Effects of Atomoxetine With and Without Behavior Therapy on the School and Home Functioning of Children With Attention-Deficit/Hyperactivity Disorder

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Objective: To evaluate the effects of atomoxetine alone and in combination with behavior therapy on the school functioning of children with attention-deficit/hyperactivity disorder (ADHD). Most atomoxetine studies have not assessed school functioning other than by measuring the change in ADHD symptoms. Combining behavior therapy with atomoxetine may be particularly beneficial for the academic domain as medication has not been found to produce sustained benefits in this realm. However, there is little research examining the effects of combining atomoxetine and behavior therapy.

Method: In an 8-week open-label trial, 56 children aged 6–12 years with ADHD diagnosed according to *DSM-IV-TR* were randomly assigned to receive atomoxetine and behavior therapy or atomoxetine alone. Behavior therapy consisted of an 8-week parenting course, a child social skills course, and a teacher-implemented daily report card of classroom behavior. The primary outcome was direct observation of the subject's classroom behavior. Secondary outcomes included change in ADHD symptoms and functioning at home and school. All data were collected between March 2007 and May 2008.

Results: Classroom observations showed that atomoxetine decreased rule violations ($P < .0001$). Moreover, atomoxetine was associated with significant improvements in ADHD and oppositional defiant disorder symptoms at home and school and enhanced functioning in both domains (Impairment Rating Scale: all $P < .001$). Combined treatment led to greater improvements in parent-rated symptoms of inattention ($P < .01$), problem behaviors ($P < .001$), and academic impairment ($P < .05$). However, teachers did not report significant group differences.

Conclusions: Atomoxetine improved ADHD symptoms and classroom functioning as measured by parents, teachers, and direct observation. The addition of behavior therapy led to further improvements at home but not at school.

Trial Registration: clinicaltrials.gov Identifier: NCT00918567

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Atomoxetine, a potent inhibitor of the presynaptic norepinephrine reuptake transporter, is a US Food and Drug Administration–approved nonstimulant medication commercially available for the treatment of pediatric attention-deficit/hyperactivity disorder (ADHD). Multiple double-blind, placebo-controlled studies in over 1,000 youth have found it to be efficacious across the spectrum of ADHD symptoms[1–5] and for reducing impairment on measures of functioning in the home.[6] However, the majority of atomoxetine studies have focused on improvement in the home environment. As parents often seek treatment for their child for ADHD because of concerns over their child's school behaviors,[7,8] it is important to assess the impact of ADHD treatments at school as well as home.

Similar to stimulant medications, behavior therapy has been found to improve ADHD symptoms and functional impairments in the classroom.[9,10] The centerpiece of any school-based behavioral intervention for children with ADHD is the development and implementation of a daily report card.[11] A daily report card consists of specific, individual, measureable treatment goals for the child that teachers evaluate throughout the day. Teachers give children feedback on their progress toward meeting identified treatment goals on a regular basis (eg, at the end of every subject), and overall performance on the goals are backed up by a reinforcement program (rewards for achieving a high percentage of goals, removal of privileges for failure to meet goals) at home. Parent training, which also has empirical support as an effective treatment for ADHD,[9] is an effective means of helping parents develop and implement the reinforcement program that supports the school-based daily report card. Research shows that this intervention is highly effective for most children with ADHD, producing significant positive changes in academic performance (seatwork completion) and classroom behavior (rule following) that are equivalent to improvement seen in response to low doses of stimulant medication.[12,13]

In comparison to stimulant medications and behavior therapy, much less is known about the effects of atomoxetine in the classroom, as few of the published studies of

atomoxetine have reported on school-based outcomes. Three studies of atomoxetine have employed teacher ratings as a secondary outcome, finding mixed results.[14–16] Weiss and colleagues[5] published the only study of atomoxetine that used school-based measures as the primary outcome. This study was a 7-week, double-blind, placebo-controlled trial of atomoxetine (N = 153) using the ADHD Rating Scale-IV Teacher Scale as the primary outcome. Of note, subjects had an unusually mild level of baseline symptoms for an ADHD study. Atomoxetine was administered once a day at a mean dose of 1.3 mg/kg. It produced significantly greater reductions than did placebo for the total score on the ADHD Rating Scale-IV ($P = .001$) with an estimated effect size of 0.63. A significantly greater number of atomoxetine subjects met criteria for response (69% vs 43% for placebo; $P = .003$). While the reported effect size is comparable to studies using parental report of symptoms, this study defined response as only a 20% or greater reduction in the ADHD Rating Scale-IV total score, in comparison to the standard of 25%–40% used elsewhere.[17] In addition to measuring change in symptom scores, the Academic Performance Rating Scale, the Brown Attention-Deficit Disorder Scales, the Social Skills Rating System, the Conners' Global Index, and a novel categorical rating of classroom behavior were administered to assess changes in classroom functioning. Atomoxetine produced significant reductions in some but not all of these measures, with very limited effects on academic performance and prosocial behaviors.[5]

The Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA) and most other ADHD studies have failed to find that medication or behavior therapy alone leads to sustained improvement in academic functioning,[18,19] suggesting that combination treatments may be needed to optimize school functioning for children with ADHD. Several studies have looked at the impact of combining behavioral therapies with stimulant medication to enhance functional outcomes as there are numerous theoretical advantages to combining behavior therapy with pharmacotherapy.[13,20] While the results have been mixed, especially in larger-scale trials,[21,22] numerous smaller studies have found additional benefits in children receiving stimulants plus behavior therapy versus medication alone.[13] For example, Kolko et al[23] found that combining behavior therapy and stimulants led to greater reductions in ADHD symptom scores and peer conflicts than either treatment administered alone. Research has also shown that combining behavior therapy with low doses of stimulants produces comparable effects to high doses of medication in classroom settings.[12,24,25] Similarly, the MTA found that combining behavior therapy with medication led to comparable improvements at lower medication doses while also improving the number of children achieving optimal response.[22,26]

Supplementation with behavior therapy may be one means of enhancing the efficacy of atomoxetine to the level seen with stimulants.[27] These benefits may be particularly useful in school settings, given the limited ability of medication alone to impact long-term academic functioning. However, only 1 prior study[28] has examined the combined effects of atomoxetine and behavioral interventions. Svanborg and colleagues[28] found little additional benefit to combined therapy versus atomoxetine alone except possibly for improved treatment adherence. However, the behavioral intervention consisted of only 4 psychoeducation sessions with no formal parent training component. Only parents attended the sessions as there was no direct contact with the children themselves.

Further complicating the assessment of ADHD treatments at school are the limitations of behavior ratings. Teacher ratings may not provide a complete and accurate picture of treatment response, especially in the classroom, where teachers must constantly attend to multiple children at one time. There is evidence that behavior ratings can produce biased data, with the informant's view of some behaviors influencing his or her views of related but distinct behaviors.[29] For instance, there is evidence that changes in a child's level of physical activity are interpreted by teachers as changes in both hyperactivity and inattention.[30] Likewise, teachers tend to interpret purely oppositional behaviors as a combination of oppositionality and hyperactivity.[31,32] In the Weiss et al study[5] described above, the unusually high placebo response rate of 43% was primarily attributed to the use of teacher-completed versus parent-completed measures as the primary outcome. Taken together, these findings suggest the need for more objective measures in school-based medication studies.

With the exception of the Weiss et al study,[5] which found largely mixed results in this area, functional measures of academic performance or classroom behavior have not been included in trials of atomoxetine. Direct observation of children in their naturalistic classroom settings as well as the use of daily report cards to track a child's ability to meet objective classroom goals provides an assessment of actual classroom functioning that should be less subject to rater bias than traditional symptom measures.[29,33]

To examine the effects of atomoxetine with and without behavior therapy in school and at home, we completed an 8-week, open-label, randomized study of atomoxetine in 56 children aged 6–12 years with ADHD, in which half of the sample was randomly assigned to receive behavior therapy in addition to medication. To address the limitations of prior work, we employed direct observations of children's classroom behaviors using a validated coding system as the primary outcome measure. The observational assessment was supplemented by measures of functional capacity, such as a daily report card, as well as traditional measures of ADHD symptoms. The behavior therapy intervention was composed of an evidence-based parent training program along with a school-based daily report card and a child social skills group.

It was hypothesized that both treatment arms would lead to improvement across measures including direct

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observation in the classroom. It was predicted that combined treatment would produce greater improvements than medication alone on measures of functional impairment, including direct observation of classroom behaviors, as well as measures of treatment satisfaction.

METHOD

Subjects

Subjects were recruited from schools, pediatric offices, and the local community through radio and print advertisement. Subjects were 56 children (45 boys and 11 girls) aged 6–12 years (mean = 8.59, SD = 1.58 years). The racial composition of the sample was 80.4% white, 10.7% African American, and 8.9% mixed, and the ethnic composition was 5.4% Hispanic and 94.6% non-Hispanic, matching the demographics of western New York State. Two sibling pairs were enrolled (1 pair was assigned to atomoxetine plus behavior therapy (atomoxetine + BT) and 1 to atomoxetine only). There were 21 subjects (37.5%) who had never been treated with stimulants. Seven subjects (12.5%) had previously used atomoxetine, including 1 who was a prior responder but had not taken atomoxetine for more than a year due to insurance issues and 6 who had started atomoxetine shortly before study entry. These 7 subjects were allowed to enroll because the primary goal of this study was to assess the effects of combined therapy versus atomoxetine alone. In addition, the efficacy of the drug had not yet been established in all but 1 of these 7 cases. The 6 subjects receiving atomoxetine at entry comprised 3 subjects who had just been started (< 2 weeks) on a relatively high dose (1.4 mg/kg/d) and 3 who were taking a potentially subtherapeutic dose (< 0.8 mg/kg/d), so that none of these met the exclusionary criteria for failure to respond to atomoxetine (see paragraph below on exclusion criteria). These subjects followed the titration protocol described below except that they entered the study on their current dose. The study was approved by the Children and Youth Institutional Review Board at the Women and Children's Hospital of Buffalo. Informed consent that included a detailed discussion of the risks of treatment was obtained from legal guardians, and written assent was obtained from children prior to data collection. Table 1 summarizes demographic and rating scale data for subjects as a function of treatment condition.

Of the 56 children, 7 (12.5%) discontinued the study prior to completion: 5 in the atomoxetine + BT group and 2 in the atomoxetine-only group. The rate of early dropout did not differ across groups ($\chi^2_1 = 1.24$, $P = .266$). Of the 7 children who stopped early, 4 discontinued because the parent believed the medication was ineffective (one of these also quit in part due to nausea while receiving atomoxetine), 2 refused ongoing medication, and 1 discontinued due to parental concerns over increased emotional lability (more prone to cry but no expression of suicidal thoughts). One-way analyses of variance (ANOVAs) comparing subjects who stopped early with those who completed the study on baseline parent and teacher ratings showed no significant differences on any of the 25 comparisons, suggesting that those who discontinued the study early were not different from those who completed the study. All available data for subjects who stopped early were included in analyses using SAS mixed models (described below).

All subjects were diagnosed with ADHD using criteria specified in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*).[38] Diagnoses were based on several sources of information, including ratings by parents and teachers on the Disruptive Behavior Disorders Rating Scale (DBD),[37] which assesses the *DSM-IV-TR* symptoms of ADHD, oppositional defiant disorder, and conduct disorder and parent report on the National Institute of Mental Health Diagnostic Interview Schedule for Children (DISC).[39] Parental report of impairing ADHD and oppositional defiant disorder symptoms was confirmed by direct interview with a master's or higher–level clinician using the Disruptive Behavior Disorders Interview.[40] If a subject was already taking ADHD medication other than atomoxetine, the other medication was stopped for at least 48 hours prior to screening (all discontinued medications were stimulants). Following *DSM-IV-TR* guidelines, diagnoses were made if a sufficient number of symptoms were endorsed (considering information from both parents on the DISC and DBD and teachers on the DBD) and if the child evidenced clinically significant impairment. The mean Clinical Global Impressions-Severity of Illness (CGI-S)[41] score for ADHD was 4.3, placing subjects in the moderate range for impairment. Of the 56 subjects, 48 (85.7%) were diagnosed with ADHD-combined type, 7 (12.5%) were diagnosed with ADHD-inattentive type, and 1 (1.8%) was diagnosed with ADHD-hyperactive/impulsive type. In addition, 22 (39.3%) met criteria for conduct disorder and 24 (42.9%) for oppositional defiant disorder, leaving only 10 subjects (17.9%) with noncomorbid ADHD.

Exclusion criteria included (1) current or past history of seizures (not including benign febrile seizures); (2) other physical conditions that precluded administration of atomoxetine (eg, marked cardiac conduction delay); (3) documented failed trial of atomoxetine, defined as 3 weeks or more on treatment with at least 0.8 mg/kg/d, or a documented inability to tolerate this dose; (4) serious forms of psychopathology other than ADHD, such as autism, bipolar disorder, schizophrenia, or any other psychopathology requiring urgent treatment with psychotropic medication; (5) any history of major depression requiring treatment (therapy or medication), or any past history of self-harm or serious suicidal ideation; (6) an intelligence quotient (IQ) of less than 75; and (7) no evidence of ADHD-related impairment at school.

Design

This study consisted of an 8-week open-label trial of atomoxetine, with one-half of the subjects (N = 29) randomly assigned to receive atomoxetine + BT and the remaining

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Table 1. Demographic and Diagnostic Measures as a Function of Treatment Group

Measure	Atomoxetine Only (n = 27)	Atomoxetine + BT (n = 29)	Statistical Comparison
Age, mean (SD), y	8.9 (1.5)	8.3 (1.6)	$F_{1,54} = 2.42$
Sex, male, n (%)	21 (77.8)	24 (82.8)	$\chi^2_1 = 0.22$
IQ, mean (SD)[a]	97 (13)	101 (16)	$F_{1,54} = 1.02$
Reading score, mean (SD)[b]	101 (16)	101 (13)	$F_{1,53} = 0.00$
Math score, mean (SD)[b]	86 (13)	92 (15)	$F_{1,53} = 2.02$
Spelling score, mean (SD)[b]	95 (14)	96 (15)	$F_{1,53} = 0.05$
Socioeconomic status, mean (SD)[c]	53 (13)	61 (17)	$F_{1,54} = 3.55$*
Stimulant-naive at baseline, n (%)	8 (29.6)	13 (44.8)	$\chi^2_1 = 1.38$
Atomoxetine-naive at baseline, n (%)	23 (85.2)	26 (89.7)	$\chi^2_1 = 0.26$
Symptom scores from parent DBD, mean (SD)[d]			
ADHD-inattention	2.15 (0.58)	2.05 (0.63)	$F_{1,53} = 0.31$
ADHD-hyperactive/impulsive	1.81 (0.59)	1.64 (0.63)	$F_{1,53} = 0.98$
Oppositional defiant disorder	1.26 (0.57)	1.35 (0.69)	$F_{1,53} = 0.27$
Conduct disorder	0.17 (0.17)	0.25 (0.37)	$F_{1,53} = 1.21$
Symptom scores from teacher DBD, mean (SD)[d]			
ADHD-inattention	1.82 (0.68)	1.79 (0.91)	$F_{1,54} = 0.02$
ADHD-hyperactive/impulsive	1.31 (0.67)	1.42 (0.88)	$F_{1,54} = 0.27$
Oppositional defiant disorder	0.89 (0.69)	1.18 (0.89)	$F_{1,54} = 1.77$
Conduct disorder	0.26 (0.27)	0.22 (0.22)	$F_{1,54} = 0.49$
Clinical diagnoses, n (%)			
ADHD subtypes			$\chi^2_2 = 1.07$
ADHD-inattentive	3 (11.1)	4 (13.8)	
ADHD-hyperactive/impulsive	0 (0)	1 (3.4)	
ADHD-combined	24 (88.9)	24 (82.8)	
Comorbidity			$\chi^2_2 = 3.03$
ADHD only	7 (25.9)	3 (10.3)	
ADHD + oppositional defiant disorder	9 (33.3)	15 (51.7)	
ADHD + conduct disorder	11 (40.7)	11 (37.9)	

[a]Full-scale IQ estimated from the block design and vocabulary subtests of the Wechsler Intelligence Scale for Children, 3rd edition.[34]
[b]Achievement scores from the Wechsler Individual Achievement Test, 2nd edition.[35]
[c]Nakao and Treas, Socioeconomic Index.[36]
[d]Average symptom rating on the DBD,[37] in which 0 is "not at all," 1 is "just a little," 2 is "pretty much," and 3 is "very much."
*$P < .10$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BT = behavior therapy, DBD = Disruptive Behavior Disorders Rating Scale, IQ = intelligence quotient.

subjects (N = 27) randomly assigned to receive atomoxetine alone.* All data were collected between March 2007 and May 2008. The clinical trial began after completion of baseline assessment, which was followed by 8 weeks of administering atomoxetine (including a 3-week titration period). Behavior therapy for children in the atomoxetine + BT condition (weeks 0 through 8) began simultaneously with the start of medication. Unless otherwise noted, outcome measures were completed before the start of treatment (week 0, referred to as pretreatment) and again at the end of treatment (week 8, referred to as posttreatment).

Behavior Therapy

The behavior therapy primarily focused on techniques that could be implemented by parents and teachers without extensive, ongoing intervention from mental health professionals at the school to mirror what could be feasibly done in outpatient mental health settings. There were 3 components to the behavior therapy: a parenting program, a social skills program, and a school-based daily report card. The parenting program consisted of 8 sessions of the Community Oriented Parent Education (COPE) program.[42] The COPE model is an evidenced-based parenting program that uses social learning principals to teach parents techniques designed to promote their child's positive behaviors, improve their self-regulation, and reduce their antisocial behaviors.[43] Topics covered included the principals of social learning theory, developing and implementing house rules, attending to positive behaviors, ignoring minor problematic behaviors, using Premack contingencies, making effective commands, using time-out effectively, managing behavior in public, problem solving in the family, and working with schools. Following the COPE model, these topics were presented and discussed in large and small group formats using videotape, modeling, and role-play. Sessions were held weekly for 2 hours and were conducted by advanced graduate students or doctoral-level clinicians in clinical child psychology. Parents attended an average of 6.7 sessions (SD = 1.9 sessions), with a range of 2 to 8 sessions. The majority of families (62%) attended all 8 sessions, with 82% completing 6 or more.

While parents were in the COPE sessions, children attended a social skills program for 8 two-hour sessions run simultaneously with the parenting program; these were modeled after established treatment programs at our center.[44,45] Each session began with a brief description of the social skill of the day, which was presented to the child

*Because the parent training group was a key component of the behavioral treatment, 2 sets of enrolled siblings were each randomly assigned as a single unit.

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didactically and through modeling and role-playing. The social skills were cooperation, participation, validation, and communication, with each topic presented in 2 separate sessions. Next, children participated in social activities (board games or recreational activities), during which social skills were monitored and praised when expressed appropriately. Social-skills sessions were conducted by graduate students in clinical psychology, with assistance from undergraduate interns.

A daily report card was developed and implemented for all children in the combined (atomoxetine + BT) treatment group. The daily report card was developed by clinical staff in consultation with the child's teacher following a standard format (available for downloading at http://ccf.buffalo.edu/pdf/Home_Daily_Report_Card.pdf). Specific behavioral goals were identified for each child targeting areas of impairment in school (eg, following rules, completing assignments accurately, complying with adults, teasing). Teachers evaluated the child's performance on these goals multiple times during the day by circling whether the child did or did not accomplish his or her goal, and teachers provided the child feedback about his or her performance. At the end of the day, teachers sent 1 copy of the daily report card home with the child. Parents were taught to monitor the daily report card and provide an appropriate consequence for the child's behavior (ie, a reward for positive performance and loss of privileges for negative performance).

Medication

All medication was dosed openly as the primary goal of the study was to compare the differences between combined therapy versus atomoxetine alone. An open-label design was selected because the efficacy of atomoxetine for improving ADHD symptoms has been well established, and the primary outcome measure of direct classroom observation has been demonstrated to be insensitive to placebo effects, minimizing the need for a blinded medication arm.[29] A weight-based dosing protocol similar to prior studies of atomoxetine was used,[5,14] with medication provided in a single, morning dose. All subjects started on 0.5 mg/kg/d (rounded to the nearest 5-mg dose) for 3 days, then 0.8 mg/kg/d for the next 4 days. On day 8, medication for all subjects was increased to 1.2 mg/kg/d in the form of a single AM dose.

Phone visits were completed by a study physician in weeks 1 and 2 to assess drug tolerability. Subjects were brought into the study center after 3 weeks of medication usage to assess tolerability and to determine whether a further dose increase was advisable. Consistent with past studies of atomoxetine, our study allowed subjects to increase dosage to a maximum of 1.8 mg/kg/d if their CGI-S score was 4 or worse.[5,14] No dose increases were allowed after completion of week 4. For the latter 2 doses (1.2 mg/kg/d and 1.8 mg/kg/d), subjects were allowed to divide the dose to address tolerability or efficacy concerns. In total, 61% of the sample was maintained on a single dose, with the other 39% using a twice-a-day dosing schedule, typically morning and dinnertime. The mean dose was higher in the split-dosing group (1.56 mg/kg/d) than in the once-a-day group (1.35 mg/kg/d) ($F_{1,54} = 6.37$, $P = .015$), which was not surprising as the most common reason for split dosing was to address residual symptoms later in the day. Subjects receiving split dosing were equally distributed across the 2 treatment groups (atomoxetine vs atomoxetine + BT).

Primary Efficacy Measure

Observations were conducted using the Student Behavior Teacher Response Observation Code (W.E.P.; A. R. Greiner, BS; E. M. Gnagy, BA; unpublished manual, March 2006; available upon request). The assessments were completed by 2 research assistants who received 10 hours of training in the observation system, including coding at least 4 videotaped assessments. After training, observers practiced coding in classrooms with a master coder. Prior to completing the observations, observers met with teachers to determine the rules and expectations for their classroom. After learning the classroom rules, observers watched children in their classrooms for 30 minutes during an academic activity and recorded each time the subject violated a classroom rule. The number of total classroom rule violations was used as the primary outcome measure for the study. Other work by our group has found that youth with ADHD will exhibit, on average, 10 rule violations per 30-minute observation period,[13] while children without ADHD will exhibit 2 or less.[46]

Reliability for this study was evaluated by having a second observer independently code approximately 30% of the total observations. Interrater reliability was 0.89, and the mean difference between raters was also not significant ($t_{42} = 0.62$, $P = .538$). The primary observer also participated in the behavior therapy arm and was therefore not blind to group assignment. However, the second (reliability) observer was blinded to group assignment, and both observers followed manualized scoring procedures for coding the observed behaviors.

Secondary Efficacy Measures

Disruptive Behavior Disorders Rating Scale. The DBD[37] consists of 45 items that are the *DSM-IV* symptoms of ADHD, oppositional defiant disorder, and conduct disorder. Items on the DBD were rated by parents and teachers using Likert scales that ranged from 0 (not at all) to 3 (very much). The factor structure, reliability, and validity of the DBD have been supported in multiple studies.[47–50] Mean scores were computed for the ADHD-inattention, ADHD-hyperactive/impulsive, oppositional defiant disorder, and conduct disorder scales and were used in analyses.

Social Skills Rating Scale (SSRS). The SSRS[51] is a 55-item (for parents) to 57-item (for teachers) scale that was completed by parents and teachers to measure children's social skills and problem behaviors. Academic competence is also evaluated on the teacher version but not the parent version. Items are rated from 0 (not at all) to 2 (very often) for the social skills and problem behaviors scales and from 0 (lowest 10%) to 5 (highest 10%) for the academic competence scale.

Academic Performance Rating Scale (APRS). The APRS[52] is a 19-item scale that was completed by teachers to measure children's academic and behavioral performance on a 1–5 Likert scale. Mean scores were computed for the academic success, academic productivity, and impulse control subscales and were used in analyses.

Impairment Rating Scale (IRS). The IRS[53] is a 6-item (for teachers) to 8-item (for parents) measure that uses visual analog scales to evaluate the child's problem level and need for treatment in developmentally important areas, such as peer relationships, adult-child relationships, academic performance, and classroom behavior. The scale is scored from 0 (no problem) to 6 (extreme problem). It was completed by parents and teachers. The scale has excellent test-retest and interrater reliability and well-supported validity.[53,54]

Pittsburgh Side Effects Rating Scale (PSERS). The PSERS[55,56] measures adverse events commonly associated with stimulant medication and has been used in multiple studies of ADHD.[57] For this study, the PSERS was completed by parents and teachers and was modified to also assess adverse emotional events that have been reported with atomoxetine, including suicidal statements. The resulting scale consisted of 13 items (for teachers) or 14 items (for parents; additional sleep item) rated from 0 (none) to 3 (severe). An overall side effects score was computed by averaging across all ratings and was used in analyses. Because of concerns over adverse emotional reactions with atomoxetine,[17] 3 specific items were examined separate from the total score: (1) suicidal statements (eg, "I wish I was dead"); (2) being crabby/irritable; and (3) being tearful, sad, depressed. In addition, weight, height, and resting blood pressure were monitored at each office visit (weeks 0, 3, and 8).

Children's Depression Rating Scale-Revised (CDRS-R). The CDRS-R[58] is a 17-item scale that measures *DSM-IV* symptoms of depression including suicidal thoughts. Items are completed using scales of 1 to 5 or 1 to 7, with 1 designating no difficulty with that symptom. It is the most widely used measure of pediatric depression in clinical trials.[59] The CDRS-R was completed in an interview format, with parents and children evaluated separately. Results were combined by taking the maximum (most depressed) scores across informant on an item-by-item basis. In cases of marked discrepancy between informants, the score deemed most reliable was used. The complete CDRS-R was administered pretreatment and posttreatment, with the suicide item (item 13) administered over the phone at weeks 1 and 2, as well. The total score and the suicide item were used in analyses.

Daily Report Card (DRC)/Individual Target Behavior Evaluation (ITBE). As described earlier, a DRC was developed for each child in the atomoxetine + BT group at the start of the clinical trial. For the DRC, teachers evaluated the child's performance on these treatment goals at least twice per day. The child's ability to meet these goals was summarized by computing the total percent of goals achieved each week. A form similar to the DRC, the ITBE,[60] was developed for children not in the behavioral treatment (atomoxetine-only group). Like the DRC, the ITBE listed behavioral goals specific to each child, and teachers evaluated children's performance on these goals throughout the day. However, for the ITBE, teachers did not provide feedback to the child about his or her performance, nor did parents monitor the form or provide a positive or negative consequence to reinforce the child's performance. Thus, the DRC served as both a measure of and treatment for children's school behavior, whereas the ITBE served as a measure of but not a treatment for school behavior.

Clinical Global Impressions (CGI) scale. The CGI[41] is a clinician-completed scale that measures treatment response and current symptom severity. The CGI-S and CGI-Improvement (CGI-I) scales were completed by the MD- or PhD-level clinician who completed the baseline and endpoint assessments for that subject.

Treatment satisfaction. At the end of treatment, parents were asked to complete ratings designed to evaluate their satisfaction with the treatments they were offered using the treatment satisfaction scale employed in the MTA (W.E.P.; D. Erhardt, PhD; E. M. Gnagy, BA; et al, manuscript submitted). Ratings were completed using Likert scales that ranged from 1 (strongly disagree) to 7 (strongly agree).

Statistical Analyses

Except as noted below, data were analyzed using SAS for Windows (version 9.1.3; SAS Institute, Inc; Cary, North Carolina) Proc Mixed, using a series of 2 × 2 ANOVAs (medication/time [pretreatment vs posttreatment] × group [atomoxetine only vs atomoxetine + BT]), with repeated measures on the medication/time factor. Significant interactions were followed up with simple effects tests and by examining means, standard deviations, and effect sizes. An advantage of SAS Proc Mixed is that it uses advanced methods for handling missing data that allow subjects with partial data to be incorporated into the analyses. Although separate ANOVAs were done for each measure, results of ANOVAs are divided by effects rather than by measure because there were numerous effects of medication/time and relatively few effects involving group.

Table 2 provides means and standard deviations for the full sample and for each treatment group and also summarizes ANOVA results. Table 3 summarizes effect sizes for the study. Two types of effect sizes were computed. First, standardized mean change effect sizes[61] were computed to evaluate the magnitude of change over medication/time for the full sample and for each treatment group. These effect sizes were computed using the following formula: (posttreatment mean – pretreatment mean)/pretreatment SD. Second, Cohen *d* effect sizes[62] were computed to evaluate the magnitude of difference between the atomoxetine-only and the atomoxetine + BT groups at posttreatment. These effect sizes were computed using the following formula: (atomoxetine-only mean – atomoxetine + BT mean)/pretreatment pooled SD. Guidelines for interpreting effect sizes include the following: less than 0.20 = minimal or no difference; 0.20 to

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Table 2. Means and Standard Deviations for Rating Scores for the Full Sample and by Treatment Group With Results From Analyses of Variance

Measure	Full Sample (N = 56)		Atomoxetine Only (n = 27)		Atomoxetine + BT (n = 29)		Results, Analysis of Variance
	Pretreatment, Mean (SD)	Posttreatment, Mean (SD)	Pretreatment, Mean (SD)	Posttreatment, Mean (SD)	Pretreatment, Mean (SD)	Posttreatment, Mean (SD)	
Daily Report Card/Individual Target Behavior Evaluation[a]	72.28 (19.29)	80.65 (18.02)	71.76 (18.72)	77.84 (21.01)	72.71 (20.01)	82.90 (15.13)	M
Observed classroom rule violations,[b] no.	9.89 (6.92)	5.14 (6.77)	9.15 (7.48)	4.69 (6.48)	10.59 (6.42)	5.60 (7.17)	M
Clinical Global Impressions-Severity of Illness scale[41]	4.31 (0.51)	3.51 (0.83)	4.31 (0.47)	3.50 (0.91)	4.31 (0.55)	3.52 (0.77)	M
Children's Depression Rating Scale-Revised[58]							
Suicidal ideation	1.37 (0.78)	1.12 (0.48)	1.46 (0.91)	1.23 (0.65)	1.26 (0.62)	1.00 (0.00)	M
Total score	25.07 (5.24)	23.20 (5.87)	24.63 (4.48)	24.46 (7.30)	25.48 (5.90)	21.78 (3.25)	G × M
Teacher ratings							
Disruptive Behavior Disorders Rating Scale[37]							
ADHD-inattentive	1.80 (0.80)	1.24 (0.71)	1.82 (0.68)	1.35 (0.66)	1.79 (0.91)	1.12 (0.77)	M
ADHD-hyperactive/impulsive	1.37 (0.78)	0.93 (0.74)	1.31 (0.67)	0.91 (0.66)	1.42 (0.88)	0.96 (0.83)	M
Oppositional defiant disorder	1.04 (0.80)	0.64 (0.66)	0.89 (0.69)	0.71 (0.66)	1.18 (0.89)	0.57 (0.66)	M
Conduct disorder	0.24 (0.24)	0.11 (0.16)	0.26 (0.27)	0.11 (0.14)	0.22 (0.22)	0.11 (0.18)	M
Social Skills Rating Scale[51]							
Social skills	26.32 (9.76)	30.88 (9.29)	27.26 (8.15)	31.28 (8.21)	25.45 (11.13)	30.50 (10.36)	M
Problem behavior	16.82 (6.54)	14.00 (6.48)	16.81 (6.32)	14.32 (6.67)	16.83 (6.84)	13.69 (6.40)	M
Academic competence	25.25 (7.89)	26.75 (7.43)	24.59 (6.92)	25.52 (6.20)	25.86 (8.77)	27.92 (8.40)	M$^+$
Academic Performance Rating Scale[52]							
Academic success	2.91 (0.90)	3.18 (0.85)	2.86 (0.80)	3.03 (0.82)	2.96 (0.99)	3.31 (0.88)	M
Academic productivity	2.85 (0.80)	3.21 (0.74)	2.82 (0.71)	3.16 (0.75)	2.87 (0.89)	3.26 (0.74)	M
Impulse control	2.40 (0.76)	2.69 (0.88)	2.40 (0.75)	2.45 (0.69)	2.40 (0.78)	2.91 (0.98)	M, G × M
Impairment Rating Scale[53]							
Peer relationships	3.61 (2.06)	2.14 (1.89)	3.56 (2.08)	2.17 (1.95)	3.66 (2.07)	2.12 (1.88)	M
Teacher relationships	3.48 (2.21)	2.20 (1.99)	3.41 (2.21)	2.38 (2.14)	3.55 (2.25)	2.04 (1.86)	M
Academic performance	4.46 (1.80)	2.71 (2.04)	4.59 (1.72)	2.83 (2.28)	4.34 (1.90)	2.60 (1.83)	M
Classroom behavior	4.14 (1.91)	2.24 (2.15)	4.19 (1.84)	2.33 (2.20)	4.10 (2.01)	2.16 (2.13)	M
Overall impairment	4.41 (1.67)	2.63 (1.98)	4.48 (1.40)	2.63 (2.14)	4.34 (1.91)	2.64 (1.85)	M
Pittsburgh Side Effects Rating Scale[55]							
Irritable, crabby	0.23 (0.52)	0.23 (0.59)	0.15 (0.36)	0.21 (0.66)	0.37 (0.79)	0.23 (0.51)	NS
Depressed, sad	0.15 (0.41)	0.23 (0.47)	0.07 (0.27)	0.21 (0.41)	0.22 (0.51)	0.23 (0.51)	NS
Suicidal thoughts	0.02 (0.14)	0.00 (0.00)	0.04 (0.19)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	NS
Overall side effects	0.20 (0.22)	0.22 (0.22)	0.19 (0.22)	0.21 (0.22)	0.24 (0.25)	0.22 (0.23)	NS
Parent ratings							
Disruptive Behavior Disorders Rating Scale[37]							
ADHD-inattentive	2.10 (0.61)	1.45 (0.66)	2.15 (0.58)	1.67 (0.67)	2.05 (0.63)	1.22 (0.57)	M, G × M$^+$
ADHD-hyperactive/impulsive	1.72 (0.61)	1.12 (0.65)	1.81 (0.59)	1.28 (0.66)	1.64 (0.63)	0.95 (0.61)	M, G$^+$
Oppositional defiant disorder	1.31 (0.63)	1.04 (0.64)	1.26 (0.57)	1.16 (0.62)	1.35 (0.69)	0.93 (0.66)	M, G × M$^+$
Conduct disorder	0.21 (0.29)	0.14 (0.16)	0.17 (0.17)	0.14 (0.14)	0.25 (0.37)	0.14 (0.19)	NS
Social Skills Rating Scale[51]							
Social skills	41.31 (11.22)	44.31 (10.15)	42.04 (9.11)	45.00 (8.56)	40.64 (13.01)	43.57 (11.79)	M
Problem behavior	20.44 (5.48)	18.25 (6.59)	19.58 (5.62)	19.72 (6.53)	21.25 (5.32)	16.65 (6.42)	M, G × M
Impairment Rating Scale[53]							
Peer relationships	3.52 (1.79)	2.76 (1.77)	3.41 (1.74)	2.84 (1.62)	3.62 (1.86)	2.67 (1.95)	M
Sibling relationships	3.84 (2.21)	2.51 (1.99)	3.67 (2.30)	2.92 (1.80)	4.00 (2.14)	2.08 (2.12)	M, G × M$^+$
Parent relationships	3.89 (1.75)	2.88 (1.83)	3.52 (2.03)	2.84 (1.70)	4.24 (1.41)	2.92 (2.00)	M
Academic performance	5.07 (0.99)	3.08 (1.79)	5.26 (0.90)	3.48 (1.71)	4.90 (1.05)	2.67 (1.81)	M, G$^+$
Classroom behavior	4.64 (1.53)	2.90 (1.83)	4.48 (1.55)	3.24 (1.71)	4.79 (1.52)	2.54 (1.91)	M, G × M$^+$
Family relationships	4.54 (1.40)	3.12 (1.74)	4.41 (1.58)	3.12 (1.64)	4.66 (1.23)	3.13 (1.87)	M
Overall impairment	4.75 (1.01)	3.24 (1.70)	4.78 (0.85)	3.52 (1.39)	4.72 (1.16)	2.96 (1.97)	M
Pittsburgh Side Effects Rating Scale[55]							
Irritable, crabby	0.82 (0.91)	0.76 (0.86)	0.78 (1.01)	0.72 (0.79)	0.93 (0.88)	0.79 (0.93)	NS
Depressed, sad	0.51 (0.74)	0.49 (0.77)	0.41 (0.57)	0.36 (0.57)	0.59 (0.87)	0.63 (0.92)	NS
Suicidal thoughts	0.06 (0.43)	0.04 (0.20)	0.00 (0.00)	0.04 (0.20)	0.10 (0.56)	0.04 (0.20)	NS
Overall side effects	0.45 (0.32)	0.37 (0.32)	0.41 (0.33)	0.34 (0.27)	0.46 (0.29)	0.38 (0.37)	NS

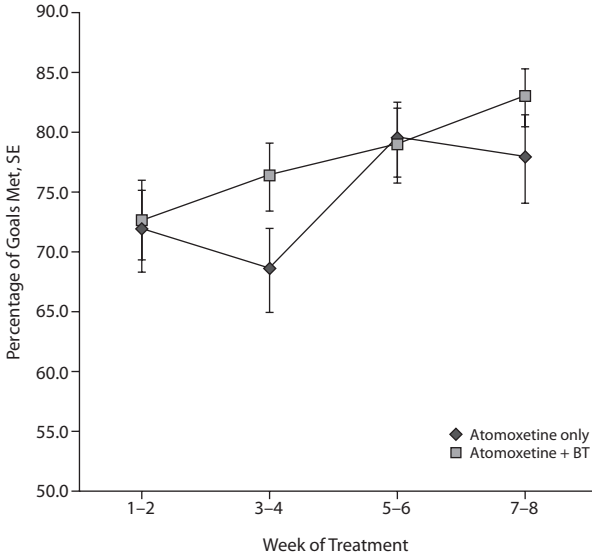
[a]Pretreatment = weeks 1 and 2; posttreatment = weeks 7 and 8.
[b]Observations were conducted using the Student Behavior Teacher Response Observation Code (W.E.P.; A. R. Greiner, BS; E. M. Gnagy, BA; unpublished manual, March 2006; available upon request).
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BT = behavior therapy, G$^+$ = marginal main effect of group ($P < .10$), G × M = significant group × medication/time interaction ($P < .05$), G × M$^+$ = marginal group × medication/time interaction ($P < .10$), M = significant main effect of medication/time ($P < .05$), M$^+$ = marginal main effect of medication/time ($P \leq .10$), NS = not significant ($P > .10$).

Table 3. Standardized Mean Change Effect Sizes and Cohen *d* Effect Sizes for Treatment Outcome Measures

Measure	Standardized Mean Change[a]			
	Full Sample (N = 56)	Atomoxetine Only (n = 27)	Atomoxetine + BT (n = 29)	Posttreatment Cohen *d*[b]
Daily Report Card/Individual Target Behavior Evaluation[c]	0.43	0.33	0.53	0.26
Observed classroom rule violations,[d] no.	0.69	0.64	0.72	−0.13
Clinical Global Impressions-Severity of Illness scale[41]	1.57	1.59	1.55	−0.04
Children's Depression Rating Scale-Revised[58]				
Suicidal ideation	0.39	0.30	0.61	0.49
Total score	0.36	0.03	0.71	0.51
Teacher ratings				
Disruptive Behavior Disorders Rating Scale[37]				
ADHD-inattention	0.70	0.59	0.84	0.29
ADHD-hyperactive/impulsive	0.56	0.51	0.59	−0.06
Oppositional defiant disorder	0.50	0.23	0.76	0.18
Conduct disorder	0.54	0.63	−0.46	0.00
Social Skills Rating Scale[51]				
Social skills	0.47	0.41	0.52	−0.08
Problem behavior	0.43	0.38	0.48	0.10
Academic competence	0.19	0.12	0.26	0.30
Academic Performance Rating Scale[52]				
Academic success	0.30	0.19	0.39	0.31
Academic productivity	0.45	0.43	0.49	0.13
Impulse control	0.38	0.07	0.67	0.61
Impairment Rating Scale[53]				
Peer relationships	0.71	0.67	0.75	0.02
Teacher relationships	0.58	0.47	0.68	0.15
Academic performance	0.97	0.98	0.97	0.13
Classroom behavior	0.99	0.97	1.02	0.09
Overall impairment	1.07	1.11	1.02	−0.01
Pittsburgh Side Effects Rating Scale[55]				
Irritable, crabby	0.00	−0.12	0.27	−0.04
Depressed, sad	−0.20	−0.34	−0.02	−0.05
Suicidal thoughts	0.14	0.29	0.00	0.00
Overall side effects	−0.09	−0.09	0.09	−0.05
Parent ratings				
Disruptive Behavior Disorders Rating Scale[37]				
ADHD-inattention	1.07	0.79	1.36	0.74
ADHD-hyperactive/impulsive	0.98	0.87	1.13	0.54
Oppositional defiant disorder	0.43	0.16	0.67	0.37
Conduct disorder	0.24	0.10	0.38	0.00
Social Skills Rating Scale[51]				
Social skills	0.27	0.26	0.26	−0.13
Problem behavior	0.40	−0.03	0.84	0.56
Impairment Rating Scale[53]				
Peer relationships	0.42	0.32	0.53	0.09
Sibling relationships	0.60	0.34	0.87	0.38
Parent relationships	0.58	0.39	0.75	−0.05
Academic performance	2.01	1.80	2.25	0.82
Classroom behavior	1.14	0.81	1.47	0.46
Impact on family	1.01	0.92	1.09	−0.01
Overall impairment	1.50	1.25	1.74	0.55
Pittsburgh Side Effects Rating Scale[55]				
Irritable, crabby	0.07	0.07	0.15	−0.08
Depressed, sad	0.03	0.07	−0.05	−0.36
Suicidal thoughts	0.05	−0.09	0.14	0.00
Overall side effects	0.25	0.22	0.25	−0.13

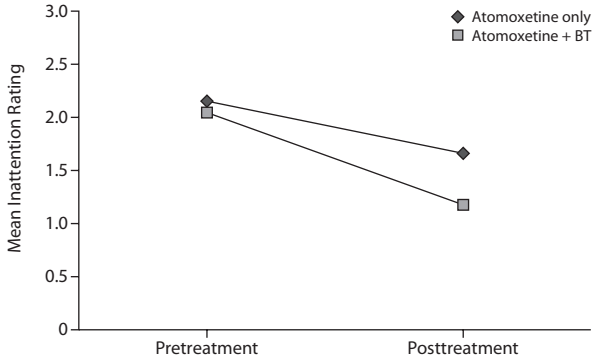
[a]Standardized mean change effect sizes[61] show magnitude of change between pretreatment and posttreatment, with positive values indicating better outcomes.
[b]Cohen *d* effect sizes[62] show magnitude of differences between groups at posttreatment, with positive values indicating better scores for the atomoxetine + BT group than for the atomoxetine-only group.
[c]Pretreatment = weeks 1 and 2; posttreatment = weeks 7 and 8.
[d]Observations were conducted using the Student Behavior Teacher Response Observation Code (W.E.P.; A. R. Greiner, BS; E. M. Gnagy, BA; unpublished manual, March 2006; available upon request).
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BT = behavior therapy.

Figure 1. Daily Report Card/Individual Target Behavior Evaluation Performance as a Function of Group and Medication/Time



Abbreviation: BT = behavior therapy.

Figure 2. Parent Ratings of ADHD-Inattention on the Disruptive Behavior Disorders Rating Scale as a Function of Group and Medication/Time



Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BT = behavior therapy.

0.49 = small to moderate difference; 0.50 to 0.79 = moderate to large difference; and 0.80 and above = large difference.[62]

The DRC/ITBE was collected weekly, starting simultaneously with or shortly after the onset of medication treatment, and was therefore examined using a 2 × 4 ANOVA (2 groups × 4 time periods [weeks 1/2 vs 3/4 vs 5/6 vs 7/8]). The CGI-I was evaluated only at posttreatment and was analyzed using a 2 × 3 χ^2 analysis (2 groups × 3 levels of improvement/nonimprovement [worse vs no change vs improved]). For treatment satisfaction data, parent responses were divided into whether or not they agreed with the statement, and the 2 treatment groups were then compared using a series of 2 × 3 χ^2 analyses (2 groups [atomoxetine only vs atomoxetine + BT] × 3 levels of satisfaction/nonsatisfaction [worse vs no change vs improved]).

RESULTS

Medication/Time Effects

The mean dose at study endpoint was 1.44 mg/kg/d (SD = 0.2988, minimum dose = 1.1, maximum dose = 2.0 mg/kg/d), with those in the atomoxetine + BT group having a mean dose of 1.40 mg/kg/d versus a dose of 1.47 mg/kg/d for the atomoxetine-only group (the difference was nonsignificant). As can be seen in Tables 2 and 3, subjects improved on nearly every measure, with small to moderate standardized mean change effect sizes for teacher ratings and moderate to large standardized mean change effect sizes for parent ratings.

Classroom observations. As shown in Table 2, the ANOVA examining classroom observation data resulted in a significant main effect of medication/time ($F_{1,49} = 18.24$, $P < .0001$). Means and effect sizes (see Tables 2 and 3) showed that subjects had a moderate to large decrease in classroom rule violations over the 8-week trial, but there was no difference between the groups posttreatment.

Daily Report Card/Individual Target Behavior Evaluation. There was a significant main effect of medication/time ($F_{3,127} = 4.75$, $P = .0036$) but no other significant effects. The main effect of medication/time showed that subjects performed better on the DRC/ITBE the longer they were receiving medication (see Tables 2 and 3). Across groups, subjects increased their weekly DRC/ITBE percentages from 72% to 81% (Figure 1). By the end of treatment (weeks 7 and 8), 75.6% of all subjects were achieving three-quarters or more of their daily goals compared to 48.9% at baseline. There were similar rates of subjects' achieving 75% of their DRC goals between the 2 treatment groups at baseline (atomoxetine only = 42.9%; atomoxetine + BT = 54.2%) and at endpoint (atomoxetine only = 71.4%; atomoxetine + BT = 79.2%).

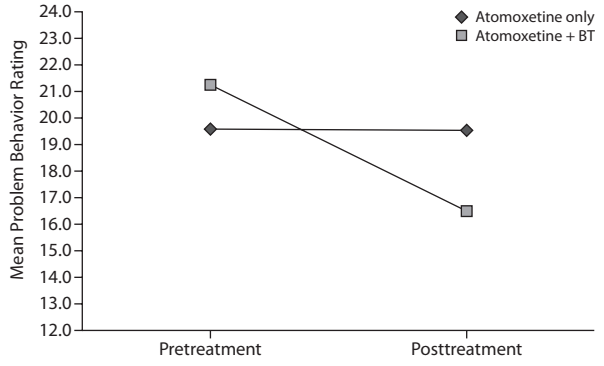
Clinical Global Impressions-Improvement scale. In the atomoxetine-only group, 14 subjects (51.9%) were rated as much or very much improved, and, in the atomoxetine + BT group, 16 subjects (55.2%) were rated as much or very much improved. The χ^2 analysis comparing groups was not significant.

Group Effects

As summarized in Table 2, there were significant or marginally significant effects involving group (atomoxetine only vs atomoxetine + BT) for parent ratings on the DBD, the SSRS, the IRS, and the CDRS-R. There were also significant effects of group for teacher ratings on the APRS. These results are reported next.

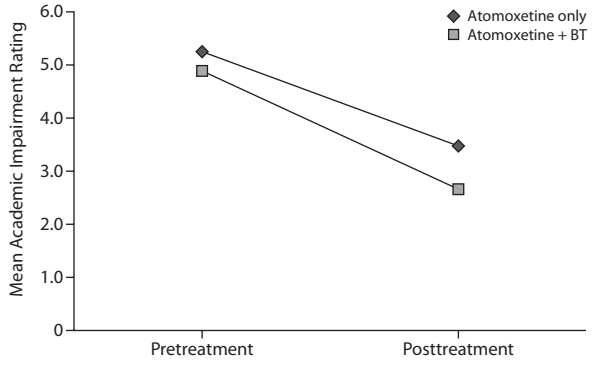
Disruptive Behavior Disorders Rating Scale. There was a marginal group × medication/time interaction for parent-rated symptoms of inattention ($F_{1,46} = 3.48$, $P = .0684$). Simple effects and examination of means (Figure 2) showed that the groups did not differ at baseline, but the

Figure 3. Parent Ratings of Problem Behavior[a] on the Social Skills Rating Scale as a Function of Group and Medication/Time



[a]Problem behavior ratings are totals for the 3 components of the problem behavior subscale of the Social Skills Rating Scale.
Abbreviation: BT = behavior therapy.

Figure 4. Parent Ratings of Academic Impairment on the Impairment Rating Scale as a Function of Group and Medication/Time



Abbreviation: BT = behavior therapy.

atomoxetine + BT group had lower inattention scores posttreatment ($F_{1,46} = 7.35$, $P = .0094$). There was also a marginal main effect of group for parent ratings of hyperactivity/impulsivity ($F_{1,54} = 2.74$, $P = .10$). The groups did not differ at baseline, but the atomoxetine + BT group had marginally lower scores at posttreatment ($F_{1,46} = 3.57$, $P = .0651$). Parent ratings of oppositional defiant disorder also showed a marginally significant group × medication/time interaction ($F_{1,46} = 3.76$, $P = .0585$), indicating that both groups improved, but improvement was largest for atomoxetine + BT. However, unlike the results for ADHD symptoms, the results for oppositional defiant disorder symptoms did not differ between groups posttreatment. There were no main effects or interactions of group for teacher ratings on the DBD.

Social Skills Rating Scale. The problem behavior subscale of the SSRS showed a significant group × medication/time interaction ($F_{1,46} = 9.42$, $P < .0001$) for parent ratings. Simple-effects follow-up tests and examination of means (Figure 3) showed that atomoxetine + BT had significantly lower parent-rated problem behaviors over medication/time ($F_{1,46} = 16.73$, $P = .0002$), but the atomoxetine-only group did not change. To assess more specific behaviors, we also analyzed the 3 subscales that make up the total problem behavior scores: externalizing, internalizing, and hyperactive. For all 3 subscales, the group × medication/time interaction remained significant, with only the atomoxetine + BT group having significantly lower parent ratings over medication/time (externalizing: $F_{1,46} = 6.18$, $P = .0166$; internalizing: $F_{1,46} = 6.81$, $P = .0122$; hyperactive: $F_{1,46} = 24.83$, $P < .0001$). No effects of group were detected for the parent-rated social skills subscale or for any teacher ratings on the SSRS.

Impairment Rating Scale. There was a marginally significant main effect of group for parent ratings of academic progress ($F_{1,54} = 4.01$, $P = .0503$). Simple-effects tests and examination of means (Figure 4) showed that groups did not differ at baseline, but the atomoxetine + BT group had less academic impairment at the end of treatment ($F_{1,47} = 4.09$, $P = .0489$). There was a marginal group × medication/time interaction for both sibling relationships ($F_{1,47} = 2.76$, $P = .10$) and classroom behavior ($F_{1,47} = 3.72$, $P = .0599$). In both cases, there was greater improvement in the combined therapy group, with effect sizes showing small to moderate advantages of atomoxetine + BT over atomoxetine only at posttreatment (see Table 3), but, unlike the results for academic progress, the differences in posttreatment group means did not reach significance. When the IRS results were analyzed categorically as impaired (3 or greater) or not impaired (less than 3), there was a trend in the overall parent IRS rating favoring combined therapy (37.5% no longer impaired in the atomoxetine + BT group vs 16% for the atomoxetine-only group; $\chi^2 = 2.9$, $P = .088$).

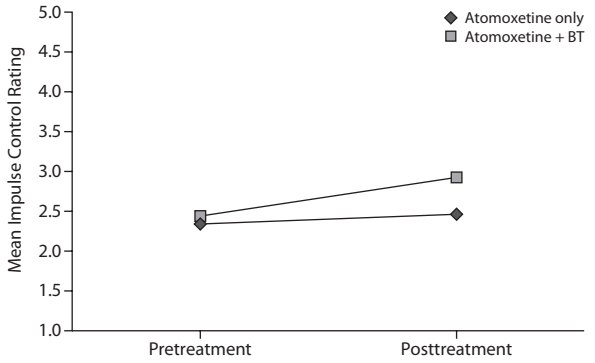
Children's Depression Rating Scale-Revised. Examination of the CDRS-R total score resulted in a significant group × medication/time interaction ($F_{1,47} = 4.72$, $P = .0349$), with the atomoxetine + BT group having marginally lower depression scores posttreatment ($F_{1,47} = 4.72$, $P = .0842$) despite comparable baseline scores between groups. Examination of the suicidal thoughts item resulted in a significant main effect of medication/time ($F_{1,47} = 4.77$, $P = .0340$), with means showing that suicidal thoughts decreased significantly over time but with no difference between groups.

Academic Performance Rating Scale. The only teacher rating to demonstrate significant group × medication/time interaction was the impulse control subscale of the APRS ($F_{1,49} = 4.15$, $P = .0470$). Simple-effects tests and examination of means (Figure 5) showed that the groups did not differ at pretreatment, but the atomoxetine + BT group had significantly better teacher-rated impulse control at posttreatment ($F_{1,49} = 4.27$, $P = .0441$). No group effects were detected for the other subscales.

Treatment Satisfaction

As shown in Table 4, the majority of parents had favorable views of the interventions, felt their child's problems

Figure 5. Teacher Ratings of Impulse Control on the Academic Performance Rating Scale as a Function of Group and Medication/Time



Abbreviation: BT = behavior therapy.

Table 4. Number and Percent of Parents Who Agree With Treatment Satisfaction Statements as a Function of Group

Satisfaction Statement	Atomoxetine Only (n = 13), n (%)	Atomoxetine + BT (n = 12), n (%)	χ^2 Value	*P* Value
1. Intervention(s) fit child's need	12 (92.3)	12 (100)	0.96	.27
2. Child's problem(s) improved	11 (84.6)	11 (91.7)	0.29	.588
3. Satisfied with child's progress	10 (76.9)	12 (100)	3.15	.076
4. Satisfied with child's medication	10 (76.9)	11 (91.7)	1.01	.315
5. Satisfied with intervention, overall	13 (100)	11 (91.7)	1.13	.288
6. Would recommend the intervention	11 (84.6)	11 (91.7)	0.29	.588
7. Optimistic about child's future	11 (84.6)	12 (100)	2.01	.157

Abbreviation: BT = behavior therapy.

had improved, felt optimistic about their child's future, and would recommend the interventions to others. In addition, the majority of parents agreed that they were satisfied with their child's progress, but satisfaction was marginally higher in the combined group ($\chi^2_1 = 3.15$, $P = .076$).

Side Effects

All PSERS items had a mean score well within the mild range (below 1). The most common adverse events reported by parents were stomachaches (12%), tiredness (10%), irritability (14%), and anxiousness (14%), whereas teachers most commonly reported tiredness (8%) and skin picking (6%). These side effects were frequently reported at baseline, with several side-effect ratings actually improving with drug treatment (parent-rated skin picking: $F_{1,47} = 5.8$, $P < .05$; teacher-rated anxiety: $F_{1,47} = 5.5$, $P < .05$). Only teacher-reported headaches significantly worsened in severity over time ($F_{1,46} = 4.30$, $P = .04$). Still, the mean endpoint severity score was negligible (0.36), placing it well within the mild range. There were no group differences in drug tolerability. From baseline to 8-week endpoint for the entire study population, there were no significant mean changes in weight (33.6 to 33.7 kg), systolic blood pressure (100.4 to 100.6 mm Hg), or diastolic blood pressure (63.5 to 63 mm Hg).

Among the subjects who discontinued early, 1 dropped out due to adverse effects, namely increased emotional lability (described by the parent as an increased propensity to cry or argue when upset). However, there was no significant worsening in the groups' mood ratings as measured on the PSERS or CDRS-R (see Table 2), nor were there any cases of self-harm.

DISCUSSION

In this 8-week open-label trial, atomoxetine was effective for improving school functioning across a variety of measures including direct observation in children with ADHD. In addition, medication treatment was associated with improved symptom control and functioning at home across a variety of domains including social skills, parent-child relationships, and academic performance. The addition of a home-based behavior therapy program with a teacher-implemented DRC led to incremental improvements in ADHD symptoms, oppositional defiant disorder symptoms, and other functional outcomes at home while improving parental perception of academic performance. The DRC results suggest that behavior therapy was also associated with more consistent performance in the classroom during the first few weeks of atomoxetine usage, emphasizing the potential value of initiating behavior therapy at the same time as or before starting treatment with atomoxetine.

On the other hand, there were no significant group differences on parent ratings of social skills and peer relationships or on most of the direct measures of classroom functioning (direct observations and teacher report), leading to the conclusion that the low-intensity school-based component of the behavior therapy arm used in this study (the DRC) provided little additional enhancement of classroom functioning beyond atomoxetine alone.

Taken together, these results suggest that the addition of a home-based behavior therapy program would be most beneficial for children taking atomoxetine whose parents still report an impairing level of oppositional defiant disorder and ADHD symptoms at home. A more intensive behavior therapy program with additional school-based interventions may be needed for children with marked peer problems or those whose teachers report persistent impairment after treatment with atomoxetine.

The DRC results support the efficacy of atomoxetine in classroom settings. It has been proposed that the DRC is a more precise estimate of actual classroom functioning than traditional rating scales like the APRS or SSRS because it is individually tailored to the needs of the specific child.[20,33,63] Across groups, subjects increased their weekly DRC/ITBE

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percentages from 72% to 81%. These results parallel those found in naturalistic trials of stimulants.[20,64] Although this change is small to moderate using effect-size metrics (see Table 3), it is noteworthy in that earning three-fourths of goals (75%) is often considered as acceptable functioning, as the child is receiving 3 pieces of positive feedback for every negative one. This 75% achievement rate has been used in prior ADHD studies as a marker of treatment response.[60] By the end of treatment (weeks 7 and 8), 76% of all subjects were achieving this benchmark compared to 49% prior to treatment.

Though groups did not differ statistically in their DRC/ITBE percentages at the end of treatment, there was a small to moderate effect size favoring the atomoxetine + BT group at the end of treatment (see Table 3). Visual inspection of group means for the DRC across each treatment week shows that children in the atomoxetine + BT group achieved treatment gains more consistently than those in the atomoxetine-only group, especially over the first 4 weeks of treatment (see Figure 1). Specifically, the 2 groups started at a virtually identical level on the DRC, but the atomoxetine + BT group showed linear increases thereafter, whereas the atomoxetine-only group showed a more variable response (ups and downs from week to week but an overall positive trajectory).

Prior studies of atomoxetine have found that optimal symptom control is not achieved until after the second week of treatment.[5,14,17] These results suggest that integrating a DRC with atomoxetine may be an effective way to achieve more consistent symptom relief in school during the time when medication is being titrated. Other work has found that in children with ADHD receiving special education services, the addition of a school DRC has lead to sustained improvement for the duration of the school year.[13] Parents used to the immediate effects of stimulants may be hesitant to initiate atomoxetine or other nonstimulants, especially during the school year, because of their delayed onset.[65] Implementation of a DRC and other school-based interventions may make use of these medications a more palatable option for parents, thereby improving initial treatment adherence and possibly enhancing long-term performance.

Most prior studies of atomoxetine have focused on parent-reported symptoms. Consequently, there are limited data collected on the efficacy of atomoxetine in school settings, especially for functional outcomes. The current study confirms the ability of atomoxetine to improve ADHD and oppositional defiant disorder symptoms at school, as rated by teachers. The effect sizes (see Table 3) are comparable to those reported in the only other school-based study of atomoxetine,[5] although they could be viewed as relatively smaller in light of the open-label design of this study. We also found improvements in functional outcomes (APRS, SSRS, IRS) across nearly all employed measures (see Tables 2 and 3), including direct classroom observation and an individualized DRC, which have not been previously employed in any atomoxetine trials. Observed effects on our global functioning measure (the IRS) were medium to large across all subscales, comparable to those observed with stimulants.[12]

Most impressively, the efficacy of atomoxetine was supported by the classroom observational data, which showed significant effects of atomoxetine, with a moderate to large decrease in classroom rule violations. While parent and teacher ratings may have been influenced by awareness that the child was getting active medication, the classroom observations were conducted using operational definitions with extensive training for raters and should therefore be relatively immune to rater bias that is inherent to parent and teacher ratings in open-label studies.[29] As stated in a review of assessment procedures for ADHD, "direct observations are the gold standard for evaluating treatment effects in controlled trials.…Direct observations avoid the biases that are inherent in rating scales—especially in treatment studies in which rater-blinding is not possible or is easily compromised."[33(p467)]

Parent ratings of school functioning also showed evidence of improvement. Parental report of children's need for treatment is a significant predictor of whether or not children receive school-based services such as special education interventions.[66–68] Therefore, enhancing parental perception of their child's school functioning may decrease the rate of special education referrals. Parent ratings of ADHD symptoms also showed large improvement in this study (see Table 3), with smaller changes in the level of oppositional defiant disorder symptoms and family relationships. Likewise, clinicians rated the majority of subjects in either group as much or very much improved on the CGI-I for ADHD.

In regard to group differences, a number of results showed that behavior therapy was associated with greater improvements in parent-rated functioning as compared to atomoxetine alone. Incremental benefits at home were seen on measures of functional impairment (SSRS, IRS) as well as symptom-driven measures (DBD). The most consistent effects of behavior therapy were reductions in parent-reported oppositional behaviors, with multiple measures of this domain (DBD oppositional defiant disorder subscale, SSRS problem behaviors subscale, and IRS sibling relationships subscale) showing incremental benefit of combined treatment versus medication alone. On the IRS, parents rated the combined group but not the atomoxetine-only group as normalized (mean endpoint IRS score < 3). This may have happened because the DRC that was part of behavior therapy provided parents with daily positive feedback from school versus the traditional standard of receiving a call from the school only when there is a concern. Hence, combining a DRC with medication may be one way of effectively providing information to parents about the benefits of the selected ADHD medication at school and thereby increasing the chances that they will continue to use it over time.

Combined therapy also led to greater reduction in problem behaviors at home. Whereas medication impacts only the child using the treatment, behavior therapy targets all

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members of the family and therefore would be more likely to effectively address conflicts between family members. For example, in the MTA, behavior therapy led to improvements in parenting skills as well as the child's symptom levels.[69] In contrast, a limited impact of behavior therapy was observed for peer relationships and social skills.[70] The few studies of ADHD documenting significant improvements in these domains used a more intensive behavior therapy program than the one employed here.[9] Combined treatment was also associated with a trend toward parents being more satisfied with their child's progress. Similar results were found in the MTA, in which parents rated treatments containing behavior therapy as more likeable and satisfying than those employing only medications (W.E.P.; D. Erhardt, PhD; E. M. Gnagy, BA; et al, manuscript submitted).

On the other hand, there were almost no differences between groups on other measures of classroom functioning. It was hypothesized that subjects in the combined treatment group would display greater improvements on the classroom observation assessment than those treated with only atomoxetine, but this did not occur. While examination of mean differences showed that combined treatment was associated with greater improvements across almost all measures in school (see Tables 2 and 3), there were no significant differences between groups except for the impulsivity subscale of the APRS. Given the APRS results favoring combined treatment, it was surprising that teachers did not report greater improvements on the hyperactivity/impulsivity scale of the DBD. One explanation for this apparent discrepancy in impulsivity ratings across forms is that the APRS queries for symptoms of impulsivity specifically as they manifest in the classroom, whereas the DBD defines impulsivity more broadly using ADHD symptoms as listed in the *DSM-IV*.

The lack of combined therapy effects at school versus home may have been due to the behavior therapy intervention's preferentially focusing on home-based behaviors. The only component of behavior therapy specifically targeting school functioning was the DRC, which was implemented in a low-intensity fashion with no ongoing feedback to the teacher to adjust goals, rewards, or target levels after the initial 2 teacher meetings and no verification that parents were providing rewards or negative consequences as appropriate. In addition, teachers in the atomoxetine-only group could have turned the study ITBE into a DRC on their own, essentially matching the effects of combined treatment at school. We elected to focus primarily on home-based interventions and employ a simple, school-based intervention to mirror what can be feasibly instituted by community clinicians in conjunction with teachers. Other research also shows that interventions targeting 1 domain often do not generalize to other domains,[71–73] lending credence to suggestions that treatments should be delivered in settings where they are intended to make change.[10,63,74]

The medication was well tolerated, with the endpoint severity ratings on our structured side-effect scale being mild or less and not appreciably greater than baseline levels. This study was one of a few ADHD trials to measure side effects using teacher and parent report—and the first to do so for a trial of atomoxetine. Overall, teachers rated fewer side effects than did parents, which is not surprising as teachers must attend to many more children than parents do at any given time, and children may be less apt to report side effects to teachers versus parents. The few studies of stimulants that gathered side-effect data from both parents and teachers found similar results.[75,76] Skin picking and anxiety ratings actually improved when atomoxetine treatment was started. The reduction in skin picking most likely was due to the removal of prior stimulant medication, while atomoxetine itself has been associated with improvements in anxiety.[77] No significant changes in weight or blood pressure were observed. While there was no weight loss observed over 8 weeks of treatment, it is possible that a placebo-treated group would have gained significantly more weight, as has been seen in other controlled trials of atomoxetine.[5]

Given recent concerns over the capacity of atomoxetine to induce adverse emotional responses,[17,78] we used the CDRS-R, the current gold standard for assessing change in depressive symptoms in children,[58,59] to look for signs of emerging depression or new-onset suicidal ideation. Children with a past history of depression requiring treatment were excluded, so it is not surprising that baseline CDRS-R ratings were within the normal range. However, CDRS-R ratings further decreased as treatment progressed, with a trend favoring a greater decline in the combined group. These findings match prior results showing that multimodal ADHD treatments lead to improvements in mood ratings in children with ADHD and severe mood dysregulation.[79] While 1 subject did discontinue due to increased emotional lability, levels of suicidal ideation reported on the CDRS-R and PSERS were essentially zero at baseline and remained at this level for the duration of the trial. There were no new cases of expressed suicidal ideation or self-harm. These results are consistent with past reports documenting that new-onset suicidal ideation during atomoxetine treatment is a rare event.[78]

Adherence to and satisfaction for the combination therapy were comparable to or better than that reported elsewhere, with nearly two-thirds of families attending all the sessions and 82% attending at least 75% of the sessions. Prior reviews on this topic have found that 40%–60% of families terminate therapy services prematurely, with session attendance waning over time.[80] In a similar ongoing study at our center looking at the combined effects of stimulants and behavior therapy, parents attended 7 of 10 mandatory sessions, on average, with only 35% making all of the sessions.[81]

Limitations

The primary limitation of this study was the lack of a control condition, thereby limiting our ability to detect the causality of observed improvements. The use of an open-label design very likely contributed to the larger effect sizes in comparison to other studies of atomoxetine,

especially for parent ratings.[2,5,14] This design was selected over a placebo-controlled intervention because this study was not a traditional efficacy trial of a single treatment, in which use of a blinded control group is essential.[29] The efficacy of atomoxetine has been established in multiple other placebo-controlled trials, including one in a school setting.[1–6] The primary goal of this study was to evaluate the incremental effects on classroom functioning of adding behavior therapy to atomoxetine, which could be accomplished without a blinded medication group. Use of an open-label design guaranteed that all subjects received at least 1 active treatment, which was important as this study primarily targeted children who were still impaired after a trial of stimulants. In a similar combined treatment study of behavior therapy and stimulants for pediatric ADHD, Abikoff and colleagues[21] also used an open-label design, while the MTA and other large combined treatment studies of child psychopathology employed open-label medication in their combined treatment arms.[21,82] Moreover, the primary outcome measure of classroom observations, as well as the secondary measure of the DRC, is relatively insensitive to rater bias effects, thereby further reducing the need for a blinded control group.[29,33]

We cannot rule out that teachers' awareness of the child's medication status may have affected their symptom reports; however, the comparable effect sizes between the teacher reports and the more objective classroom observations (see Table 3), as well as the teacher ratings from the prior placebo-controlled school study of atomoxetine,[5] suggest that teacher expectations of medication did not markedly alter their symptom ratings. The generally low level of teacher-reported side effects at baseline and during treatment (with only headache increasing during atomoxetine usage) made it unlikely that the presence of medication-related adverse events in the classroom influenced teacher ratings. Despite these promising results, without further controlled data, we cannot definitively conclude that either atomoxetine or behavior therapy leads to sustained improvements in academic functioning.

The large effect sizes for many measures in the medication-only arm made it difficult to detect sizable additional improvements in the combined treatment group, possibly contributing to the marginal incremental effects of combined therapy. We had expected that the addition of behavior therapy to atomoxetine would produce larger incremental gains in relationships with parents and siblings since behavior therapy focused on improving compliance with parental requests. Typically, ADHD medications have produced lesser gains in these functional domains than for symptom scores.[22,33,83] However, since atomoxetine alone essentially normalized many of the parent impairment ratings in these realms (< 3 on the IRS is indicative of not being clinically impaired), there was little room for additional improvement from behavior therapy. Similarly, atomoxetine alone normalized all teacher IRS ratings, making it difficult to detect incremental improvement.

The large medication effects may have been due in part to the open-label design with a titration to a final mean medication dose that was at the US Food and Drug Administration maximum. Past studies of atomoxetine have employed comparable dosages.[5,14,84] Prior work by our group has shown that combined treatment produces differential effects versus medication alone at lower dosages but not at higher ones.[12,85] When these facts are considered, it is remarkable that the addition of behavior therapy provided any additional increment over atomoxetine, although it clearly did in several areas (see Tables 2 and 3). Hence, while behavior therapy did not produce significant improvements beyond medication alone in a number of realms, further controlled studies are needed to definitively evaluate the separate and combined effects of behavior therapy and atomoxetine.

The study was powered to detect group differences on the classroom observation measure and therefore may not have had sufficient subjects to detect group differences on secondary measures (eg, teacher ratings and/or the DRC). Some of the group effects may have reached significance with a larger sample size as there were numerical advantages for most outcomes in favor of combined therapy. In addition, 12.5% of the sample dropped out prior to completion, further impacting the ability to detect group differences.

While parents reported a high level of ADHD symptoms, subjects had lower levels of externalizing symptoms by teacher report. Even though all subjects met full ADHD criteria, baseline symptom ratings on the teacher DBD were equivalent to an ADHD Rating Scale-IV score of 29, with an especially low level of hyperactive/impulsive symptoms. In the Weiss et al study[5] and the Preschool ADHD Treatment Study (PATS),[86] baseline symptom scores were lower for teacher ratings than for parent ratings. It is possible that the less severe baseline presentations in school versus home could be an artifact of recruiting for a study in which the primary referral source (parents) is different than the primary rater (teachers). To address this concern, we did verify that all subjects exhibited impairing ADHD symptoms in school at the time of screening.

Due to scheduling conflicts with teachers and the intensive time and staffing demands of completing the classroom observations, we were not able to complete all the observational assessments prior to the first dose of study treatments. There was an average of 7 days between the first dose of medication and the baseline observation (no differences between groups), with the observational assessments of 66% of subjects being completed during the same school week that medication and behavior therapy were started. Given the delayed therapeutic onset of atomoxetine and behavior therapy, this delay in observational assessment was not likely to have made a meaningful impact on the results. Nonetheless, beginning treatment 1 week prior to the baseline observation may have improved behavior during the baseline classroom observation, especially in the combined treatment group, potentially making it harder to detect treatment effects over time. However, we still found significant improvement for

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both groups on this measure. In an attempt to complete the baseline classroom observation as closely as possible to the start of study treatments, we used a primary observer who served as one of the therapists for the child therapy group. This observer was then not blinded to group status, creating the possibility for rater bias in favor of combined treatments. However, the standardized scoring protocol for the observations limits the potential for rater bias. Furthermore, the second observer was blinded to group status, and the excellent agreement between observers suggests that rater bias by the unblinded rater was not a major factor.

For the satisfaction ratings, 48% of atomoxetine-only parents and 41% of atomoxetine + BT parents completed the measure (no difference in the response rate between groups), limiting the strength of these findings. The satisfaction ratings were completed separately, several weeks after the end of the study, and returned via mail. All other measures were completed at the last medication visit. In contrast to the Weiss et al study,[5] which was missing teacher data in 20%–30% of the cases, we collected 90% of the teacher ratings and 88% of parental ratings, other than the satisfaction ratings. There was a trend for families in the combined group to have higher socioeconomic status, which may have impacted results. However, both groups were solidly in the middle class range,[36] and there were no differences in any other demographic factors, suggesting that the impact of this statistical difference would not be large. Last, with an 8-week study, we cannot comment on the long-term effect of treatment, which is particularly important given the limited data indicating that treatment of ADHD translates into sustained academic improvement.

CONCLUSION

These results support the efficacy of atomoxetine to improve the classroom functioning of children with ADHD. Evidence of positive medication effects was found across assessment methods ranging from teacher report to direct observation for both symptoms scores and functional outcomes. Similarly, treatment improved ADHD symptoms and functioning at home. Although the impact of combining atomoxetine with behavior therapy was less clear, there was evidence of incremental improvements at home and improved parental perception of academic functioning. There was not a clear incremental benefit of combined therapy for school functioning or for peer relationships. Yet, it would be premature to conclude that combined therapy offers little additional impact versus atomoxetine alone in these domains unless these findings are replicated in placebo-controlled studies using a more intensive school-based behavior therapy intervention. The medication was well tolerated at home and school, with scant evidence of adverse emotional responses. Overall, our findings support the efficacy of atomoxetine in the classroom, warranting longer-term studies assessing the sustained impact of atomoxetine on academic performance and classroom functioning.

Drug name: atomoxetine (Strattera).
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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.