

# Atomoxetine Treatment in Children and Adolescents with Attention-Deficit Hyperactivity Disorder: What Are the Long-Term Health-Related Quality-of-Life Outcomes?

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## ABSTRACT

**Objective:** Numerous investigations have examined the efficacy of pharmacological treatment for attention-deficit/hyperactivity disorder (ADHD) in children. However, relatively few studies have addressed the impact of treatment on long-term subjective, psychosocial outcomes, such as health-related quality of life (HRQL). This study examines the long-term effects of pharmacological treatment with atomoxetine on HRQL in children and adolescents with ADHD.

**Methods:** Participants included 6- to 17-year-old children and adolescents ( $n = 912$ ) with ADHD enrolled in a 24-month, multicenter, open-label trial of atomoxetine. Outcomes included clinician ratings of ADHD, parent ratings of ADHD, and a widely used measure of HRQL (The Child Health Questionnaire (CHQ)). Treatment response rates were calculated based on a CHQ improvement of at least 1 standard error of measurement.

**Results:** Significant improvements in HRQL were found following both acute and long-term treatment for psychosocial but not physical health. Of participants who completed treatment ( $n = 312$  or 34.2% of those enrolled), 81% responded to acute treatment and 78% responded to long-term treatment. Improvements noted after acute treatment were maintained during long-term treatment with the majority of participants (86%) continuing to respond to treatment.

**Conclusions:** Atomoxetine is associated with improvements in HRQL, and the improvements are generally stable over time.

## INTRODUCTION

**A**TENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is a frequently occurring childhood mental health disorder that often results

in a number of functional impairments including academic difficulties (Faraone et al. 2001; Pastor and Reuben 2002), social skills deficits (Bagwell et al. 2001; Greene et al. 2001; Thurber et al. 2002), and strained family rela-

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tionships (Johnston and Mash 2001). In addition, longitudinal studies have indicated that ADHD is associated with higher rates of substance use (Weiss et al. 1985; Biederman et al. 1998; Tapert et al. 2002) as well as lower academic and occupational attainment (Manuzza et al. 1997; Hansen et al. 1999; Barkley et al. 2002).

Given the impact of ADHD on multiple domains of functioning and the chronic nature of the disorder, ADHD recently has been viewed as a disorder that can significantly impact health-related quality of life (HRQL). HRQL is distinct from both disorder symptoms and objective functional outcomes in that it is multidimensional and subjectively examines physical, social, and psychological aspects of health (Wallander et al. 2001). In children and adolescents with ADHD, HRQL is related to disease symptomatology, but provides information beyond that obtained from traditional symptom measures (Matza et al. 2004). When comparing children with ADHD to normative data, worse HRQL in psychosocial health has been noted in children with ADHD (Landgraf et al. 1996). Consistent findings were found in a large-scale study of Australian children and adolescents ( $n = 3597$ ), even after controlling for age, gender, family structure, and health status (Sawyer et al. 2002). These studies of HRQL in children with ADHD suggest that this is an important outcome that is not fully captured by traditional ADHD symptom measures. Not surprisingly, studies have consistently indicated that the impact of ADHD on HRQL seems to be specific to psychosocial health as opposed to physical health (Landgraf et al. 1996; Sawyer et al. 2002).

With regard to the management of ADHD and its associated symptoms, pharmacotherapy and behavior therapy are considered to be the standard of care. In fact, a number of studies have attested to the efficacy of these treatments in the management of the disorder (for reviews, see Pelham et al. 1998; Barkley 2002; Greenhill, et al. 2002; Kratochvil et al., 2003). Although numerous studies have addressed the effect of treatment on core ADHD symptoms, HRQL has not been addressed as frequently in well-controlled trials of ADHD treatments. This is despite the fact that the American Academy of

Pediatrics (AAP) has suggested that treatment outcomes should include improved functionality as well as decreased core symptomatology (American Academy of Pediatrics 2001). Some of the functional improvements areas highlighted by the AAP can be captured by psychosocial aspects of HRQL measures as has been done in double-blind, placebo-controlled trials of atomoxetine. These trials have noted that atomoxetine improved psychosocial HRQL as well as core ADHD symptoms (Michelson et al. 2001; Perwien et al. 2004).

Although well-designed long-term studies, such as the landmark Multimodal Treatment Study of Attention Deficit/Hyperactivity Disorder (MTA Cooperative Group, 1999), have noted the effectiveness of medication treatment for core ADHD symptomatology, HRQL has only recently been examined. A 9-month randomized, double-blind, placebo-controlled study of atomoxetine treatment responders found that medication was superior to placebo in improving HRQL as well as in maintaining core ADHD symptom response (Michelson et al. 2004).

In summary, research has shown both short- and long-term negative outcomes associated with childhood ADHD. Although clinical trials have consistently supported the efficacy of pharmacotherapy, less data are available on the long-term effects of these medications. Even though the psychosocial aspects of HRQL have been identified as an area of concern for children with ADHD, few studies have systematically examined the effect of treatment on HRQL, let alone response to long-term treatment. The present study builds on earlier research that supported the positive effect of acute treatment with atomoxetine on HRQL. Although core symptom response to atomoxetine was examined in this study, the primary objective of this report is to investigate the long-term outcome of atomoxetine treatment on HRQL. It was hypothesized that psychosocial HRQL would improve following 10-week acute treatment and would be maintained over a 24-month treatment phase. Given that previous research indicates poor HRQL in ADHD is specifically associated with psychosocial health, no changes in physical health following treatment were expected.

## METHODS

### *Participants*

Children and adolescents diagnosed with ADHD who ranged in age from 6 to 17 years were enrolled in a multicenter (55 sites), open-label trial of atomoxetine. Participants were recruited through physician referrals and by advertisement. To qualify for participation in the study, participants had to meet diagnostic and severity criteria for ADHD. Potential participants were excluded if they had a history of bipolar disorder or psychosis (including use of antipsychotic medication within 8 weeks of study enrollment), cognitive impairment (i.e., IQ <80), seizure disorder, and/or significant medical condition(s). Children also were excluded if they had a history of alcohol or drug abuse within the past 3 months. Although a history of psychotropic medication use was permitted, participants were required to be free of any psychotropic medication, including stimulant medications, and health food supplements with purported central nervous system activity for at least 5 half lives prior to study enrollment. For example, children had to be free of short-acting stimulants for at least 24 hours and long-acting stimulants for 1–2 days (Concerta® and Adderall XR® for at least 17.5 hours and 48 hours, respectively).

### *Measures*

Trained mental health providers (e.g., psychiatrists, psychologists) administered the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present/Lifetime Version (K-SADS-PL; Ambrosini 2000) to document the presence of ADHD and to determine the subtype (combined, predominately inattentive, predominately hyperactive/impulsive). The K-SADS-PL is a semistructured psychiatric interview that allows the interviewer to incorporate data from multiple informants (i.e., parent and child) to determine diagnoses. The behavioral (ADHD, oppositional defiant disorder, conduct disorder), affective, and anxiety disorder sections were administered. The K-SADS has been found to have adequate reliability and validity (Am-

brosini 2000). To assess ADHD symptom severity, the clinician-rated version of the ADHD Rating Scale (ADHD-RS; Faries et al. 2000) was completed by trained mental health providers, on the basis of an interview with the parent/guardian, while the parents directly rated the child's behavior using the Conners' Parent Rating Scale–Revised: Short-Form (CPRS-R:S; Conners 1997). The ADHD-RS includes 18 items, each of which corresponds to a specific ADHD symptom. For entry into the study, children were required to be at least one standard deviation (SD) above the norm on the ADHD-RS for their diagnostic subtype. The CPRS-R:S is a 27-item rating scale that assesses behavioral problems related to ADHD and includes the following subscales: ADHD Index, Hyperactivity, Cognitive Problems, and Oppositional.

To assess HRQL, the child's caregiver completed the Child Health Questionnaire (CHQ) (Landgraf et al. 1996). The CHQ is a generic HRQL measure that has been used in studies of children with a variety of chronic conditions including ADHD (Landgraf et al. 1996; Sawyer et al. 2002). Although a child self-report version of the CHQ exists, the parent version was selected because it is more widely researched, has normative data available, and may be used with a broad age range (children 5–18 years of age). The 50-item parent report version of the CHQ includes two summary measures (physical and psychosocial health) and 11 domain scales. Scales assessing physical functioning, pain, physical role functioning, and health perceptions address physical health. Scales measuring emotional/behavioral role functioning, behavior, mental health, self-esteem, parental time impact, parental emotional impact, and family functioning examine psychosocial health. The psychometric properties of the CHQ are described fully in the test manual (Landgraf et al. 1996) and support the internal consistency ( $\alpha = 0.66$ – $0.94$  for CHQ scales), factor structure, and validity of the measure. Higher scores on the CHQ signify better HRQL.

### *Procedures*

For each participating site, either an Institutional Review Board (IRB) at the site or a cen-

tralized IRB approved the investigational procedures. Informed consent was obtained from each participant's parent or guardian and assent was obtained from each child. Following the informed consent process, children were evaluated to determine whether ADHD diagnostic and severity criteria were met without the presence of any exclusionary criteria. During the first 10 weeks of the study (acute phase), participants were seen on a weekly basis. During the long-term phase, visit intervals were every 3 months until either study completion (24 months) or study discontinuation. Throughout the study, children received twice-a-day dosing of atomoxetine (morning and late afternoon) with a target dose of 1.25 mg/kg per day (mean final dose = 1.13, SD = 0.45). The CHQ was completed at baseline, after acute treatment (10 weeks or discontinuation) and after long-term treatment (24 months or discontinuation). Clinician ratings on the ADHD-RS were obtained to examine severity of core ADHD symptoms at each visit during the acute and long-term treatment phases. Children were not permitted to begin new psychotropic medication treatments during the trial.

#### *Data analyses*

To examine baseline HRQL, *t* scores were calculated for the ADHD sample using age-based norms provided in the CHQ user's manual (Landgraf et al. 1996). All acute-phase participants with a baseline CHQ score were included in this analysis regardless of whether or not they completed the long-term study. Due to the longitudinal nature of the study, age-based norms also were used in all subsequent analyses.

Analyses examining the response of treatment included all participants who completed long-term treatment. The analysis sample was restricted to this particular group because the primary interest of this study was long-term effects of atomoxetine treatment, and the acute effects from double-blind placebo controlled trials of atomoxetine have been described elsewhere (Michelson et al. 2001; Perwien et al. 2004). Due to the sparseness of the HRQL data collection points, the primary assessment was

based on change scores between HRQL measurement points rather than employing repeated measures models. A sensitivity analysis, using repeated measures models, was also conducted. The change scores computed included: (1) Baseline to acute-phase end point and (2) acute-phase end point to the end of the long-term treatment phase. Using intent-to-treat analyses, paired *t*-tests were employed to assess whether changes were statistically different from 0 for completers (i.e., participants with 24 months of treatment). To understand better HRQL changes for participants who discontinued the investigation prematurely, secondary analyses were conducted for participants who discontinued long-term treatment ( $\geq 6$  months and  $< 24$  months).

To assess the clinical meaningfulness of the change scores, response rates were calculated. Although there is no gold standard approach to dichotomizing scores into response categories, participants were labeled as responders if they had an increase of at least one standard error of measurement (SEM) in their CHQ psychosocial summary score. The SEM, the standard deviation multiplied by the square root of 1 minus the reliability coefficient, represents a change above and beyond that expected by chance for an individual (Wyrwich et al. 1999). Compared to response definitions based on *t* scores, this approach reduces problems due to participant baseline scores in or near the normative range. Based on the SEM criterion, participants were categorized into four mutually exclusive groups: (1) Acute and long-term treatment responder, (2) acute treatment responder only, (3) long-term treatment responder only, and (4) nonresponder. Because the SEM criterion simply indicates individual improvement as opposed to "normal functioning," percentages of participants within the normative range (within 1 and 1.5 standard deviations of the normed mean) also are reported.

Last, potential predictors of changes during the long-term phase of the study were assessed. ANOVA models were utilized to assess long-term changes with the following dependent variables: Investigational site, acute end point CHQ and ADHD-RS scores, age, gender, race, ADHD subtype, oppositional defiant disorder diagnosis, and previous stimulant use.

## RESULTS

### *Participant characteristics*

Of the 912 participants originally enrolled in the trial, 80% ( $n = 728$ ) completed the 10 weeks of atomoxetine treatment ("acute participants"), 65% ( $n = 591$ ) completed at least 6 months of treatment ("long-term participants"), and 34% ( $n = 312$ ) completed the entire 24-month study ("completers"). Participant data for each phase of the study including the number of participants retained at each phase of the trial and the most common reasons for study discontinuation are presented in Fig. 1.

Table 1 presents characteristics of acute participants, long-term participants, and completers. As shown in Fig. 2, participants in the present study had baseline CHQ scores that were significantly lower (indicating worse HRQL) compared to normative data (Landgraf et al. 1996). Because the CHQ assesses the past 4 weeks and some long-term participants ( $n = 209$ ) and completers ( $n = 132$ ) were treated with stimulant medications within this timeframe, it was possible that these participants had different baseline HRQL scores compared to untreated participants due to having received treatment for ADHD. To examine this issue, participants were divided into two groups: Those taking a stimulant within 30 days prior to baseline assessment and those who had not received any stimulant medications. Because there was no significant difference between the groups in baseline psychosocial HRQL ( $t = 1.55$ ,  $p = 0.12$ ), all other analyses employed the combined group.

### *Treatment outcomes*

Table 2 summarizes HRQL and ADHD core symptom baseline and change scores for the completers. Following acute treatment with atomoxetine, significant improvements were observed on the psychosocial summary scale ( $t$  statistic = 19.1,  $p < 0.01$ ) as well as all psychosocial domains (Table 2). Improvements on the psychosocial summary scale were maintained following long-term treatment ( $t = 0.4$ ,  $p = 0.71$ ) and psychosocial subscale improve-

ments were either maintained or slightly improved after 24 months of treatment (Table 2). Compared to the magnitude of change on the psychosocial summary scale between baseline and acute phases, the magnitude of change from acute to long-term was relatively small. However, the 24-month scores for the psychosocial summary scale and all psychosocial domains represent significant improvement over the study entry scores. The pattern of HRQL improvements was consistent with those found for core ADHD symptoms. Specifically, clinician ratings based on parent interviews (ADHD-RS Total) and direct parent reports (CPRS) of ADHD symptoms indicate significant improvement after acute treatment ( $t = -39.6$ ,  $p < 0.01$  and  $t = -33.2$ ,  $p < 0.01$ , respectively), and these improvements were maintained or slightly improved after long-term treatment (ADHD-RS Total  $t = -2.7$ ,  $p = 0.01$  and CPRS  $t = -1.2$ ,  $p = 0.23$ ). As expected, no significant improvements were found on the CHQ Physical Summary Scale or its related domain subscales after acute or long-term treatment.

As noted earlier, 279 long-term participants discontinued treatment prior to the end of the 24-month study and end point CHQ measurements were available for 182 of these cases. For these participants, psychosocial functioning after long-term treatment declined from the levels observed at the end of the acute phase (psychosocial summary score mean change =  $-7.7$ ,  $SD = 14.4$ ,  $t = -7.7$ ,  $p < 0.01$ ). However, the end point scores still represent an improvement from the original baseline ( $M = 6.0$ ,  $SD = 14.6$ ,  $t = 5.5$ ,  $p < 0.01$ ). Repeated measures analysis employing all patients was performed as a sensitivity analysis for the psychosocial summary score and showed a similar pattern as the primary assessment: A significant increase during the acute phase ( $p < 0.001$ ) followed by stability from the acute to long-term phase ( $p = 0.360$ ).

Assessment of predictors did not yield consistent results across analyses. Oppositional defiant disorder, past treatment with stimulants, age, prior HRQL ratings, and ADHD symptoms were all significant predictors ( $p < 0.05$ ) of long term improvement in either the analysis of completers or of all long term par-

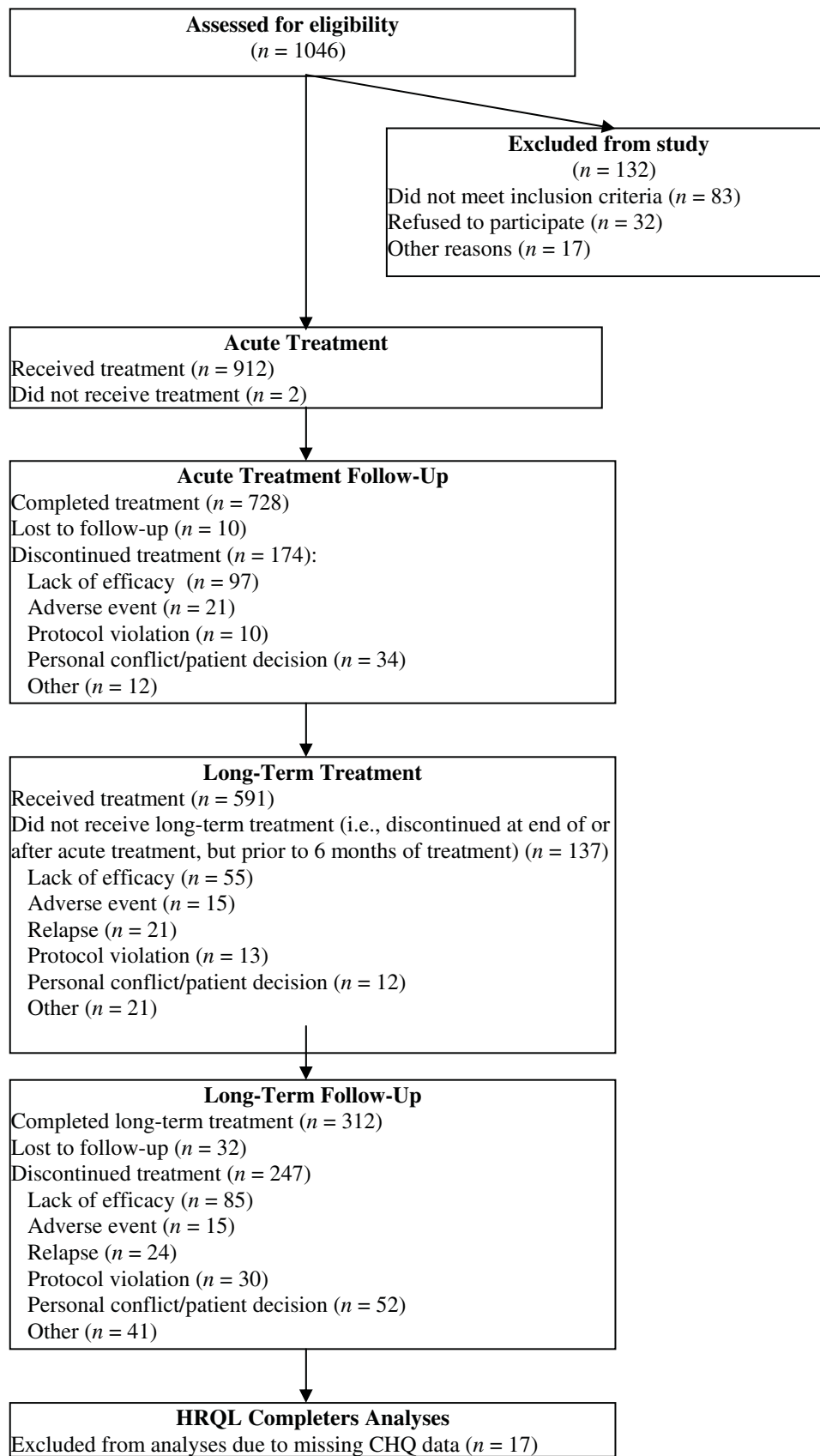


FIG. 1. Flow diagram of trial phases. CHQ = The Child Health Questionnaire; HRQL = health-related quality of life.

TABLE 1. SAMPLE CHARACTERISTICS

	Acute participants (n = 728)	Long-term participants (n = 591)	Completers (n = 312)
Age, mean (SD)	11.1 (2.8)	11.1 (2.7)	10.9 (2.6)
Male	76.1%	76.5%	78.2%
Ethnicity			
White non-Hispanic	82.8%	82.6%	83.7%
Hispanic	7.3%	7.6%	8.3%
African American	5.6% <sup>a</sup>	5.2% <sup>b</sup>	2.6% <sup>a,b</sup>
Other	4.3%	4.6%	5.5%
ADHD subtype			
Hyperactive/impulsive	3.3%	3.0%	4.2%
Inattentive	35.0%	35.9%	35.9%
Mixed	61.7%	61.1%	59.9%
Oppositional defiant disorder	37.2% <sup>a</sup>	36.0% <sup>b</sup>	32.1% <sup>a,b</sup>
History of stimulant treatment	75.6%	75.4%	76.5%
Family history of ADHD	55.1%	54.4%	56.9%
ADHD-RS <i>t</i> score (SD)	78.8 (11.4)	78.7 (11.4)	78.1 (11.9)

Acute participants = participants who completed acute (10 weeks) of treatment; long-term participants = participants who completed at least 6 months of atomoxetine treatment; completers = participants who completed the entire 24-month study.

SD = standard deviation; ADHD = attention-deficit/hyperactivity disorder; ADHD-RS = ADHD Rating Scale.

<sup>a</sup>Significant differences ( $p < 0.05$ ) between completers and acute participants who were not completers.

<sup>b</sup>Significant differences ( $p < 0.05$ ) between completers and long-term participants who were not completers.

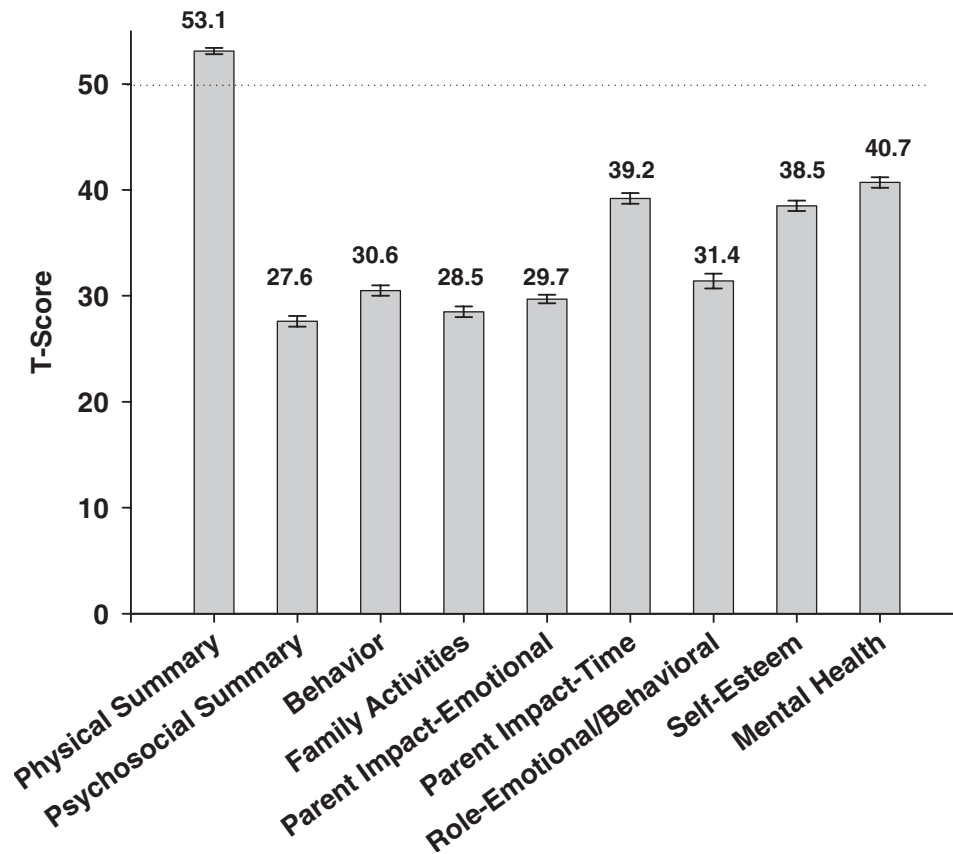


FIG. 2. Baseline Child Health Questionnaire *t* scores for acute participants.

TABLE 2. SUMMARY OF HRQL BASELINE AND CHANGE SCORES IN ADHD FOR COMPLETERS

Outcome measure	n	Baseline mean (SD)	Baseline to acute change		Acute to long-term change	
			mean (SD)	p	mean (SD)	p
CHQ <i>t</i> scores (age-based)						
Physical summary	281	53.2 (7.9)	-0.8 (8.6)	0.117	0.1 (8.1)	0.769
Psychosocial summary	281	29.0 (13.1)	15.1 (13.3)	<0.001	0.2 (11.2)	0.709
Behavior	294	32.5 (12.3)	13.6 (11.1)	<0.001	0.1 (9.4)	0.813
Family activities	294	29.9 (14.1)	12.2 (13.4)	<0.001	0.6 (11.5)	0.375
Parental impact-emotional	292	30.6 (10.8)	10.8 (13.4)	<0.001	2.5 (14.0)	0.003
Parental impact-time	294	39.4 (11.6)	8.0 (12.5)	<0.001	1.2 (11.4)	0.067
Role-emotional/behavioral	295	32.1 (19.3)	14.2 (21.0)	<0.001	-0.4 (15.2)	0.682
Self esteem	292	39.6 (11.9)	7.9 (12.1)	<0.001	-0.8 (11.8)	0.260
Mental health	293	42.4 (13.6)	7.5 (14.0)	<0.001	-0.7 (11.0)	0.249

All patients with a baseline, acute treatment, and 24-month, long-term treatment score were included in the analysis. SD = standard deviation; CHQ = Child Health Questionnaire; HRQL = health-related quality of life; ADHD = attention-deficit/hyperactivity disorder.

Participants. For the completers, lack of prior stimulant use, older age, less severe ADHD symptoms at acute treatment end point, and worse HRQL at acute treatment end point were predictive of greater HRQL improvements. In examining all long-term participants, only worse HRQL following acute treatment and the lack of oppositional defiant disorder were predictive of more improved HRQL.

#### Response rates

Using the response definition of an improvement in the psychosocial summary score of at least one SEM, the majority of completers were responders at the end of long-term treatment (Table 3). A total of 81.1% ( $n = 228$ ) of the completers were responders at the end of the acute phase and 78.3% ( $n = 220$ ) were responders after 24 months of treatment. Of the completers who responded after acute treatment, 86% ( $n = 196$ ) continued to meet response criteria at the end of the study. Consistent with response rate data for the completers, the majority of long-term participants met response criteria at their final measurement (Table 3). Of the long-term participants who were responders after the acute phase, 78.4% ( $n = 283$ ) continued to meet response criteria at end point. Using *t* scores to examine response rates, the majority of completers were responders following long-term treatment. Specifi-

cally, 67.3% ( $n = 189$ ) and 80.1% ( $n = 225$ ) of these participants were within the normative range using 1.0 and 1.5 SD range definitions, respectively.

TABLE 3. RESPONSE RATES FOR LONG-TERM PARTICIPANTS AND COMPLETERS

Responder category	Long-term participants (n = 456)	Completers (n = 281)
Acute and long-term treatment responder	62%	70%
Acute treatment only responder	17%	11%
Long-term treatment only responder	8%	9%
Nonresponder	13%	10%

Long-term participants = participants completing at least 6 months of treatment; completers = participants completing the entire 24-month study.

Response definition is based on the following criterion: a baseline to end point increase of at least one standard error of measurement (SEM) in CHQ psychosocial summary score.

Acute and long-term treatment responder = participant responded after both the acute (10 weeks of treatment) and long-term treatment phases; acute treatment only responder = participant responded after acute treatment but not after long-term treatment; long-term treatment only responder = participant responded after long-term treatment but not after acute treatment; non-responder = participant did not respond after acute or long-term treatment.

CHQ = Child Health Questionnaire.



## DISCUSSION

At baseline, participants in this study were experiencing significantly worse HRQL in areas of psychosocial health compared to normative data. These findings are consistent with other investigations (Landgraf et al. 1996; Sawyer et al. 2002), and indicate that HRQL is an area of concern for children with ADHD. In addition, research indicates that HRQL is an outcome that is not fully captured by the measurement of core ADHD symptomatology (Matza et al. 2004). Therefore, the assessment of HRQL should be viewed as a complementary procedure because HRQL represents a domain beyond traditional health status (e.g., ADHD core symptoms) by examining the subjective impact of a disorder. In fact, the AAP also has recognized the importance of evaluating treatment across outcome domains, including behavioral, academic, and psychosocial functioning (American Academy of Pediatrics 2001). This type of multidimensional evaluation is likely to capture a full picture of treatment effectiveness including meaningful HRQL outcomes such as social functioning, family relationships, and psychological functioning.

In terms of outcomes of treatment with atomoxetine, findings from this study add to previously published data from acute, double-blind placebo controlled clinical trials. These trials, which have examined treatment effects over relatively short periods of time (i.e., 8–10 weeks), support the efficacy of atomoxetine on core ADHD symptoms as well as HRQL outcomes (Michelson et al. 2001; Perwien et al. 2004). The present study further supports earlier results by indicating that the HRQL improvements observed after acute treatment with atomoxetine were generally maintained. These data suggest that improvements found after acute treatment were durable rather than transitory. This pattern is consistent with changes found for core ADHD symptoms. Finally, consistent with the symptoms of the disorder and data previously reported by Perwien et al. (2004), HRQL improvements were specific to areas of psychosocial rather than physical health.

Although some improvement was observed from acute to long-term end point related to the impact of ADHD on parents emotional adjustment, the majority of psychosocial HRQL domains remained stable. One possibility is that the failure to document further improvement may be due to ceiling effects and/or response shift. In a previous study (Perwien et al. 2004), less psychosocial impairment at baseline was associated with less improvement following acute treatment with atomoxetine. Thus, participants who evidenced better baseline HRQL scores were more limited in the amount of improvement they could experience compared to participants who had worse baseline scores. Therefore, it is possible that participants in the present study who had high HRQL at the beginning of the study had less opportunity to improve significantly beyond their acute scores. Response shift offers another explanation as to why there were not further improvements from acute to long-term treatment for the majority of psychosocial health scales. It has been defined as, "a change in the meaning of one's self-evaluation of quality of life (QOL) as a result of changes in internal standards, values, and the conceptualization of QOL" (Sprangers and Schwartz 2000, p. 14) following a change in health status. Parents in this study may have experienced response shift because their children's health status (i.e., ADHD core symptoms) improved, resulting in a change in their internal standard of HRQL measurement (recalibration). If the recalibration were more stringent, it would be more difficult to demonstrate improvement over the course of long-term treatment.

The findings of this study should be interpreted with some caution due to the open-label study design and the attrition rate. Despite the open-label design, however, the acute findings were consistent with double-blind placebo controlled trials, suggesting that the design did not unduly bias the results. Furthermore, it could be hypothesized that if the influence of receiving a medication overly influenced perceived HRQL, treatment effects might be less likely to be maintained because the novelty of the treatment would decrease over time. Attrition rates are generally a chal-

lenge for long-term treatment studies, and the present investigation is no exception. In this study, only 52.8% of participants who began long-term treatment completed the full 24-month study and only 34.2% of the patients that began acute treatment finished the full 24-months of the study. It is possible that participants who completed the study were the most receptive to treatment with atomoxetine. In fact, those who remained in the study for the full 24-month duration had greater improvements on HRQL compared to those who discontinued participation prematurely.

Several unanswered issues remain and are of potential interest for future investigation. For example, whether HRQL improvements plateau or fluctuate following long-term treatment cannot be determined from this study because of the limited measurement points (i.e., baseline, acute end point, long-term end point). Future studies should include children's perceptions of their own HRQL. Including both parent and child informants would not only provide a more complete picture of the effect of treatment on HRQL, but would also give insight into the consistency between parent and child reports for children with ADHD. In fact, some studies indicate that parents and children have different perceptions of children's HRQL (Vogels et al. 1998; Sawyer et al. 1999; Levi and Drotar 1999).

Another area for future investigation is the effect of multimodal treatment. Although the MTA study (MTA Cooperative Group 1999) did not indicate superior effects for the combined treatment arm (medication plus behavior therapy) compared to optimally administered medication alone, it is possible that some of the HRQL outcomes may be amenable to combination treatments that include a psychotherapeutic component. In addition, additional study is needed to assess potential predictors of improvement further in HRQL.

Finally, atomoxetine appears to be a particularly attractive medication intervention because it does not have some of the potential limitations of stimulant medications (Kratohvil et al. 2003) and appears to provide continuous symptom improvement (Kelsey et al. 2004). Although this study cannot address whether or not these characteristics of atomox-

etine have a positive effect on HRQL, it is possible that these factors play a role in improving HRQL. For example, continuous symptom relief may allow for a child to have improved interactions with family members which may, in turn, enhance family functioning aspects of HRQL.

Notwithstanding the aforementioned limitations and examined in conjunction with previous findings (Michelson et al. 2001; Perwien et al. 2004), this study supports the positive response to atomoxetine treatment on HRQL in children and adolescents. As these data indicate, improved HRQL is present following acute treatment and is maintained over long-term treatment. Although medications for chronic conditions, such as ADHD, are developed to improve specific symptoms and evaluated on disease-related health status measures (e.g., core ADHD symptoms), successful treatment may be better indicated by improvement in both health status and functional outcomes. This may be especially important in chronic conditions that have been documented to be associated with relatively poor HRQL. The present investigation provides a model for evaluating ADHD treatment on domains of functioning not previously documented in other studies.

## DISCLOSURE

At the time this research was conducted, Dr. Perwien was an employee of Eli Lilly and Company. Dr. Faries is currently an employee and stockholder in Eli Lilly and Company. Dr. Kratochvil is a paid consultant for Eli Lilly and Company, GlaxoSmithKline, Forest, Cephalon, Novartis, McNeil, Organon USA, AstraZeneca, and Pfizer. Dr. Spencer is a paid consultant for Eli Lilly and Company, McNeil, Novartis, Shire, Johnson & Johnson, and Janssen. Dr. Brown is a paid consultant for Shire. Ms. Vaughan has no conflict of interest or financial ties to disclose.

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