Atomoxetine and Adult Attention-Deficit/Hyperactivity Disorder: The Effects of Comorbidity

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Objective: The objective of this study was to determine if measures of broad clinical psychopathology or neuropsychological performance could aid in the prediction of therapeutic response to the highly selective norepinephrine transporter inhibitor, atomoxetine, among adults with attention-deficit/hyperactivity disorder (ADHD).

Method: We analyzed data from 2 double-blind, placebo-controlled, parallel design studies of adult patients (Study I, N = 280; Study II, N = 256) with DSM-IV–defined ADHD who were recruited by referral and advertising. Subjects were randomly assigned to 10 weeks of treatment with atomoxetine or placebo and were assessed with Conners' Adult ADHD Rating Scales (CAARS), the General Well-Being Schedule (GWB), the Sheehan Disability Scale, the Stroop Color-Word Test (SCWT), and the Structured Clinical Interview for DSM-IV (SCID) before and after treatment.

Results: Therapeutic improvement on atomoxetine as evidenced by reduced CAARS scores was reliably predicted by the presence of a lifetime comorbid diagnosis of depression or posttraumatic stress disorder at baseline, while improvement on subscales of the GWB and Sheehan Disability Scale were predicted by these and other SCID endorsements, such as alcohol and substance use, as well as demographics such as age and gender. In light of the exploratory nature of this work and the many comparisons that were examined in the corresponding regression models, these findings should be regarded as tentative pending replication and extension in another dataset.

Conclusion: From these findings, we conclude that the variable responsiveness of individuals to atomoxetine cannot be largely accounted for by differences in broad-spectrum psychopathology or neuropsychological indicators of attentional capacity.

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Several compounds have demonstrated sufficient efficacy in reducing hyperactivity and increasing attention to be recognized as first-line treatments for attention-deficit/hyperactivity disorder (ADHD). The most effective of these include amphetamine derivatives and methylphenidate, which target the dopamine transporter, and the more recently formulated atomoxetine, which selectively inhibits the reuptake of norepinephrine.[1] Although large proportions of adult patients with ADHD will receive some benefit from treatment with one or more of these compounds, therapeutically meaningful responsiveness is not always observed.[2,3]

Many factors, including genetically and environmentally regulated biological processes, demonstrate compelling preliminary evidence for a relationship with individual responsiveness to these medications. For example, the 10-repeat allele of the variable-number tandem-repeat polymorphism in the 3' region of *DAT1* (*SLC6A3*) (the gene that codes for the dopamine transporter) has been associated with favorable response to methylphenidate among children with ADHD.[4] In addition to such genetic moderators of treatment response, features of a child's environment, such as parental depressive symptoms[5] or maternal low self-esteem,[6] also influence the effectiveness of pharmacotherapy, either alone or in combination with behavioral interventions. Furthermore, individual patterns of comorbid psychopathology[7] and neuropsychological performance[8] can be used to reliably predict who will benefit least or most from treatment with methylphenidate.

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Although similar relationships between these variables and treatment outcomes may be observed in adults with ADHD, such investigations have yet to be conducted, and much less is known about the relationship of these variables to treatment outcomes on other classes of compounds, such as atomoxetine.

The identification of highly reliable and accurate predictors of responsiveness to atomoxetine and other psychopharmacologic agents may yield substantial benefits to patients, including more efficient first-line treatment selection (which may reduce the duration of untreated periods and improve prognosis) and fewer side effects (which may increase the likelihood of adherence), resulting in a net reduction in the burden of ADHD. Thus, to facilitate this scenario, the present study was conducted to determine if psychopathology or neuropsychological performance could effectively and reliably predict clinical responsiveness to atomoxetine among adults with ADHD, for whom this compound has previously shown marked effectiveness relative to placebo.

METHOD

Subjects, Clinical Assessment, and Neuropsychological Testing

Two identical randomized, double-blind, placebo-controlled studies were conducted concurrently at 17 (Study 1, N = 280) and 14 (Study 2, N = 256) outpatient sites in North America. Adults who met DSM-IV[9] criteria for ADHD as assessed by clinical interview and confirmed by the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID)[10] were recruited from clinics and by advertisement. Patients were required to have at least moderate symptom severity, and the diagnosis had to be corroborated by a second reporter for either current symptoms (by a significant other) or childhood symptoms (by a parent or older sibling).

Comorbid psychiatric diagnoses were assessed by clinical interview and by the Structured Clinical Interview for DSM-IV (SCID).[11] Patients who met diagnostic criteria for current major depression or anxiety disorder, or for current or past bipolar or psychotic disorders, were excluded, as were patients with serious medical illness or habitual substance abuse. Urine screening for drugs of abuse was performed at the initial visit and could be repeated at any time during the trial at the investigator's discretion.

Subjects were also administered one of the commonly used clinical versions of the Stroop Color-Word Test (SCWT)[12] at baseline and their last visit. The SCWT consists of 3 tasks, each lasting 45 seconds: (1) the word task, which involves reading the names of colors printed in black ink; (2) the color task, which involves naming the colors of semantically meaningless symbols (e.g., XXXX) printed in colored ink (i.e., red, blue, or green); and (3) the color-word task, which involves reading the names of colors printed in colored ink such that the word and the ink color do not match (e.g., the word "blue" is printed in red ink and the correct response is "red"). Each task yields a score (color, word, and color-word), based on the number of items completed correctly. In addition, an interference score is computed from these 3 scores to assess resistance to interference separately from processing speed.

Atomoxetine and Placebo Administration

Following an initial 1-week medication washout and evaluation period, patients entered a 2-week placebo lead-in phase (modified double-blind, since efficacy raters were blind to the protocol but others at the investigative sites were not). Patients who continued to meet the initial severity criteria required for study entry were randomly assigned to receive atomoxetine or placebo for a 10-week period, during which visits were biweekly. Patients were randomly assigned according to computer-generated treatment codes obtained from an interactive voice-response system. Study drug materials for both treatment groups were identical in appearance.

Atomoxetine was administered in evenly divided doses in the morning and late afternoon/early evening beginning at a total daily dose of 60 mg. Patients with residual symptoms had their dose increased to 90 mg/day after 2 weeks and to 120 mg/day after 4 weeks. If tolerability problems developed, the dose could be decreased to the last tolerated dose or an increase in dose could be omitted. Safety and tolerability were assessed at each visit by open-ended questioning for adverse events and by monitoring of vital signs and laboratory data.

Each site's institutional review board evaluated and approved the study protocol. After description of the procedures and purpose of the study, and prior to the administration of any study procedure or dispensing of study medication, written informed consent was obtained from 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.[13]

Outcome Measures and Predictor Variables

The outcome measures examined in this study were derived from the Conners' Adult ADHD Rating Scales (CAARS),[14] the Sheehan Disability Scale,[15] and the General Well-Being Schedule (GWB).[16] An investigator completed the Sheehan Disability Scale and the GWB before and after the treatment regimen, while both the subject and an investigator completed the CAARS before and after treatment. Prior to starting the study, efficacy raters were required to attend a training session using observed interviews and group discussion to standardize rating practices for the CAARS. Efficacy raters for the primary outcome measure were blind to all details of the study design, including severity criteria for entry, dose titration,

Table 1. Predictor of Therapy Outcome in Patients With ADHD as Measured by the Sheehan Disability Scale

			Predictor of Outcome Irrespective of Therapy			Predictor of Outcome Specific to Atomoxetine		
Condition	Condition Present Mean ± SD	Condition Absent Mean ± SD	Test t Statistic	df	Significance	Test F Statistic	df	Significance
Depression NOS	19.3 ± 7.4	12.6 ± 7.4	3.1	437	.002	0.7	436	.499

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, NOS = not otherwise specified.

Table 2. Predictors of Therapy Outcome in Patients With ADHD as Measured by the General Well-Being Schedule

	Condition		Predictor of Outcome Irrespective of Therapy			Predictor of Outcome Specific to Atomoxetine		
Subscale	Present Mean ± SD	Absent Mean ± SD	t Test	df	p Value	t Test	df	p Value
Self-Control subscale								
Gender	11.8 ± 2.6 (male)	11.0 ± 2.8 (female)	2.7	507	.007	2.0	507	.050
Atomoxetine	11.7 ± 2.7 (male)	11.2 ± 2.7 (female)						
Placebo	11.9 ± 2.6 (male)	10.7 ± 3 (female)						
PTSD	9.0 ± 2.7	11.5 ± 2.7	–2.5	503	.013	0.9	501	.350
Alcohol use	10.3 ± 2.2	11.5 ± 2.7	–2.1	502	.033	0.8	500	.410
Nonalcoholic substance use	8.3 ± 4.2	11.5 ± 2.7	–3.0	498	.003	1.0	496	.326
Lifetime substance use	10.3 ± 3.5	11.5 ± 2.7	–2.0	504	.050	0.1	502	.936
General Health subscale								
Age	…	…	0.3	505	.741	2.2	506	.029
PTSD	9.4 ± 2.2	11.4 ± 2.3	–2.2	502	.026	1.0	500	.326
Positive Well-Being subscale								
PTSD	8.3 ± 3.4	11.7 ± 3.7	–2.5	501	.013	0.7	499	.493

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, PTSD = posttraumatic stress disorder.

and timing of the initiation of therapy, and were not allowed to evaluate or ask about adverse events.

The 3 groups of primary criteria variables in this study thus included: (1) investigator-rated Sheehan Disability Scale endpoint total score; (2) investigator-rated GWB endpoint scores for the Positive Well-Being, Self-Control, General Health, and Vitality subscales; and (3) self- and investigator-rated inattention, hyperactivity/impulsivity, total symptoms, and ADHD index endpoint scores derived from the 18 DSM-IV diagnosis extraction items from the CAARS.[17] The primary predictor variables in this study included the following: (1) demographics, including age and gender; (2) lifetime SCID diagnoses, including those for major depressive disorder, depression not otherwise specified (NOS), dysthymia, panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, manic-depression, hypomania, alcohol use, alcohol abuse, nonalcoholic substance (drug) use, substance (alcohol or drug) use, and psychosis; and (3) indicators of performance on the SCWT, including baseline and endpoint performance in the color, word, and color-word conditions, and the interference score.

Statistical Methods

Results were analyzed on an intent-to-treat basis. We used an analysis of covariance model that modeled each endpoint score as a function of the following terms: *baseline score on the outcome measure*, *therapy group* (drug vs. placebo), *baseline by therapy group* interaction, *predictor of outcome*, and the *predictor by therapy group* interaction. For the endpoint score, we used the last observation carried forward. The *predictor of outcome* term indicates if the predictor variable predicts outcome irrespective of therapy group. The *predictor by therapy* interaction indicates if the predictor variable predicts outcome differently for the atomoxetine- and placebo-treated groups. All tests used a 2-sided significance level of .05. All values in the text represent mean ± standard deviation, unless otherwise noted.

RESULTS

Sheehan Disability Scale

Total scores on the Sheehan Disability Scale were not related to age, gender, or neuropsychological test performance and were largely unrelated to other dimensions of psychopathology as measured by the SCID. The exception was depression NOS, which did positively correlate with this outcome measure (Table 1). However, this item predicted response to placebo and atomoxetine equally well, suggesting that it mediates response to treatment rather than response to atomoxetine pharmacotherapy specifically.

General Well-Being Schedule

Scores on the Self-Control subscale of the GWB were highly influenced by gender, which also interacted significantly with therapy to influence this outcome measure (Table 2). Decomposition of this interaction re-

Table 3. Predictors of Therapy Outcome in Patients With ADHD as Measured by the Conners' Adult ADHD Rating Scales

	Condition		Predictor of Outcome Irrespective of Therapy			Predictor of Outcome Specific to Atomoxetine		
Subscale	Present Mean ± SD	Absent Mean ± SD	t Test	df	p Value	t Test	df	p Value
Investigator-rating Index subscale								
Depression NOS	20.1 ± 6.1	15.3 ± 7.2	2.7	496	.007	1.6	494	.121
Major depressive disorder	15.6 ± 8.5	15.5 ± 7.1	0.4	499	.670	–2.2	500	.028
Atomoxetine	13.4 ± 7.9	14.8 ± 7.3						
Placebo	19.8 ± 8.1	16.2 ± 6.9						
Investigator-rating Hyperactivity subscale								
Depression NOS	14.1 ± 6.0	11.0 ± 6.1	2.2	496	.029	3.9	494	.051
Major depressive disorder	11.0 ± 6.2	11.0 ± 6.1	1.2	499	.243	–2.1	500	.033
Atomoxetine	9.5 ± 5.9	10.5 ± 5.9						
Placebo	14.0 ± 5.8	11.6 ± 6.2						
PTSD	17.8 ± 7.1	10.9 ± 6.0	1.7	504	.196	–2.3	505	.020
Atomoxetine	11.0 ± 7.0	10.4 ± 5.9						
Placebo	20.7 ± 5.1	11.4 ± 6.0						
Self-rating Hyperactivity subscale								
PTSD	17.2 ± 6.5	11.3 ± 5.8	2.5	426	.011	3.3	424	.069
Depression NOS	13.6 ± 1.6	11.4 ± 5.9	1.5	414	.217	2.0	415	.049
Atomoxetine	15.5 ± 4.4	10.6 ± 5.7						
Placebo	11.2 ± 7.1	12.1 ± 6.1						
Investigator-rating Inattention subscale								
Depression NOS	17.9 ± 6.3	14.6 ± 6.4	2.1	495	.033	–2.1	495	.035
Atomoxetine	13.8 ± 6.7	13.9 ± 6.4						
Placebo	18.5 ± 6.0	15.5 ± 6.3						
PTSD	19.1 ± 7.8	14.7 ± 6.4	0.5	504	.606	–2.2	505	.031
Atomoxetine	11.0 ± 9.2	13.9 ± 6.4						
Placebo	22.6 ± 4.0	15.5 ± 6.3						
Investigator-rating Total subscale								
Depression NOS	32.1 ± 11.1	25.6 ± 11.2	2.3	495	.024	2.2	495	.028
Atomoxetine	35.1 ± 9.1	23.8 ± 11.1						
Placebo	28.6 ± 12.7	27.3 ± 11.1						
Major depressive disorder	26.4 ± 12.0	25.7 ± 11.1	1.1	499	.292	–2.0	500	.046
Atomoxetine	23.3 ± 11.6	24.3 ± 11.1						
Placebo	32.5 ± 10.7	27.1 ± 11.0						
PTSD	36.9 ± 13.5	25.6 ± 11.0	0.9	504	.368	–2.4	505	.016
Atomoxetine	22.0 ± 14.7	24.3 ± 11.1						
Placebo	43.3 ± 6.4	26.9 ± 10.8						
Self-rating Total subscale								
PTSD	35.2 ± 12.9	26.0 ± 10.5	2.0	424	.05	1.8	422	.069
Depression NOS	30.5 ± 9.8	26.0 ± 10.7	1.1	412	.288	2.0	413	.045
Atomoxetine	32.8 ± 8.3	24.3 ± 10.6						
Placebo	27.5 ± 11.5	27.5 ± 10.6						

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, NOS = not otherwise specified, PTSD = posttraumatic stress disorder.

vealed that female patients improved slightly on this measure with atomoxetine, while male patients showed no change. Scores on the PTSD, alcohol use, nonalcoholic substance use, and substance use dimensions of the SCID significantly and inversely related to Self-Control scores as well, but these effects were similar for those receiving either placebo or atomoxetine. Performance on the SCWT did not significantly influence outcomes on this measure.

Age did not predict outcomes on the General Health subscale of the GWB, but the interaction of this factor with therapy type was significant, as age and general health were inversely correlated in placebo-treated subjects ($r = –0.21$, $p < .0001$) but not in those receiving atomoxetine ($r = 0.04$, $p = .379$). Scores on the PTSD dimension of the SCID also predicted outcomes on this subscale and on the Positive Well-Being subscale, but to no greater or lesser extent for those receiving placebo or atomoxetine. All other demographic, neuropsychological, and psychopathologic variables failed to influence these outcome measures. Similarly, scores on the Vitality subscale of this assessment schedule were not influenced by any of these variables or interactions of these variables with therapy type.

Conners' Adult ADHD Rating Scales

Index. Investigator ratings of the CAARS Index were reliably predicted by SCID depression NOS, but this dimension did not interact with therapy type, indicating that SCID depression NOS does not reliably predict responsiveness to atomoxetine (Table 3). On the contrary, while SCID major depressive disorder did not by itself relate to CAARS Index scores, this measure did interact with therapy type to influence this outcome measure. Further inspection of this interaction revealed that improvement on atomoxetine was greater in those with major depres-

sive disorder than in those without. No other SCID variable, nor any demographic or neuropsychological variable, reliably influenced this measure.

Hyperactivity. Investigator ratings of CAARS Hyperactivity were reliably influenced by SCID depression NOS scores, but not by the interaction of this factor with treatment type. Alternatively, therapy type did interact with both SCID major depressive disorder and PTSD to influence CAARS Hyperactivity scores, but neither measure individually influenced this outcome. The interactions between these SCID measures and CAARS Hyperactivity were mediated by much larger improvements on atomoxetine among those with either major depression or PTSD than among those without depression or PTSD. For self-ratings on this CAARS subscale, SCID PTSD influenced this outcome measure, but the interaction of SCID PTSD score with therapy type was not significant. Conversely, the SCID depression NOS significantly influenced self ratings, but only in combination with therapy type. Of note, this interaction indicated that improvement on atomoxetine was restricted to those without depression NOS, while those with depression NOS actually improved less on atomoxetine than on placebo.

Inattention. Similar effects were seen for investigator ratings on the CAARS Inattention subscale but not self-ratings of this measure. For example, investigator-rated CAARS Inattention was significantly influenced by SCID depression NOS as well as the interactions of therapy type with both depression NOS and PTSD. The interactions between these SCID measures and CAARS Inattention were mediated by much larger improvements in patients on atomoxetine therapy among those with either depression NOS or PTSD than among those without depression NOS or PTSD. Conversely, self ratings of CAARS Inattention were not influenced by any of these predictors or any of the other demographic, psychopathologic, or neuropsychological variables.

Total. Neither investigator- nor self-rated CAARS Total scores were significantly influenced by demographic or neuropsychological variables. Investigator ratings of CAARS Total scores were significantly influenced by SCID depression NOS scores. Further, the effects of therapy type on this measure were moderated by SCID major depressive disorder, depression NOS, and PTSD scores. The interactions between these SCID measures and CAARS Total scores were mediated by greater improvements in patients on atomoxetine therapy among those with either disorder than among those without. Self-ratings of CAARS Total scores were also influenced by SCID PTSD ratings and by the interaction of therapy type with SCID depression NOS but not by SCID major depressive disorder or other SCID dimensions. Individuals with SCID depression NOS improved less on atomoxetine than placebo, while those without this comorbidity improved slightly.

DISCUSSION

It is clear from prior work that atomoxetine is a highly effective treatment for the symptoms of ADHD in adulthood, paralleling the high rate of effectiveness observed for traditional pharmacologic agents such as amphetamine derivates and methylphenidate. However, it is also clear that neither this compound nor any of the other currently designated first-line treatments for this disorder are effective for all patients. One avenue of research into improving the pharmacologic treatment and management of ADHD and other complex disorders is focused on increasing the specificity of the effects of new putative pharmacologic agents through the application of principles of medicinal chemistry and receptor pharmacology. Another line of investigation acknowledges the reasonable effectiveness of existing compounds while trying to identify the characteristics of their intended patient population that may predispose individuals within it to respond poorly or favorably to each of the currently available treatments. Since atomoxetine has emerged as a highly effective treatment for ADHD, with a dramatically different physiologic mechanism of action than traditional stimulant medications such as amphetamine derivatives and methylphenidate, research to determine the factors that predispose toward differential responsiveness to these various compounds is now greatly needed; yet, unfortunately, such research has yet to be published for adult patients with ADHD.

In the present report, we have attempted to address this void by predicting levels of responsiveness to atomoxetine (as assessed by improvements on an ADHD symptom rating scale, a social disability scale, and a general well-being schedule) based on preexisting psychopathology and lifetime comorbidity with ADHD, demographic information, and neuropsychological performance on a test of visual attention. Unfortunately, the results of this work identified few reliable predictors of improvement on atomoxetine therapy.

Of the various measures obtained, ratings of lifetime psychopathology on the SCID served as the best predictors of improvement across the broadest range of outcome measures. Specifically, the SCID dimensions of major depressive disorder, depression NOS, and PTSD reliably predicted atomoxetine-associated improvement on a number of clinical indicators. For example, one or more of these measures influenced outcomes on each of the 4 CAARS dimensions, including the Index, Hyperactivity, Inattention, and Total scores. Furthermore, at least one of these 3 SCID dimensions had a main effect on total Sheehan Disability Scale score or on a subscale of the GWB, but these SCID dimensions did not interact with therapy type to influence these outcomes, suggesting that comorbidity of these forms of psychopathology with ADHD did influence amenability to treatment but not responsiveness to atomoxetine per se.

In addition to these broadly associated SCID dimensions, other areas of psychopathology documented on the SCID (e.g., alcohol and substance use) were found to be associated with level of improvement on the Self-Control subscale of the GWB. Demographic information rarely related to measures of symptom improvement, with significant interactions with therapy type noted only for the Self-Control (gender) and General Health (age) subscales of the GWB. Notably, performance on the SCWT also influenced only one indicator of improvement on atomoxetine (CAARS Index score).

These findings must be viewed in light of the limitations of this study. First, these analyses were performed on data collected from patient groups matched on various characteristics but not explicitly matched for levels of comorbidity or neuropsychological performance. A prospective study with appropriate matching between placebo- and atomoxetine-treated subjects on key variables such as neuropsychological performance or psychiatric comorbidity might yield a very different pattern of results. Second, a number of important predictors were not tested in this study, including compliance and numerous neuropsychological measures. Third, the large number of predictors entered into the regression models used for this study may have increased the likelihood of false-positive discoveries. As this was an exploratory investigation wherein relationships between the putative predictors and outcome measures were not specified a priori, no correction for multiple testing was applied; thus, some of the significant results reported here may have capitalized on chance. However, these findings do suggest testable hypotheses for future work relating psychopathologic comorbidity with ADHD to treatment responsiveness for atomoxetine and, if they are supported, may highlight some clinical characteristics useful for identifying those patients who are most and least likely to benefit from atomoxetine pharmacotherapy.

Drug names: atomoxetine (Strattera), methylphenidate (Ritalin, Metadate, and others).

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REFERENCES

1. Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology 2002;27:699–711
2. Kratochvil CJ, Vaughan BS, Harrington MJ, et al. Atomoxetine: a selective noradrenaline reuptake inhibitor for the treatment of attention-deficit/hyperactivity disorder. Expert Opin Pharmacother 2003;4: 1165–1174
3. Wilens TE, Biederman J, Spencer TJ, et al. Pharmacotherapy of adult attention deficit/hyperactivity disorder: a review. J Clin Psychopharmacol 1995;15:270–279
4. Kirley A, Lowe N, Hawi Z, et al. Association of the 480 bp DAT1 allele with methylphenidate response in a sample of Irish children with ADHD. Am J Med Genet B Neuropsychiatr Genet 2003;121:50–54
5. Owens EB, Hinshaw SP, Kraemer HC, et al. Which treatment for whom for ADHD? moderators of treatment response in the MTA. J Consult Clin Psychol 2003;71:540–552
6. Hoza B, Owens JS, Pelham WE, et al. Parent cognitions as predictors of child treatment response in attention-deficit/hyperactivity disorder. J Abnorm Child Psychol 2000;28:569–583
7. March JS, Swanson JM, Arnold LE, et al. Anxiety as a predictor and outcome variable in the multimodal treatment study of children with ADHD (MTA). J Abnorm Child Psychol 2000;28:527–541
8. Aman MG, Turbott SH. Prediction of clinical response in children taking methylphenidate. J Autism Dev Disord 1991;21:211–228
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
10. Epstein J, Johnson D, Connors CK. Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID). North Tonawanda, NY: Multi-Health Systems, Inc; 2003
11. First MB, Spitzer GM, Spitzer RL, et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version. New York, NY: Biometrics Research, New York State Psychiatric Inst; 2000
12. Golden CJ. Stroop Color and Word Test: A Manual for Clinical and Experimental Use. Chicago, Ill: Stoelting Co; 1978
13. World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects. Available at http://www.wma.net/e/policy/b3.htm. Accessed January 25, 2006
14. Conners CK, Erhardt D, Sparrow E. Conners' Adult ADHD Rating Scales (CAARS). North Tonawanda, NY: Multi-Health Systems, Inc; 1999
15. Leon AC, Olfson M, Portera L, et al. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J Psychiatry Med 1997;27:93–105
16. Dupuy HJ. The Psychological General Well-Being (PWGB) Index. In: Wenger NK, Mattson ME, Furberg CD, et al, eds. Assessment of Quality of Life in Clinical Trials of Cardiovascular Therapies. New York, NY: LeJacq Publishing, Inc; 1984:170–183, 353–356
17. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. Biol Psychiatry 2003;53:112–120

