Long-Term, Open-Label Study of the Safety and Efficacy of Atomoxetine in Adults With Attention-Deficit/Hyperactivity Disorder: An Interim Analysis

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Background: Attention-deficit/hyperactivity disorder (ADHD) is an early-onset neuropsychiatric disorder that affects 3% to 7% of school-age children and 4% of adults. Its pathophysiology is thought to involve the dopaminergic and noradrenergic pathways associated with attention control and impulsivity. These symptoms have largely been defined in the childhood population, but the course of the condition and expression in the adult population are not as well characterized.

Method: This is an ongoing, 3-year, open-label study consisting of adults with DSM-IV ADHD who were previously enrolled in 1 of 2 double-blind, acute-treatment studies of atomoxetine. The results of the interim analysis reported here were derived from the study of 384 patients at 31 sites who had been studied for a period of up to 97 weeks. The primary efficacy measure was the Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV) total ADHD symptom score. In addition, safety, adverse events, and vital sign measurements were assessed.

Results: Significant improvement was noted with atomoxetine therapy, with mean CAARS-Inv:SV total ADHD symptom scores decreasing 33.2% from 29.2 (baseline of open-label therapy) to 19.5 (endpoint of open-label therapy) ($p < .001$). Similar and significant decreases were noted for the secondary efficacy measures. Adverse events consisted primarily of pharmacologically (noradrenergic) expected effects, such as increases in heart rate and blood pressure and a slight decrease in weight.

Conclusion: The results of this interim analysis of an ongoing, open-label study of adults with ADHD support the long-term efficacy, safety, and tolerability of atomoxetine for the treatment of adult ADHD.

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Attention-deficit/hyperactivity disorder (ADHD) is a common and impairing neuropsychiatric disorder affecting 3% to 7% of school-aged children[1] and 4% of adults.[2,3] Symptoms of ADHD include difficulty sustaining attention, forgetfulness, distractibility, hyperactivity, and problems with impulse control.[1] ADHD has been extensively studied in children,[3] but its persistence into adulthood was not recognized until the mid-1970s.[4] Symptoms of ADHD in adulthood are similar to those in childhood, except that overt hyperactivity becomes less pronounced, being manifested instead as a sense of inner restlessness.[5] The disorder can lead to substantial social, academic, and occupational impairment and is associated with increased familial stress and driving risks.[6]

The presumed pathophysiology of ADHD is an abnormality in central dopaminergic and noradrenergic tone,[7] and the only pharmacotherapies that have been shown to be effective in both children and adults have been those affecting these 2 neurotransmitters.[8,9] Pharmacotherapies shown to work in adults include stimulant medications, such as methylphenidate, pemoline, dextroamphetamine and mixed amphetamine salts, and antidepressants such as bupropion and desipramine.[9–11] The value of these trials for guiding clinical practice in adults, however, has been

limited by the short duration of systematic evaluation and treatment (only 1 study followed patients out to at least 1 year[12]) and the small numbers of patients treated in most studies.

The nonstimulant medication atomoxetine is a potent inhibitor of presynaptic norepinephrine transport and is generally free of effects on other noradrenergic receptors or other neurotransmitter receptors or systems (including direct dopaminergic, cholinergic, and serotonergic effects).[13] Atomoxetine has been shown to be effective in large-scale studies in children,[14–16] a preliminary study in adults,[17] and 2 recent large-scale, placebo-controlled, 10-week trials of acute atomoxetine therapy in adults.[18]

The ongoing efficacy and safety of ADHD pharmacotherapy is important, as ADHD is most commonly conceptualized as a chronic disorder. However, longer-term treatment data in adults are rather scant.[19] Thus, the purpose of the present study was to examine (1) overall response of ADHD symptoms to longer-term atomoxetine therapy, (2) possible effects of increasing length of atomoxetine treatment on ADHD symptoms, and (3) longer-term safety of atomoxetine therapy. We now report data from up to 97 weeks from this ongoing, open-label study in order to provide clinicians with the longest-term data available on the safety and efficacy of atomoxetine for adult ADHD. To our knowledge, these data represent the longest period of pharmacologic treatment yet studied in adults with ADHD.

METHOD

In this multicenter trial conducted at 31 sites in the United States and Canada, adults who met DSM-IV criteria for ADHD as determined by clinical history and confirmed by a structured interview were eligible to participate in either of 2 identical, 10-week, acute-treatment studies using atomoxetine. The design and results of these studies have been previously reported and are described in detail elsewhere.[18] At the end of the acute-treatment period, atomoxetine was either tapered over 4 weeks or stopped abruptly. Patients assigned to placebo continued taking placebo during this period. The tapering/abrupt discontinuation phase was a part of the study design for the double-blind trials and was included to determine if there was a withdrawal effect once atomoxetine was discontinued. This aspect of the study will not be elaborated upon further in the present article.

Patients who participated in the acute studies and wished to continue treatment (including those patients taking placebo) could enter an open-label continuation study in which all patients received atomoxetine. Overall, patients who opted to enter the open-label trial improved significantly more during acute treatment than those who did not ($p = .003$). Specifically, the mean (SD) change in the Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV)[20] total ADHD symptom score for patients who entered the extension study was –6.9 (9.6) for placebo patients and –11.0 (10.8) for atomoxetine patients. Conversely, for those patients who did not enter the extension study, the mean (SD) change in the total ADHD symptom score from the CAARS-Inv:SV was –4.3 (7.7) for placebo patients and –7.6 (9.3) for atomoxetine patients.

Atomoxetine was initiated in the acute studies at a dose of 30 mg/day b.i.d. and restarted at 25 mg b.i.d. on visit 1 in the open-label study. At the physician's discretion, a patient's dose was increased at any subsequent visit to 40 mg b.i.d. and further increased to 60 mg b.i.d. after at least 1 additional visit interval if the overall Clinical Global Impressions-Severity of Illness (CGI-S)[21] score was 2 or greater. Dosage was decreased using the same dose steps (for example, 60 mg b.i.d. to 40 mg b.i.d. to 25 mg b.i.d.) at any visit if needed for reasons of safety or tolerability. During the open-label portion of the study, the entire daily dose could be taken as a single daily dose or divided (equally or unequally). No more than 120 mg was taken at any single dose, and the maximum total daily dose did not exceed 160 mg/day. The study was designed such that patients were seen every other week for the first 4 visits, monthly for 4 visits, and then every 3 months for the duration of the study (up to 3 years). Assessments included the CAARS Inv:SV and Self-Rated (Self:SV) versions,[20] CGI-S,[21] 17-item Hamilton Rating Scale for Depression (HAM-D-17),[22,23] Hamilton Rating Scale for Anxiety (HAM-A),[24] Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS),[25] and Sheehan Disability Scale.[26]

Investigators assessed adverse events by open-ended questioning at each visit. In addition, a number of laboratory tests were performed to ensure patient safety. At visit 1, patients completed the following safety assessments: routine chemistry, hematology, and urinalysis tests and a thyroid-stimulating hormone test. These assessments were scheduled for approximately 3, 16, 27, and 36 months after the beginning of the study. Drug screens, pregnancy tests (female patients), and ethyl alcohol tests were required at visit 1 for all patients and at any other visit at the discretion of the investigator. A blood sample was drawn for cytochrome P450 2D6 (CYP2D6) genetic testing at visit 1 only if these data had not been collected in a previous study. A blood sample was drawn for pharmacokinetic analysis of plasma if a patient was found to have new-onset neurologic signs or symptoms at any visit following the initiation of study-drug therapy or if a patient experienced a serious adverse event or a clinically significant overdose. An electrocardiogram was completed within 30 days of visit 1 to ensure the availability of baseline data for safety monitoring. For patients who had laboratory assessments repeated at visit 1, administration of study drug could be delayed until those results were available.

Each site's institutional review board approved the conduct of the trial. Written informed consent was obtained after the procedures and purpose of the study were described to each patient. The study was conducted in accordance with the ethical standards of each of the investigative sites' institutional review boards and with the Declaration of Helsinki 1975, as revised in 2000.

Data Analysis

Data analysis examined treatment effects on the study sample from baseline of the open-label trial to the end of open-label treatment. The primary outcome variable was the 18-item CAARS-Inv:SV total ADHD symptom score. Each of the 18 items corresponds to 1 of the 18 DSM-IV symptoms for ADHD and is rated on a 4-point scale. Secondary outcome variables were CAARS-Inv:SV ADHD subscale scores (inattentive and hyperactive/impulsive), CAARS-Self:SV total ADHD symptom and subscale scores, CGI-S, HAM-A, and HAM-D-17 total scores, WRAADDS total scores, and Sheehan Disability Scale subscale (total, work, family, social) scores.

These analyses included all patients with a baseline and at least 1 postbaseline measurement. Safety analysis included all patients who took at least 1 dose of study drug. All efficacy and safety analyses of continuous measures were performed using a last-observation-carried-forward approach to compare mean change values from baseline to endpoint using a paired t test. In addition, for the primary efficacy variable, a repeated-measures analysis was performed with effects for investigator, visit, and baseline in the model. All tests were performed using a 2-sided significance level of .05.

RESULTS

Patient flow throughout the trials was as follows: 536 patients were randomly assigned to treatment with atomoxetine or placebo in the initial acute trials,[18] and of these 536 patients, 385 (71.8%) entered the open-label continuation treatment study. All patients in the acute studies were given the opportunity to roll over into the open-label study. Therefore, continuing into the open-label study was not dependent on a patient completing or responding to treatment in the acute studies. Of these 385 patients, 1 patient never took a dose of atomoxetine in the continuation study and was excluded from all analyses, making a total of 384 patients whose results are reported here.

At the end of the acute treatment period, atomoxetine was either tapered over 4 weeks (N = 88, 22.9%) or stopped abruptly (N = 76, 19.8%). Patients assigned to placebo (N = 185, 48.2%) continued taking placebo during this period. (Note that 35 [9.1%] of the 384 patients rolled into the open-label trial without entering the discontinuation period of the double-blind studies.)

Table 1. Demographic Characteristics of Adults With ADHD Receiving Open-Label Atomoxetine Therapy (N = 384)

Characteristic	Value
Male, N (%)	246 (64.1)
Female, N (%)	138 (35.9)
Age, mean (SD), y	42.4 (11.2)
Prior stimulant exposure, N (%)	180 (46.9)
Origin, N (%)	
White	354 (92.2)
Hispanic	14 (3.6)
African American	8 (2.1)
Eastern Asian	4 (1.0)
Western Asian	2 (0.5)
Other	2 (0.5)
ADHD subtype, N (%)	
Combined	260 (67.7)
Inattentive	117 (30.5)
Hyperactive/impulsive	7 (1.8)

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Patient characteristics for those receiving open-label atomoxetine therapy (N = 384) are summarized in Table 1. Characteristics of patients in the open-label studies were similar to those of patients in the double-blind studies (Table 2). However, mean baseline CAARS-Inv:SV total ADHD symptom score and CGI-S score were lower for the open-label trial than for the double-blind studies. This was expected because patients rolled into the open-label trial with up to 10 weeks of double-blind therapy.

At the time of the analysis reported here, 259 patients (67.4%) had discontinued from the study (Table 3). The mean length of treatment was 40 weeks, with a maximum length of open-label atomoxetine therapy of 97 weeks. Of the 373 patients with at least 1 postbaseline rating and at least 2 weeks of treatment, 94 (25.2%) were on therapy for ≤ 10 weeks (a fairly standard duration of therapy of acute-treatment trials in adult ADHD), 87 (23.3%) for > 10 to 24 weeks, 39 (10.5%) for > 24 to 48 weeks, 39 (10.5%) for > 48 to 72 weeks, and 114 (30.6%) for > 72 weeks.

Reasons for discontinuation are noted in Table 3. Of the 96 patients (25.0%) who reportedly discontinued due to lack of efficacy, 58 (60.4%) showed improvement in CAARS-Inv:SV total ADHD symptom scores, 5 (5.2%) experienced no change, and 33 (34.4%) worsened. Of the 58 subjects who showed improvement but reportedly discontinued due to lack of efficacy, 35 (60.3%) experienced a 20% improvement, 30 (51.7%) experienced a 25% improvement, and 23 (39.7%) experienced a 30% improvement. (Note that patients who discontinued due to perceived lack of efficacy were included in subsequent analyses if they received at least 1 post–open-label atomoxetine therapy rating.) There was, however, a significant difference between those patients who discontinued due to lack of efficacy and those who did not. Those who discontinued due to lack of efficacy had lower mean change in CAARS total ADHD symptom scores (mean [SD] = –4.1 [9.9]) compared with those who did not dis-

Table 2. Comparison of Double-Blind and Open-Label Studies of Atomoxetine for Adult ADHD: Patient Characteristics and Baseline Test Scores

Characteristic	Double-Blind Study 1		Double-Blind Study 2		Open-Label Atomoxetine Study
	Atomoxetine (N = 141)	Placebo (N = 139)	Atomoxetine (N = 129)	Placebo (N = 127)	(N = 384)
Sex, N (%)					
Male	91 (64.5)	87 (62.6)	83 (64.3)	87 (68.5)	246 (64.1)
Female	50 (35.5)	52 (37.4)	46 (35.7)	40 (31.5)	138 (35.9)
Origin, N (%)					
White	124 (87.9)	121 (87.1)	124 (96.1)	118 (92.9)	354 (92.2)
Other	17 (12.1)	18 (12.9)	5 (3.9)	9 (7.1)	30 (7.8)
Age, mean (SD), y	40.2 (11.7)	40.3 (11.6)	43.0 (10.3)	41.2 (11.2)	42.4 (11.2)
ADHD subtype, N (%)					
Combined	101 (71.6)	100 (71.9)	80 (62.0)	75 (59.1)	260 (67.7)
Inattentive	39 (27.7)	38 (27.3)	46 (35.7)	44 (34.6)	117 (30.5)
Hyperactive/impulsive	1 (0.7)	1 (0.7)	3 (2.3)	8 (6.3)	7 (1.8)
Previous stimulant exposure, N (%)	62 (44.0)	68 (48.9)	65 (50.4)	55 (43.3)	180 (46.9)
CAARS-Inv:SV total ADHD symptom score, mean (SD)	33.6 (7.2)	33.2 (7.8)	34.9 (6.9)	34.2 (7.5)	29.1 (11.4)
CGI-S score, mean (SD)	4.7 (0.8)	4.7 (0.7)	4.6 (0.6)	4.6 (0.7)	4.3 (1.1)

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CAARS-Inv:SV = Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version, CGI-S = Clinical Global Impressions-Severity of Illness scale.

Table 3. Patient Disposition Through an Open-Label Study of Atomoxetine for Adult ADHD

Characteristic	Value
Patients entering open-label study, N	385
Patients receiving atomoxetine, N	384
Continuing open-label study after 97 weeks, N (%)	125 (32.6)
Reason for discontinuation, N (%)	
Lack of efficacy	96 (25.0)
Adverse event	42 (10.9)
Protocol violation	11 (2.9)
Other (lost to follow-up, etc.)	110 (28.6)

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

continue due to lack of efficacy (mean [SD] = –11.6 [12.7]; $p < .001$). Baseline characteristics for these 2 groups did not differ, but baseline scores did. Mean baseline CAARS total ADHD symptom score for subjects who discontinued due to lack of efficacy was higher (mean = 31.3, SD = 9.9) than for those patients who did not (mean = 28.4, SD = 11.8, $p = .027$). Likewise, mean baseline CGI-S score for subjects who discontinued due to lack of efficacy was higher (mean = 4.6, SD = 1.0) than for those patients who did not (mean = 4.2, SD = 1.1, $p < .001$).

The maximum final dose allowed in the open-label study (160 mg/day) was somewhat higher than in the acute studies (120 mg/day). Thus, in the open-label study, the mean final dose was 98.6 mg/day with a median final dose of 120 mg/day, compared to the acute studies, for which the mean final dose was 94.3 mg/day with a median final dose of 90 mg/day.

Primary Efficacy Analyses

Significant improvement occurred with atomoxetine open-label therapy (Table 4), with mean CAARS-Inv:SV total ADHD symptom scores decreasing 33.2% from 29.2 at baseline to 19.5 at endpoint ($p < .001$). In addition, the repeated-measures analysis showed significant improvement in CAARS-Inv:SV total ADHD symptom scores over time ($p < .001$). Similar significant change from baseline to endpoint decreases were noted on the CAARS-Inv:SV subscales, WRAADDS, Sheehan Disability Scale, and CGI-S scores. No effects were seen on the HAM-A scores (Table 4).

Additional Analyses

Significant improvement was also noted on all Sheehan Disability Scale subscale scores (total, family, social, and work). Sheehan Disability Scale total and family scores improved 26%, social scores improved 27%, and work scores improved 25% (Table 4). A slight increase (mean change = 0.6) was noted in HAM-D-17 scores, which was statistically significant ($p = .018$). It is not likely that this change has any clinical relevance, given the small magnitude of the difference and the overall low level of depression in the sample.

Safety Analyses

During open-label therapy, the pattern and frequency of adverse events were consistent with those observed during the acute studies,[18] consisting primarily of pharmacologically expected (noradrenergic) effects (Table 5), increased heart rate (mean change = 5.1 beats/minute), increased systolic and diastolic blood pressure (mean change for each < 2.0 mm Hg), and a mean decrease in weight of 1.3 kg (Table 6). The discontinuation rate due to adverse events during open-label therapy was 10.9%, whereas that observed during the acute studies was 8.5%. There were no clinically significant changes in laboratory

Table 4. Symptom Improvement Measures in an Open-Label Study of Atomoxetine for Adult ADHD[a]

Measure	N	Baseline, Mean (SD)	Endpoint, Mean (SD)	Change, Mean (SD)	p Value
CAARS-Inv:SV					
Total ADHD symptom	372	29.2 (11.5)	19.5 (10.6)	–9.7 (12.5)	< .001
Inattentive subscale	372	16.4 (6.5)	11.4 (6.5)	–4.9 (6.9)	< .001
Hyperactive/impulsive subscale	372	12.8 (6.4)	8.1 (5.1)	–4.7 (6.3)	< .001
CGI-Severity of Illness	372	4.3 (1.1)	3.2 (1.3)	–1.1 (1.3)	< .001
CAARS-Self:SV					
Total ADHD symptom	327	29.3 (10.8)	21.0 (10.8)	–8.2 (10.6)	< .001
Inattentive subscale	327	16.5 (6.2)	12.2 (6.5)	–4.4 (5.9)	< .001
Hyperactive/impulsive subscale	329	12.8 (6.0)	8.9 (5.4)	–3.8 (5.3)	< .001
WRAADDS	335	14.9 (6.2)	10.0 (6.2)	–4.9 (6.4)	< .001
HAM-A	340	6.2 (4.6)	6.5 (5.4)	0.3 (5.1)	.343
HAM-D-17	338	4.8 (3.9)	5.4 (4.8)	0.6 (4.6)	.018
Sheehan Disability Scale					
Total	333	15.0 (7.2)	11.1 (7.8)	–3.9 (7.9)	< .001
Work subscale	333	5.2 (2.8)	3.8 (2.9)	–1.3 (3.1)	< .001
Family subscale	333	5.4 (2.7)	4.0 (2.8)	–1.4 (2.9)	< .001
Social subscale	333	4.5 (2.7)	3.3 (2.8)	–1.2 (2.9)	< .001

[a]Based on data from baseline of open-label study through endpoint of open-label study. On all scales, lower scores indicate improvement.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CAARS-Inv:SV = Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version, CGI = Clinical Global Impressions scale, HAM-A= Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, Self:SV = Self-Rated: Screening Version, WRAADDS = Wender-Reimherr Adult Attention Deficit Disorder Scale.

Table 5. Adverse Events Reported by at Least 5% of Adult Subjects With ADHD Treated With Atomoxetine (N = 382)

Event	N (%)
Dry mouth	92 (24.1)
Headache	81 (21.2)
Insomnia	71 (18.6)
Erectile dysfunction[a]	40 (16.4)
Nausea	57 (14.9)
Constipation	53 (13.9)
Dyspepsia	36 (9.4)
Nasopharyngitis	36 (9.4)
Upper respiratory tract infection	33 (8.6)
Urinary hesitation	32 (8.4)
Irritability	31 (8.1)
Back pain	30 (7.9)
Fatigue	29 (7.6)
Dizziness	28 (7.3)
Arthralgia	27 (7.1)
Sinusitis	26 (6.8)
Appetite decreased	23 (6.0)
Abnormal dreams	22 (5.8)
Cough	22 (5.8)
Libido decreased	22 (5.8)
Anxiety	21 (5.5)
Pharyngitis	21 (5.5)
Middle insomnia	19 (5.0)

[a]Percentage computed from male subjects (N = 244).
Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Table 6. Vital Signs of Adults With ADHD Treated With Atomoxetine (N = 373)

Vital Sign	Baseline, Mean (SD)	Endpoint, Mean (SD)	Change, Mean (SD)	p Value
Heart rate, bpm	73.4 (10.2)	78.5 (11.3)	5.1 (11.2)	< .001
Diastolic BP, mm Hg	77.6 (8.7)	78.8 (9.7)	1.2 (8.9)	.012
Systolic BP, mm Hg	120.7 (11.5)	122.5 (12.9)	1.8 (11.4)	.002
Weight, kg	84.1 (18.8)	82.8 (18.8)	–1.3 (4.2)	< .001

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BP = blood pressure, bpm = beats per minute.

measures and no clinically relevant changes in QTc (Fridericia) during the open-label trial.

DISCUSSION

This report presents an interim analysis of the findings of an ongoing 3-year evaluation of the effects of atomoxetine in adult ADHD. The data reported here, consisting of up to 97 weeks of open-label treatment with atomoxetine, represent the longest systematic evaluation of any medication therapy in adult ADHD reported to date and support the long-term efficacy of atomoxetine in adult ADHD. Long-term atomoxetine treatment was well tolerated, as the discontinuation rate from adverse events was 10.9% during the open-label study following a discontinuation rate of 8.5% in the acute trials. Significant improvement was seen on all measures of ADHD symptoms (CAARS-Inv:SV and -Self:SV, WRAADDS, Sheehan Disability Scale, and CGI-S) with open-label atomoxetine treatment, and effects on subtypes of ADHD symptoms (inattentive vs. hyperactive/impulsive) were similar. Furthermore, repeated-measures analysis indicated continued improvement throughout the study.

The significant effect seen with CGI-S scores is consistent with improvement in global functioning documented by the Sheehan Disability Scale results. Increased functionality in work, family, and social domains was

noted in the highly significant change in ratings on the Sheehan Disability Scale total and subscale scores. Although these findings may be exaggerated due to the open nature of the study, they may represent important features of improvement of day-to-day functioning of adults who receive atomoxetine therapy. These findings are consistent with improved academic, family, and social function documented in the pediatric trial of atomoxetine.[14]

Atomoxetine was generally well tolerated, and no unexpected adverse events or side effects were noted, as was expected from the acute studies. However, at the time of this interim investigation, 7 patients had experienced a serious adverse event during the open-label trial, although none were considered related to study drug by the investigator. Because one quarter of the patients were reported as discontinuing due to lack of efficacy, further evaluation was initiated to investigate whether or not these patients who discontinued showed improvement on the CAARS-Inv:SV total ADHD symptom score, the primary efficacy measure in the study. The results indicated that the majority (60.4%) of these patients actually improved at endpoint, possibly indicating either that they were classified incorrectly or that improvement on efficacy measures might not necessarily correlate with perceived improvement.

Significant symptom improvement was noted during both the acute studies as well as the open-label study. Atomoxetine has been shown to be effective during both acute (10 weeks)[18] and longer-term (up to 97 weeks) therapy. Data from this long-term, open-label trial provide information on the beneficial effects of atomoxetine and its use in adult ADHD. As this is an ongoing study, further results will be disclosed in a future report.

Drug names: amphetamine (Adderall and others), atomoxetine (Strattera), bupropion (Wellbutrin and others), desipramine (Norpramin and others), dextroamphetamine (Dexedrine, Dextrostat, and others), methylphenidate (Metadate, Ritalin, and others), pemoline (Cylert and others).

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