance abuse disorders, organic brain syndrome, neurologic disease, psychosis, and active suicide risk were excluded. Other comorbid conditions were permitted if in the opinion of the investigator they did not require treatment with psychotropic medication other than those provided for in the protocol.

A power analysis using a type 1 error probability (alpha) of 0.05 and a 2-sample comparison would yield a power of 0.80 to detect an effect size of .89 with a sample of 20 patients in each of the 4 treatment groups. To account for a potential 20% attrition, target enrollment was set at 100 patients. Ninety-eight adults were randomly assigned to 1 of the 4 study arms.

Procedures

Participants were randomly assigned using a block randomization schedule such that the number of patients in each of the 4 treatment arms would be proportionate at

each site. After a full baseline assessment, eligible participants entered a 1-week single-blind placebo washout.

Medication was titrated by weekly increments to the participants' optimal dose over a 4-week titration phase. Optimal dose was defined either as a Clinical Global Impressions-Improvement scale (CGI-I) score of "much improved" or "very much improved" or by the maximum dose of medication that could be tolerated and above which there could be no further improvement. Paroxetine was initiated at 20 mg/day p.o. and increased by 10-mg increments to a maximum of 40 mg/day p.o. Dextroamphetamine was initiated at 5 mg p.o. b.i.d. and increased by 5-mg increments to a maximum of 20 mg p.o. b.i.d. Patients randomly assigned to both paroxetine and dextroamphetamine had both medications increased simultaneously and blindly. A b.i.d. double dummy design was used for all treatment groups. Following titration, patients were seen in acute treatment every 2 weeks (for 6 sessions) and twice subsequently in follow-up at 15 and 20 weeks. Data were collected from August 2000 until May 2002.

Problem-Focused Therapy

A manualized psychotherapy (available upon request) appropriate for the treatment of adults with ADHD was developed by the authors. Problem-focused therapy provided education about ADHD, support to establish effective coping strategies, and assistance with understanding how to optimize strategies to moderate deficits associated with the disorder. Specific modules to address common problems among adults with ADHD (e.g., finance, relationships, work problems, parenting) were included in the manual. Participants received 9 sessions of problem-focused therapy in conjunction with the scheduled study visits.

Measures of Psychiatric Status

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)[22] was administered to identify DSM-IV disorders and document comorbid and exclusionary conditions. Diagnoses of persistent ADHD from childhood to adulthood were confirmed through clinical interview and the Conners' Adult ADHD Diagnostic Interview for DSM-IV.[23]

Primary Outcome Measures

ADHD symptoms were measured using the ADHD Rating Scale for DSM-IV, investigator version (ADHDRS-IV-Inv).[24] The ADHDRS-IV-Inv contains 18 items that correspond to the DSM-IV symptoms for ADHD. Clinicians rate each symptom on a 4-point Likert scale ranging from 0 (never or not at all) to 3 (very frequently or very much). Anxiety and depression were rated using the Hamilton Rating Scales for Anxiety (HAM-A)[25] and Depression (HAM-D).[26]

Secondary Outcome Measures

The CGI-I[27] was used to measure clinicians' observations of overall change for patients from baseline to endpoint. A clinician rating of "much improved" or "very much improved" was used to determine the percentage of patients who would be considered treatment responders. Clinicians rated patients' change over time in 3 different domains: ADHD symptoms (CGI-I-ADHD), mood and anxiety symptoms (CGI-I-Int), and overall improvement (CGI-I). Global Assessment of Function (GAF) rating and proportion of SCID mood and anxiety disorders at study endpoint were also evaluated.

Weight, blood pressure, pulse, adverse events, and concomitant medications were collected at each visit. Adverse events were rated as mild, moderate, severe, or serious.

Study Drugs

Study drugs, including placebo, were encapsulated to disguise the identity of the contents. Custom encapsuled dose formulations were prepared for paroxetine (10, 20, 30, and 40 mg) and dextroamphetamine (5, 10, 15, and 20 mg). Identical capsules were filled with lactose to serve as placebo. Compliance with medication was measured at each visit by pill counts. Participants were required to maintain 75% compliance with medication in order to remain in the study.

Statistical Analysis

The analysis of primary outcome variables (ADHDRS-IV-Inv, HAM-A, HAM-D) employed a 2 × 2 factorial model, that is, dextroamphetamine (DEX and PAR/DEX) versus no dextroamphetamine (PAR and placebo) × paroxetine (PAR and PAR/DEX) versus no paroxetine (DEX and placebo). Baseline values of the primary outcome measures were tested for treatment differences that may have occurred despite randomization. If there were no group differences at baseline, outcome was measured using endpoint analysis of variance. For the primary outcome analysis, study endpoint measures rather than measures of change from baseline were selected for analysis. While the mixed-model random regression has become a popular method for evaluation of longitudinal trials, nonrandom patient attrition is common in placebo-controlled clinical trials, which precludes the use of this technique. Furthermore, the largest changes in symptoms and other efficacy measures are often seen during medication titration phases, with decreasing magnitude of change in later treatment visits. Such conditions do not satisfy the assumption of linearity in the random regression approach.

Data from study endpoint (week 20) were analyzed for patients who completed the study. An intent-to-treat (ITT) sample was also analyzed, in which missing data were imputed from the last study visit at which randomized

medication was taken by a participant, referred to as "last observation carried forward."

Analyses of the secondary efficacy measures (CGI-I) were conducted using χ^2 tests, and Fisher exact test when cell sizes were less than 5. This secondary analysis compared the 4 treatment conditions (PAR, DEX, PAR/DEX, and placebo).

Paired t tests were employed to document change from baseline to endpoint (20 weeks) on measures of vital signs. Analyses of adverse events were largely descriptive, but statistical tests were conducted when there were sufficient observations. Two-tailed statistical significance was set at the p = .05 level for all tests.

RESULTS

Participant Retention and Loss

One hundred forty participants attended the initial baseline screening visit. Fifteen participants did not meet inclusion criteria, 18 withdrew consent, and 9 were lost to follow-up. The final sample consisted of 98 adults with ADHD, of which 64 (65%) remained enrolled for the entire 20 weeks. Eighteen out of 34 patients discontinued due to adverse events (by medication, PAR: N = 6, DEX: N = 3, PAR/DEX: N = 7, and placebo: N = 2). There was no significant association between study completion and the assignment to a medication treatment (62% completion) versus placebo treatment (77% completion). There was no statistically significant difference between treatment arms in discontinuation for adverse events overall, but there were more severe adverse events in the group receiving both stimulant and SSRI. Other reasons given for discontinuation (not independent of adverse events) included lack of treatment efficacy (N = 5), protocol deviation (N = 1), treatment noncompliance (N = 5), lost to follow-up (N = 5), and unknown reasons (N = 2).

Participant Characteristics

Sixty-four percent of the sample was male. Thirty-six percent of the sample was inattentive type, 4% was hyperactive-impulsive type, and 60% was combined type. The mean GAF score was 53.10 (SD = 7.93). The mean age of the sample was 37.48 (SD = 10.75) years, and 85% of the sample was white with the remaining subjects being of various ethnicities. Thirty-three percent of the total sample met SCID criteria for a current diagnosis of at least 1 mood or anxiety disorder, and 53% met criteria for a lifetime mood or anxiety disorder. There was no statistically significant difference between any of the treatment arms on these variables with the exception of there being more women randomly assigned to PAR (p = .04) and fewer women randomly assigned to placebo.

The mean level of ADHD symptom severity as measured by the ADHDRS-IV-Inv was 32.20 (SD = 7.55), or well within the clinically significant range. Mean anxiety score on the HAM-A was 12.70 (SD = 6.56) and the mean depression severity score on the HAM-D was 9.20 (SD = 5.71). These scores are higher than what would be considered normal but below the threshold of what would be considered clinically significant. There were no significant treatment group differences among the baseline clinical characteristics, nor were there group differences on baseline CGI-Severity of Illness ratings. Analysis of baseline levels of the primary outcome measure of those patients who completed the full 20 weeks of treatment also showed no significant group differences.

Dosing

One half of participants (52.6%) received the maximum allowable dose (paroxetine 40 mg/day, dextroamphetamine 40 mg/day) prior to early termination or study completion. In the placebo condition, 68% of participants reached the equivalent of maximum dose. There was a significant group difference in the mean number of dose increases during titration in the 4 treatment groups ($F = 2.842$, df = 3,91; p = .042). Post hoc comparisons using the Fisher Least Significant Difference test showed the mean number of dose increases in the PAR/DEX group to be significantly lower than that in the PAR or placebo groups (p = .027 and p = .009, respectively). The low doses in the PAR/DEX group were for both PAR and DEX, as both medications were titrated simultaneously in this combined treatment. Generally, side effects prevented dose increases.

Endpoint Analysis Symptom Outcome

Endpoint analysis of the ITT sample revealed a trend of lower ADHDRS-IV-Inv symptoms for all participants who received dextroamphetamine (DEX and PAR/DEX groups) relative to those who did not receive dextroamphetamine (PAR and placebo groups) ($F = 3.51$, df = 1,94; p = .064; Table 1).

ADHD symptoms at 20 weeks were significantly lower among patients in the completer group who received dextroamphetamine (DEX and PAR/DEX) ($F = 6.694$, df = 1,58; p = .012).

There were no significant effects of PAR and no significant interactions between DEX and PAR in either the completer or ITT samples on endpoint ADHDRS-IV-Inv scores. Analysis of endpoint HAM-A and HAM-D data did not reveal significant treatment group interaction or main effects in either the completer or ITT samples.

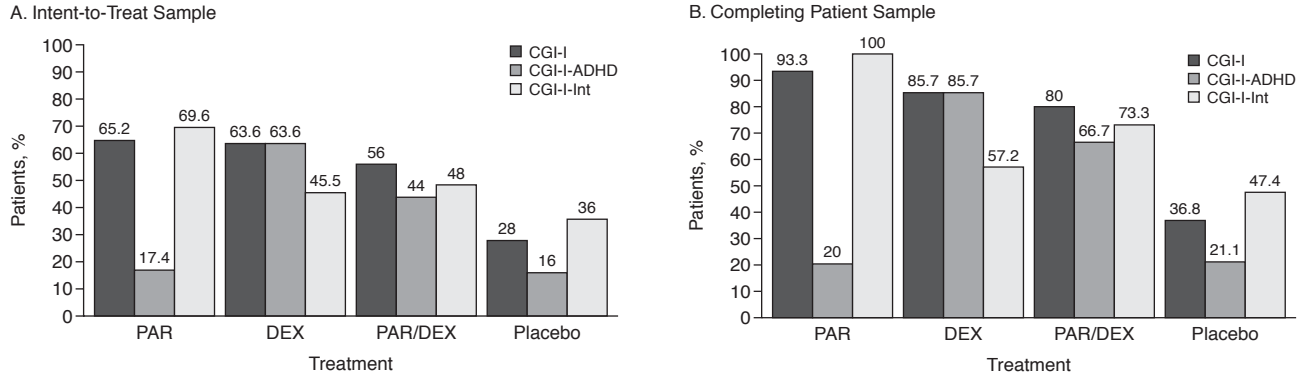
Completing patients who received dextroamphetamine (DEX and PAR/DEX) had significantly higher GAF ratings than patients who did not receive dextroamphetamine (PAR and placebo) ($F = 4.53$, df = 1,60; p = .037). This difference in GAF ratings was not apparent in the ITT sample.

Table 1. Results of Factorial Analyses of Endpoint Measures in Adult Attention-Deficit/Hyperactivity Disorder (ADHD) Patients

Measure	PAR[a] Mean (SD)	DEX[b] Mean (SD)	PAR/DEX[c] Mean (SD)	Placebo[d] Mean (SD)	p Value: PAR and PAR/DEX vs DEX and Placebo	p Value: DEX and PAR/DEX vs PAR and Placebo	p Value: Interaction
ADHDRS-IV-Inv							
ITT	24.71 (9.47)	20.78 (9.65)	19.52 (10.07)	23.50 (12.14)	.99	.06	.56
CC	23.73 (9.56)	16.83 (8.18)	16.93 (10.02)	23.55 (11.51)	.96	.01	.99
HAM-A							
ITT	7.29 (4.60)	9.17 (7.80)	8.28 (7.36)	7.69 (4.47)	.60	.33	.85
CC	5.73 (4.43)	8.27 (6.69)	7.07 (6.69)	7.15 (3.51)	.35	.38	.94
HAM-D							
ITT	4.83 (4.26)	7.56 (7.25)	6.44 (6.71)	6.00 (3.29)	.31	.16	.98
CC	3.60 (3.96)	7.00 (6.46)	5.40 (6.87)	5.30 (3.11)	.22	.19	.97
GAF							
ITT	61.04 (13.31)	60.00 (15.89)	62.88 (14.66)	58.88 (9.84)	.36	.59	.89
CC	66.93 (6.97)	68.71 (9.08)	69.60 (14.21)	60.05 (10.52)	.15	.04	.26

[a]Intent-to-treat condition (ITT): N = 24; Completer condition (CC): N = 15.
[b]ITT: N = 23; CC: N = 14 (sample size based on number of patients completing the trial; however, endpoint ADHDRS-IV-Inv data were not obtained from 2 patients, and endpoint HAM-A and HAM-D data were not obtained from 3 patients.
[c]ITT: N = 25; CC: N = 15.
[d]ITT: N = 26; CC: N = 20.
Abbreviations: ADHDRS-IV-Inv = ADHD Rating Scale for DSM-IV, investigator version, DEX = dextroamphetamine, GAF = Global Assessment of Functioning, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, PAR = paroxetine, PAR/DEX = paroxetine and dextroamphetamine combined.

Figure 1. Treatment Response in Adult ADHD Patients



Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGI-I = Clinical Global Impressions-Improvement scale, CGI-I-ADHD = CGI-I for ADHD symptoms, CGI-I-Int = CGI-I for mood and anxiety symptoms, DEX = dextroamphetamine, PAR = paroxetine, PAR/DEX = paroxetine and dextroamphetamine combined.

There was no significant difference between the treatment arms in the number of patients with current mood or anxiety disorders after treatment, either for completers or for the ITT sample.

Clinical Global Impressions of Patient Improvement

The CGI-I-ADHD scores for the ITT sample (Figure 1A) showed statistically significant benefit for participants who received dextroamphetamine (DEX and PAR/DEX) ($\chi^2 = 15.975$, df = 3,95; $p < .001$). The percentage of participants rated as treatment responders (much or very much improved on CGI) for ADHD in the ITT group were DEX: 64%, PAR/DEX: 44%, PAR: 17%, and placebo: 16%. Similarly, for completers (Figure 1B) there were significantly more ADHD treatment responders among patients receiving dextroamphetamine ($\chi^2 = 20.309$, df = 3,63; $p < .001$). The percentage of participants rated as responders in the completer group were DEX: 86%, PAR/DEX: 67%, PAR: 20%, and placebo: 21%.

Clinicians rated more of the completing patients as CGI-I-Int responders (much or very much improved for mood/anxiety symptoms on CGI) if they received paroxetine (PAR: 100%, PAR/DEX: 73%, DEX: 57%, and placebo: 47%) ($\chi^2 = 11.78$, df = 3,63; $p = .003$). In the ITT group, paroxetine alone was associated with the highest proportion of CGI-I-Int responders, but this difference was not statistically significant (PAR: 70%, PAR/DEX: 48%, DEX: 46%, and placebo: 36%).

Analysis of clinician ratings of overall global improvement (CGI-I) showed significantly more treatment responders within the active medication treatment conditions than within the placebo conditions for the ITT sample ($\chi^2 = 8.728$, df = 3,95; p = .033) and for the completer sample ($\chi^2 = 16.604$, df = 3,63; p = .001).

Safety

Eighty-three percent of participants reported at least 1 adverse event during the course of the study. There was no statistically significant difference between medication groups in the numbers of participants who discontinued due to adverse events (PAR: N = 6, DEX: N = 3, PAR/DEX: N = 7, and placebo: N = 2) ($\chi^2 = 4.662$, df = 3,98; p = .198) or in the mean number of adverse events per participant (F = 2.121, df = 3,90; p = .103). Adverse events were generally reported to be mild or moderate. Significantly more severe adverse events (a side effect that interferes with functioning or requires a change in treatment, e.g., anger, irritability, insomnia, headache, sexual dysfunction) were reported in the PAR/DEX treatment group ($\chi^2 = 18.662$, df = 9,471; p = .028), and of these many were psychiatric in nature.

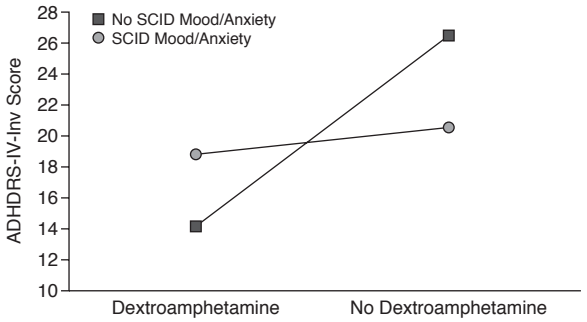
Clinically and statistically significant decreases in body weight from baseline to endpoint were evident for the DEX (3 kg) (t = 4.354, df = 21, p < .001) and PAR/DEX (1.7 kg) (t = 3.422, df = 24, p = .002) groups. Minor but statistically significant weight gain of approximately 1.3 kg was evident for the PAR treatment group (t = 2.248, df = 21, p = .035). The PAR/DEX treatment group showed increased pulse (9.8 bpm) relative to baseline (t = 4.325, df = 24, p < .001) but no change in blood pressure. There was a statistically significant decrease in diastolic blood pressure in the placebo group (t = 2.136, df = 23, p = .044).

Outcome in Patients With Lifetime Internalizing Disorders

A post hoc analysis was done to determine whether the presence of a SCID lifetime diagnosis of internalizing disorder moderated response to dextroamphetamine or paroxetine treatment. Since more than half the sample met this criterion, and since we did not find any differential effect of paroxetine on internalizing symptoms for the sample as a whole, the question arose as to whether these results might be different for patients who had demonstrated vulnerability to internalizing disorders. We also wanted to determine whether internalizing symptoms might moderate response to dextroamphetamine since this has not been done previously.

For the completing patient sample, presence of a SCID lifetime internalizing disorder did not differentially alter response on any outcome measure for patients who received paroxetine versus those who received no paroxetine. Presence of a lifetime internalizing disorder on the SCID did attenuate the response to dextroamphetamine as measured by the ADHD-RS. On the ADHDRS-IV-Inv (Figure 2), patients with a lifetime SCID internalizing disorder had lower response to dextroamphetamine than did patients with no internalizing diagnosis (F = 4.33, df = 1,58; p = .042). This pattern of results was also true for dimensional values of the CGI-I-ADHD (F = 4.37, df = 1,59; p = .041). Evidence for a moderating effect of lifetime SCID internalizing disorder was not evident in the ITT sample.

Figure 2. Moderator Analysis of the Response to Dextroamphetamine by Lifetime History of a SCID Internalizing Diagnosis



Abbreviations: ADHDRS-IV-Inv = Attention-Deficit/Hyperactivity Disorder Rating Scale for DSM-IV, investigator version; SCID = Structured Clinical Interview for DSM-IV.

DISCUSSION

This study investigated the intermediate-term outcome of dextroamphetamine and/or paroxetine in adults with ADHD. Patients who remained on stimulant medication had a statistically significant improvement in ADHD symptoms versus those who were randomly assigned to paroxetine or placebo. There was no improvement in ADHD symptoms with paroxetine. Mood/anxiety symptoms on the Hamilton scales were low to start with and did not show differential response with treatment.

Clinician ratings identified a significantly larger proportion of ADHD responders (CGI-I-ADHD) in patients who received dextroamphetamine and a significantly larger proportion of mood/anxiety responders (CGI-I-Int) among patients who received paroxetine. Overall clinician ratings of treatment response (CGI-I) showed a greater number of responders among patients who received any medication than those who received placebo.

The clinical characteristics of the population as determined by the SCID were consistent with what has been demonstrated in other studies that have looked at levels of current comorbid depressive and anxiety disorders.[28] One third of the study sample met SCID criteria for a current mood/anxiety disorder. What was unique in this study,

however, was the examination of the comorbid internalizing outcomes typical of an ADHD clinical trial population. Generally, the focus is placed exclusively on outcome of the primary disorder and not comorbid or associated mood and anxiety symptoms. If we had included patients who definitely needed treatment with an antidepressant or anxiolytic, we suspect that we would have had Hamilton scales scores in the clinical range and greater response to paroxetine.

It should be noted that ADHD patients complain of problems that may be perceived as falling within the internalizing spectrum such as difficulties with sleeping,[29] dysregulated appetite,[30–33] agitation, moodiness, edginess, lack of motivation, procrastination, perseveration, problems with memory, difficulty reading, reactivity, temper outbursts, poor self-esteem, difficulty concentrating, careless mistakes, and mood lability.[34] This study found that when a population is selected for ADHD as the primary diagnosis, excluding internalizing disorders of sufficient severity to require treatment in their own right and excluding patients who are currently on treatment for these disorders, significant residual internalizing difficulties remain.

The baseline values of the HAM-A and HAM-D were low enough that we most likely encountered a floor effect in showing a statistically significant difference between treatments. Previous studies have demonstrated that there are significant limitations to the Hamilton scales,[35,36] and the present findings strongly suggest that the Hamilton scales are sensitive neither to the subjective associated mood and anxiety problems experienced by ADHD patients nor to the way in which patients experience improvement when they take SSRIs. Our data do suggest that the Hamilton scales were insensitive in our population; those with SCID diagnoses had scores that were only slightly above those who did not. A recent psychometric evaluation of the Hamilton scales[36] has emphasized significant deficits in these scales' sensitivity to the cognitive aspects of internalizing symptoms as well as their usage of anchor points that are inappropriate to a nondepressed sample. This study may therefore have failed to find an effect that would have been manifest if a more appropriate scale had been used.

Despite the absence of a statistically significant effect on the Hamilton symptom scales scores, 100% of completing patients who received paroxetine were described by their clinicians as responders in the mood/anxiety domain. The percentage of patients who were considered responders in the mood/anxiety domain was significantly lower among those who did not take paroxetine. The discrepancy in the results between the Hamilton scales and the CGI suggests that the mood and anxiety disorder symptoms present in patients with ADHD are not identified by the Hamilton scales but are reported by patients and are seen as clinically significant on the CGI by the clinician. This finding on the CGI would need to be confirmed by other studies using scales that tap the affective symptoms of which ADHD patients complain. It further remains to be determined whether this improvement is clinically meaningful, which could be accomplished by looking at other dimensions of outcome such as patient functioning and quality of life.

Patients who received both paroxetine and stimulant showed clinical improvement in both ADHD and internalizing domains, but the difference between the combined treatment and the monotherapy was not dramatic. Furthermore, the combined treatment group showed slightly lower improvement in ADHD symptoms than those who received dextroamphetamine alone and slightly lower improvement in internalizing symptoms than those who received paroxetine alone. While combined treatment may offer a broader spectrum of response, this outcome may come at the cost of greater adverse events. The combined group had more severe adverse events than the other treatment arms, many of which were psychiatric in nature. These adverse events most likely limited further dose increases, since the patients in the combined group tolerated lower doses than those who received monotherapy. This may explain why combined treatment was associated with clinical response in both ADHD and internalizing symptoms but slightly lower symptom response in each dimension than monotherapy for one or the other disorder.

There have been clinical reports of dysphoria, nervousness, insomnia, and decreased appetite with dextroamphetamine[37] and behavioral activation and suicidal ideation with paroxetine.[38–42] Thus, while ADHD symptoms may be decreased in the combined medication treatment group, activating effects of paroxetine may counterbalance the benefits of dextroamphetamine. Similarly, whereas internalizing symptoms may be decreased in the combined medication treatment group, dysphoric effects of dextroamphetamine may counterbalance the benefits of paroxetine.

Although psychological treatment was included to facilitate patient retention and to justify inclusion of patients taking placebo in an intermediate outcome study, patients who received psychological treatment and placebo did benefit significantly over time. Nonetheless, this study demonstrated a higher number of responders on overall CGI scores with medication plus psychotherapy than with placebo plus psychotherapy.

A post hoc analysis was done to see whether our findings could be explained by the presence or absence of a lifetime SCID internalizing disorder. The clinicians' perception that patients on paroxetine treatment showed improvement in subjective mood and anxiety was no different in those with or without SCID diagnoses. This finding suggests that this response is not based on secondary internalizing symptoms but represents an improvement in patients that is outside the core ADHD symptoms but cor-

related to the ADHD diagnosis itself. Of interest is that those patients who had a history of a mood or anxiety disorder did less well on dextroamphetamine treatment.

Limitations

In this study, we attempted to follow a randomized sample for 5 months. We included psychological treatment as an incentive to stay in the study as well as to justify that patients on placebo or paroxetine treatment (neither of which has demonstrated efficacy for ADHD) would receive benefit from participation. This design had 2 major limitations. First, we anticipated a 20% discontinuation and had a 35% discontinuation. Most patients discontinued treatment because of adverse events or lack of efficacy. This compromised the ITT analysis since differences between treatments were minimized by the large number of patients who were no longer in treatment. Although clinical trials may have problems with retention that are not present in clinical practice, and vice versa, recent studies of persistence with stimulant treatment in children indicate that less than half of patients are still taking medication 4 months later,[43] and only 11% persist with medication at longer-term follow up.[44] Our retention rate may be better than what is seen in clinical practice and suggests that a pharmacoepidemiologic study of persistence with treatment in adults with ADHD would be valuable.

The results of the combined medication treatment need to be understood in the context of both medications being titrated blindly as well as administered at the same time, rather than sequentially. The interpretation of both benefit and side effects is only applicable to the fixed titration schedule used in this study and may have been different if participants were titrated naturalistically or sequentially using a flexible dose design. Doses in the PAR/DEX group were significantly lower. This, however, was a function of the treatment itself, in that higher titration was limited by both side effects and clinicians blind to the treatment condition.

Dextroamphetamine was dosed twice a day, and, since the duration of action of this medication is 5 to 6 hours, we anticipate that this offered approximately 12 hours of coverage. However, it should be noted that many adults with ADHD are now treated with long-duration stimulants, which offer more consistent coverage.

The study was powered to detect a large effect size based on the large effect sizes typically seen in placebo-controlled studies of dextroamphetamine and paroxetine. The power calculation did not account for the effect of the psychotherapy, which proved more helpful than had been anticipated, and minimized our capacity to show differences between different medications and between medication and placebo. No conclusions can be made about the results that would have been found in a study in which psychotherapy had not been included.

Clinical Implications

The clinical implications of these findings are that physicians need to ask patients presenting with affective symptoms about ADHD, for, if present, ADHD symptoms do not respond to SSRIs alone. Equally important, however, is to raise awareness that physicians need to ask patients presenting with ADHD about internalizing symptoms. They should additionally determine if depression or anxiety is present and whether or not it resolves with treatment with stimulants alone. Our data suggest that a history of comorbid internalizing disorders may be a predictor of diminished responsiveness of ADHD symptoms to stimulants. Previous studies have tried to control for comorbid internalizing symptoms using the Hamilton scales, but this study suggests that a lifetime SCID diagnosis may be a better way to identify patients who may show compromised response to treatment of ADHD. The clinicians in this study saw improvement when they treated patients with paroxetine. This finding implies that when physicians start SSRI medication in patients with ADHD, even in the absence of a DSM internalizing diagnosis, they may see improvement that may lead them to continue the prescription. More research is needed to explore response of ADHD and atypical symptoms to treatment in patients both with and without internalizing problems.

Drug names: dextroamphetamine (Dexedrine, Dextrostat, and others), paroxetine (Paxil, Pexeva, and others).

Financial disclosure: Dr. Weiss is a consultant to and has served on the speakers or advisory boards for Novartis, Eli Lilly, Purdue, Shire, and Janssen; has received grant/research support from Canadian Institute of Health Research, Human Early Learning Project, Eli Lilly, Janssen, and Shire; and has received honoraria from Cephalon, Psych CME, and Haymarket. Dr. Hechtman serves as a consultant to Eli Lilly, Janssen-Ortho, Shire, and Purdue; has received grant/research support from Eli Lilly, Janssen-Ortho, GlaxoSmithKline, and Purdue; has received honoraria from and served on the speakers or advisory boards for Eli Lilly, Janssen-Ortho, Shire, and Purdue; and has received other financial or material support from Shire. Dr. Conners has served on the speakers or advisory boards for Shire, Eli Lilly, and McNeil. Dr. Looper has received honoraria from Wyeth. Dr. Jain has received grant/research support from GlaxoSmithKline. Dr. Brown is a consultant to Eli Lilly, McNeill, Novartis, and Shire; has received grant/research support from Eli Lilly, GlaxoSmithKline, and McNeill; has served as a speaker for Eli Lilly, Janssen Cilag, McNeill, Shire, and Wyeth; and has received other financial or material support from American Psychiatric Press, Psychological Corporation, and Yale University Press. Drs. Johnson, Greenfield, Ochs, Wasdell, Bomben, Murray, Quinlan, and Guthrie report no other significant commercial relationships relevant to the study.

Acknowledgments: Members of the Adult ADHD Research Group are C. Keith Conners, Ph.D., Diane Johnson, Ph.D., Department of Psychiatry, Duke University Medical Center, Durham, N.C.; Brian Greenfield, M.D., Karl Looper, M.D., Eric Ochs, Ph.D., Department of Psychiatry, McGill University, Montreal, Quebec, Canada; Michael Wasdell, M.A., Melissa Bomben, M.S., Candice Murray, Ph.D., Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada; Umesh Jain, M.D., University of Toronto, Centre for Addiction & Mental Health, Toronto, Ontario, Canada; Thomas E. Brown, Ph.D., Donald M. Quinlan, Ph.D., Department of Psychiatry, Yale University, New Haven, Conn.; and Donald Guthrie, Ph.D., Private Consultant.

REFERENCES

1. Kessler R. Prevalence of adult ADHD in the United States: results from the National Comorbidity Survey Replication (NCS-R). Psychol Med. In press
2. Shekim WO, Asarnow RF, Hess E, et al. A clinical and demographic profile of a sample of adults with attention deficit hyperactivity disorder, residual state. Compr Psychiatry 1996;31:416–425
3. Murphy KR, Barkley RA. Prevalence of DSM-IV symptoms of ADHD in adult licensed drivers. J Atten Disord 1996;1:147–162
4. Marks DJ, Newcorn JH, Halperin JM. Comorbidity in adults with attention-deficit/hyperactivity disorder. Ann N Y Acad Sci 2001; 931:216–238
5. Pliszka SR. Comorbidity of attention-deficit/hyperactivity disorder with psychiatric disorder: an overview. J Clin Psychiatry 1998;59 (suppl 7):50–58
6. Wilens TE, Biederman J, Spencer TJ. Attention deficit/hyperactivity disorder across the lifespan. Annu Rev Med 2002;53:113–131
7. Biederman J, Faraone SV, Spencer T, et al. Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry 1993;150:1792–1798
8. Kessler RC, Adler LA, Barkley R, et al. Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: results from the national comorbidity survey replication. Biol Psychiatry 2005;57:1442–1451
9. Fones CS, Pollack MH, Susswein L, et al. History of childhood attention deficit hyperactivity disorder (ADHD) features among adults with panic disorder. J Affect Disord 2000;58:99–106
10. Safren SA, Lanka GD, Otto MW, et al. Prevalence of childhood ADHD among patients with generalized anxiety disorder and a comparison condition, social phobia [brief report]. Depress Anxiety 2001;13:190–191
11. Pliszka SR, Greenhill LL, Crismon ML, et al. The Texas Children's Medication Algorithm Project: Report of the Texas Consensus Conference Panel on Medication Treatment of Childhood Attention-Deficit/ Hyperactivity Disorder, pt 2: tactics: attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2000;39:920–927
12. Weiss M, Trokenberg Hechtman L, Weiss G. ADHD in Adulthood: A Guide to Current Theory, Diagnosis and Treatment. Baltimore and London: Johns Hopkins University Press; 1999
13. Gammon GD, Brown TE. Fluoxetine augmentation of methylphenidate attention deficit and comorbid disorders. J Child Adolesc Psychopharmacol 1993;3:1–10
14. Spencer T, Wilens T, Biederman J, et al. A double-blind, crossover comparison of methylphenidate and placebo in adults with childhood-onset attention-deficit hyperactivity disorder. Arch Gen Psychiatry 1995;52:434–443
15. Quist JF, Kennedy JL. Genetics of childhood disorders: XXIII: ADHD, pt 7: the serotonin system. J Am Acad Child Adolesc Psychiatry 2001; 40:253–256
16. Rauch SL. Neuroimaging and attention-deficit/hyperactivity disorder in the 21st century: what to consider and how to proceed. Biol Psychiatry 57:1261–1262
17. Giedd JN, Blumenthal J, Molloy E, et al. Brain imaging of attention deficit/hyperactivity disorder. Ann N Y Acad Sci 2001;931:33–49
18. Hawi Z, Dring M, Kirley A, et al. Serotonergic system and attention deficit hyperactivity disorder (ADHD): a potential susceptibility locus at the 5-HT(1B) receptor gene in 273 nuclear families from a multicentre sample. Mol Psychiatry 2002;7:718–725
19. Zoroglu SS, Erdal ME, Alasehirli B, et al. Significance of serotonin transporter gene 5-HTTLPR and variable number of tandem repeat polymorphism in attention deficit hyperactivity disorder. Neuropsychobiology 2002;45:176–181
20. Nakamura K, Kurasawa M. Serotonergic mechanisms involved in the attentional and vigilance task performance of rats and the palliative action of aniracetam. Naunyn Schmiedebergs Arch Pharmacol 2000; 361:521–528
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Press; 1994
22. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-I). Washington, DC: American Psychiatric Press; 1997
23. Conners CK, Epstein JN, Johnson D. Conners Adult ADHD Diagnostic Interview for Adults. North Tonawanda, NY: Multihealth Systems; 2001
24. Faries DE, Yalcin I, Harder D, et al. Validation of the ADHD rating scale as a clinician administered and scored instrument. J Atten Disord 2001; 5:39–47
25. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
26. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
27. National Institute of Mental Health. CGI (Clinical Global Impression Scale)-NIMH. Psychopharmacol Bull 1985;21:839–843
28. Spencer T, Biederman J, Wilens T, et al. A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:456–463
29. Cohen-Zion M, Ancoli-Israel S. Sleep in children with attention-deficit hyperactivity disorder (ADHD): a review of naturalistic and stimulant intervention studies. Sleep Med Rev 2004;8:379–402
30. Agranat-Meged AN, Deitcher C, Goldzweig G, et al. Childhood obesity and attention deficit/hyperactivity disorder: a newly described comorbidity in obese hospitalized children. Int J Eat Disord 2005;37:357–359
31. Altfas JR. Prevalence of attention deficit/hyperactivity disorder among adults in obesity treatment. BMC Psychiatry 2002;2:9
32. Holtkamp K, Konrad K, Muller B, et al. Overweight and obesity in children with attention-deficit/hyperactivity disorder. Int J Obes Relat Metab Disord 2004;28:685–689
33. Levitan RD, Masellis M, Lam RW, et al. Childhood inattention and dysphoria and adult obesity associated with the dopamine D4 receptor gene in overeating women with seasonal affective disorder. Neuropsychopharmacology 2004;29:179–186
34. Reimherr FW, Marchant BK, Strong RE, et al. Emotional dysregulation in adult ADHD and response to atomoxetine. Biol Psychiatry 2005;58: 125–131
35. Bagby RM, Ryder AG, Schuller DR, et al. The Hamilton Depression Rating Scale: has the gold standard become a lead weight? Am J Psychiatry 2004;161:2163–2177
36. Zimmerman M, Posternak MA, Chelminski I. Is it time to replace the Hamilton Depression Rating Scale as the primary outcome measure in treatment studies of depression? J Clin Psychopharmacol 2005; 25:105–110
37. Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry 2002;41:26S–49S
38. Carlson GA, Mick E. Drug-induced disinhibition in psychiatrically hospitalized children. J Child Adolesc Psychopharmacol 2003;13:153–163
39. Go FS, Malley EE, Birmaher B, et al. Manic behaviors associated with fluoxetine in three 12- to 18-year-olds with obsessive-compulsive disorder. J Child Adolesc Psychopharmacol 1998;8:73–80
40. Hoehn-Saric R, Harris GJ, Pearlson GD, et al. A fluoxetine-induced frontal lobe syndrome in an obsessive compulsive patient. J Clin Psychiatry 1991;52:131–133
41. Hoehn-Saric R, Lipsey JR, McLeod DR. Apathy and indifference in patients on fluvoxamine and fluoxetine. J Clin Psychopharmacol 1990; 10:343–345
42. Weiss M, Walkup J, Garland EJ. Stimulants and SSRIs. Child Adolesc Psychopharmacol News 1997;2:11–12
43. Miller AR, Lalonde CE, McGrail KM. Children's persistence with methylphenidate therapy: a population-based study. Can J Psychiatry 2004;49:761–768
44. Bussing R, Zima BT, Mason D, et al. Use and persistence of pharmacotherapy for elementary school students with attention-deficit/ hyperactivity disorder. J Child Adolesc Psychopharmacol 2005;15:78–87