Moderators and Mediators of Symptoms and Quality of Life Outcomes in an Open-Label Study of Adults Treated for Attention-Deficit/Hyperactivity Disorder

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Objective: The Quality of Life, Effectiveness, Safety, and Tolerability (QU.E.S.T.) study was designed to evaluate effectiveness of long-acting amphetamines in adults with attention-deficit/hyperactivity disorder (ADHD) in community practice settings. This article reports moderators and mediators of symptoms and quality of life outcomes.

Method: This was an open-label study of 725 adults with *DSM-IV*–diagnosed ADHD, treated with mixed amphetamine salts extended release and followed for up to 8 months. Multiple regressions were used to determine if patient moderators impact response in ADHD symptoms and how ADHD symptoms and medication satisfaction mediate quality of life. The study was conducted from December 2003 to December 2004.

Results: Amphetamine treatment of ADHD resulted in a robust and enduring symptom response. Patient characteristics such as age, female gender, severity of illness, and treatment-naive status moderate improved symptom outcome. Symptom change and satisfaction with medication independently mediate change in mental but not physical quality of life outcomes. There is no time lag between changes in symptoms and improved quality of life. Attention is a stronger mediator of ADHD-specific quality of life outcomes than disruptive behavior.

Conclusions: If symptoms and quality of life improve simultaneously, improvement in quality of life can be understood as more than just a downstream, secondary effect of symptom remission. Satisfaction with medication is a direct measure of the complex interplay of symptom change, tolerability, and patient perception of treatment that predicts self-report of quality of life benefits. Although the disruptive symptoms of ADHD are more obvious, adults self-report that attention has greater impact.

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Attention-deficit/hyperactivity disorder (ADHD) is now well characterized as being a prevalent,[1,2] impairing,[3–7] and treatable[8] condition in adults. It has been demonstrated that ADHD symptoms in adults respond to both medication[9] and psychological treatment.[10] Treatment studies have, for the most part, been limited to efficacy studies.

Efficacy trials are typically double-blind, randomized, placebo-controlled trials with short-term outcomes, carried out in select populations. Efficacy trials are necessary to demonstrate that a treatment can work in controlled conditions. Effectiveness studies examine whether or not a treatment actually works in practice and are often open-label and assess longer-term outcomes, such as tolerability and compliance.[11] Effectiveness studies are typically exploratory, observational, and conducted in community-based samples. The targets of effectiveness studies may include symptoms, comorbid psychopathology, psychiatric side effects, functioning, and quality of life.[11–13] Effectiveness studies often do not include a placebo control group when the study is of longer duration for ethical reasons but may include a comparator arm of a local normal control group or a treatment-as-usual group.

There are several effectiveness studies of ADHD treatment in children. Ambrosini et al[13] reported significant improvement in both ADHD symptoms and quality of life, as measured by the Pediatric Quality of Life Inventory measure in a community-based study of 2,968 children. The Attention-Deficit Hyperactivity Disorder Observational Research in Europe (ADORE) project[14] looked at approximately 1,500 children in 10 European countries to determine time to diagnosis, response to treatment, persistence with treatment, and non–symptom-based outcomes, such as success in school, social disabilities, and quality of

life. The Multimodal Treatment Study of Children With ADHD (MTA)[15] was originally designed as a randomized trial comparing 4 treatment conditions including medication, psychological treatment, combination, and treatment as usual in the community. Following the completion of the randomized trial, the MTA study[15] was extended to provide observational data for up to 10 years on a wide range of outcomes, and a local normal control group was added to provide information as to whether children who were improved had actually normalized.[15] There are no comparable effectiveness studies of treatment in adults with ADHD.

In children with ADHD, it has been established that ADHD symptoms, functional impairment, and health-related quality of life (HRQL) represent overlapping but distinct domains.[16] The correlation between symptoms and functioning in ADHD in children has been variously reported as ranging from modest to moderate,[17] depending to some extent on which measure of functioning is used. There are no studies of adults with ADHD to evaluate whether improvement in symptoms mediates improvement in HRQL.

Previous studies have demonstrated that ADHD in adults is associated with impairment in quality of life, as measured by generic measures of quality of life such as the short health survey (SF-36)[18] or more specific measures of ADHD-specific changes in quality of life (AAQoL).[19] Adults with ADHD showed impairment in all mental component subscores of the SF-36 (vitality, role-emotional, social functioning, and mental health), and this impairment was responsive to treatment with atomoxetine.[18] While there is evidence that ADHD in adults is associated with impaired quality of life, there are no studies that look at whether improvement in ADHD symptoms mediates improvement in quality of life and, if so, whether or not this occurs immediately or only when symptom improvement is consolidated.

The Quality of Life, Effectiveness, Safety, and Tolerability (QU.E.S.T.) study[20] was designed as an effectiveness study of community-based treatment of adults with ADHD managed with a long-acting amphetamine, mixed amphetamine salts extended release (MAS XR), over 30 weeks. The study design and interim outcome findings have been reported previously.[20] This article reports moderator and mediator effects on final symptom and quality of life outcomes.

METHOD

Sample

Seven hundred twenty-five patients were enrolled at 83 community and hospital sites across Canada and the United States. The study was conducted from December 2003 to December 2004, following institutional review board approval. Patients were treated open-label for up to 8 months with MAS XR from December 2003 to December 2004. Patients were included if they had a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[21] primary diagnosis of any subtype of ADHD (including not otherwise specified [NOS]) based on a psychiatric evaluation conducted by a trained clinician and were willing to participate in the study.

Patients were excluded as good clinical practice if there was a medical or psychiatric contraindication to stimulant use in general or MAS XR in particular. This included a severe Axis I or II diagnosis other than ADHD requiring treatment in its own right, pregnancy, recent drug abuse (as evidenced by history or testing), past failure to respond to MAS XR/amphetamine, documented adverse reactions to MAS XR, medications for which MAS XR is a contraindication, recent seizures, Tourette syndrome, glaucoma, or cardiac illness.

Patients were also excluded if there was recent history of suspected substance dependence or abuse (excluding nicotine) or if they were living in a setting where there was a history of suspected substance dependence or abuse; a positive urine drug screen at screening or baseline (other than any current stimulant therapy); or a specific cardiac condition that would require exclusion or taking other medications that would affect blood pressure or heart rate, other than any other ADHD therapy. These exclusion criteria follow good clinical practice and the recommendation of current practice guidelines for use of stimulants in adults with ADHD.[22]

Procedures

After the study had been described to the subjects, written informed consent was obtained, and the study was carried out according to the Declaration of Helsinki and in accordance with International Conference of Harmonisation Good Clinical Practices and all applicable regulatory requirements. A preliminary report[20] of outcome at 10 weeks describes the study procedures in detail. Patients were "washed out" from any previous medication (5 half-lives) and stabilized prior to baseline assessment. Of the 725 patients, 387 (53%) had no prior stimulant treatment, 281 (39%) had previous stimulant treatment, and 57 (8%) had previous nonstimulant treatment. Patients were titrated to their own optimal dose of MAS XR by 10–20 mg intervals according to clinician judgment, starting at 20 mg per day and going up to a maximum dose of 60 mg for 8 months. Dose reductions to 10 mg daily were allowed. The study visit schedule was consistent with typical visit schedules in a community clinic setting so that the study findings might be generalized to treatment as usual.

Measures

Diagnosis. All patients were assessed for ADHD using the criteria established in the *DSM-IV-TR* using a structured interview with specific prompts and training to augment the reliability of the investigator-rated ADHD Rating Scale (ADHD-RS-IV).[23,24] Comorbid diagnoses were confirmed using the Structured Clinical Interview for *DSM-IV-TR* (clinician version) with Psychotic Screen (SCID-CV).[25] Medical diagnoses were established from the patient's medical history,

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physical examination, laboratory work-up, pregnancy test, electrocardiogram, and vital signs.

ADHD symptoms. Attention-deficit/hyperactivity disorder outcome was measured with the ADHD Rating Scale for *DSM-IV*, investigator version (ADHD-RS-IV),[23] a clinician-administered questionnaire based on *DSM-IV* symptoms. Clinicians were provided with the Adler/Spencer prompts[26] to use as an option for better characterizing ADHD symptoms, but as per treatment as usual, the symptom severity was based on clinical impression using all data, rather than a structured interview. The ADHD-RS-IV[23] produces a total ADHD score, as well as separate scores for the inattentive (IA) and hyperactive/impulsive (HI) subscales. This measure is well validated[23] and is considered superior to either self-report or other report alone because it allows the clinician to probe for further information and use all data when rating ADHD symptom severity.

Clinical Global Impression. The severity of impairment for the sample was assessed at baseline using the Clinical Global Impressions-Severity of Illness scale (CGI-S),[27] a clinician-rated measure of symptom severity and functioning that does not refer to specific symptoms, with scores ranging from 1 (normal) to 7 (among the most extremely ill). Overall clinical improvement was assessed with the Clinical Global Impressions-Improvement scale (CGI-I),[27] which assesses the participant's degree of change from baseline on a scale ranging from 1 (very much improved) to 7 (very much worse).

Health-related quality of life. Health-related quality of life was measured using a generic measure that allows for comparison of burden of illness between different disorders. The Short Form-36 Health Survey questionnaire, version 2 (SF-36v2)[28] is a well-validated generic measure of HRQL that has been used in studies of many medical and psychiatric conditions. The SF-36v2 includes 8 subscales and 2 broad outcomes, a physical and a mental composite. The SF-36v2 is the gold standard for measurement of HRQL in health care, and the Mental Component Summary (MCS) score permits accurate assessment of the burden of illness associated with psychiatric illness in particular.

Quality of life in adults with ADHD. The advantage of generic measures of HRQL is that they allow for comparison of quality of life outcomes between different disorders. The disadvantage of such measures is that they fail to capture serious and clinically impairing consequences that are unique to the disorder in question. For example, ADHD in adults has been found to have specific and disabling effects on risk for substance use,[29] driving,[30] divorce, lost years of schooling, unemployment, misemployment,[24] poor self esteem,[31] and risk for other disorders.[1] Generic measures also have the potential disadvantage of emphasizing areas of disability that are inappropriate to the disorder in question. For example, items regarding pain or immobility may be irrelevant for a disorder characterized by hyperactivity.

The ADHD Impact Module for Adults (AIM-A) is a validated measure of quality of life in adults with ADHD.[32] The AIM-A items were derived from interviews with adults with ADHD varying in subtype, severity, and length of diagnosis of ADHD; treatment for ADHD; and type of clinical expert conducting the interview (psychologists and psychiatrists). The reliability, validity, and sensitivity of the AIM-A were empirically demonstrated using a comprehensive process of psychometric evaluation.[32] The AIM-A measures the following multi-item concepts: living with ADHD; general well-being; performance and daily functioning at work, home, school; relationships/communication; bothersomeness of symptoms on daily life; and interference of symptoms on daily life. Items from the AIM-A subscales used in the analyses are included in Figure 1.

The SF-36v2 and the AIM-A both use a 0-to-100 metric, with higher scores representing better quality of life.

Medication satisfaction. The Medication Satisfaction Scale (MSS) (available from authors upon request) is an 11-item patient self-report scale designed to assess satisfaction with current treatment using a 6-point Likert-type response option that ranges from strongly agree to strongly disagree. The MSS asks about satisfaction with medication, dosing, side effects, and compliance. Individual MSS items show a positive skew and ceiling effects. The inter-item reliability of the scale as a whole incorporating all items is acceptable at .82 (unpublished data on file, University of British Columbia).

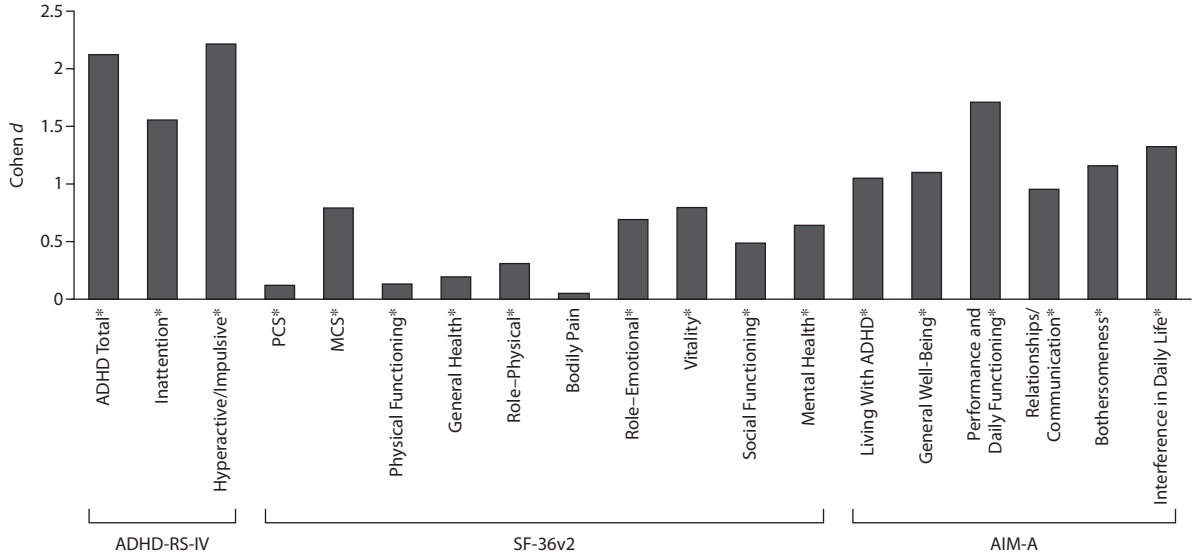
Analyses

Unless otherwise specified, analyses were conducted using a last-observation-carried-forward, intent-to-treat (ITT) procedure. As the protocol stated that patients would leave the study 30 days after the commercial availability of the study drug following a final study visit, the duration of time in the study varied between participants. All analyses were replicated in the subset of the sample that completed the maximum 8-month duration of the study, but there were no meaningful differences in the results when the per-protocol group was examined, as compared to the entire ITT sample.

Outcome analyses. Changes in ADHD-RS-IV, SF-36v2, and AIM-A scores were examined using 2-tailed, paired *t* tests. Effect sizes were calculated using Cohen *d*, which divides the mean difference between the baseline and post-treatment scores by the pooled standard deviation of the baseline and posttreatment scores. The pooled standard deviation is calculated as the square root of half the sum of the squared standard deviations of the 2 sets of scores. Cohen *d* thus provides a measurement of the number of standard deviations separating the 2 group means, taking into account any differences in standard deviation between the 2 sets of scores.

Moderator and mediator analyses. A moderator is a variable that precedes treatment, and a mediator occurs during treatment. Treatment moderators specify for whom

Figure 1. Baseline to Termination Comparisons of ADHD Symptom and Health-Related Quality of Life Outcomes



[a]Cohen *d* graphed as absolute values.
*$P < .001$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale for DSM-IV, investigator version; AIM-A = ADHD Impact Module for Adults; MCS = Mental Component Summary; PCS = Physical Component Summary; SF-36v2 = Short Form-36 Health Survey questionnaire, version 2.

a treatment works, while treatment mediators may identify possible mechanisms through which a treatment achieves its effects. The concept of moderator and mediator variables was initially developed by Baron and Kenny[33] and later operationalized by Helen Kraemer and colleagues[34] for use in exploratory post hoc analyses in randomized controlled trials. Kraemer et al[34] noted that moderator and mediator analyses were inherently exploratory, post hoc but defined a priori, and should be presented as hypothesis-generating rather than hypothesis-testing.

Kraemer et al[34] noted that moderator and mediator analyses in an open-label design were limited by the possibility that the effects might be nonspecific. Possible nonspecific or artifactual effects in an open-label study include effects of time, placebo effects, and regression to the mean. This is a specific case of the generic limitation of open-label studies that do not include control groups, in that nonspecific influences on outcome are not ruled out or controlled for.

As observational studies and patient registries gain increasing favor as methods for evaluating effectiveness, moderator and mediator analyses become crucial tools for generating meaningful hypotheses. To some extent, the risk of identifying a variable as a moderator or mediator when the effect is nonspecific is mitigated by differential comparison of relationships to variables chosen a priori to be conceptually distinct from one another. By definition, nonspecific effects are unlikely to be unique to a given variable. Kraemer et al[34] noted that as *P* values are dependent on sample size, measures of effect size are the most meaningful index of moderation and mediation, as a large study can find statistically significant effects of trivial magnitude.

Kraemer et al[34] also noted that the importance of moderators and mediators of outcome is independent from the overall effectiveness of the treatment. For example, such analyses primarily serve the purpose of hypothesis generation by identifying subgroups who may show differential treatment response and by identifying potential mechanisms of treatment effects. Exploratory studies of moderators produce the background information needed to identify stratification variables in future randomized controlled trials. Studies of mediators inform the restructuring of treatment trials and allow for the development of a priori hypotheses that address specific mediators affecting treatment outcome. Thus, if properly viewed as hypothesis-generating rather than hypothesis-confirming, examination of moderator and mediator variables in open-label trials can similarly serve this purpose, particularly when applied to treatment modalities that have already been supported in randomized controlled trials.

Four potential moderators of outcome were examined: age, gender, severity of illness, and previous treatment. All of these are set prior to treatment and, in a repeated measures study, uncorrelated with treatment. The total strength of the effect of treatment and any nonspecific factors is measured by the change from baseline to termination in total ADHD-RS-IV scores. The effect of the potential moderators on treatment outcome was assessed by entering them as predictors into a backward stepwise multiple regression

predicting change in total ADHD-RS-IV scores from baseline to termination. The R^2 associated with this regression equation thus provides a measure of the degree to which these baseline variables moderate the amount of change in the ADHD-RS-IV total score.

Two mediator analyses were conducted to test whether improvement in HI and IA symptoms and medication satisfaction mediated improvement in HRQL and ADHD quality of life (ADHD-QoL). The effects of treatment and any nonspecific factors were again measured by the change from baseline to termination in our outcome measures, in this case, the SF-36v2 MCS as our HRQL outcome measure, since no meaningful changes in the Physical Component Summary (PCS) were identified, and the 6 AIM-A subscales as our measure of ADHD-QoL. Mediators, by definition, are affected by treatment; therefore, our potential mediator variables were change in HI and IA ADHD-RS-IV scores from baseline to termination and the MSS. To determine the extent to which these variables accounted for changes from baseline to treatment, the changes in HI and IA scores were entered as predictors of the SF-36v2 MCS and the AIM-A subscales. Thus, the R^2 associated with this regression equation provided a measure of the degree to which these variables associated with treatment mediated the amount of change in the SF-36v2 MCS and the AIM-A subscales.

Temporal analyses. It is often assumed that quality of life or patient functioning will improve only after the patient has been symptom-free for a while. However, this has never been tested empirically. To test the temporal correlation between improvement in symptoms and improvement in HRQL, we examined the correlations between change scores from one observation to the next in the ADHD symptom and HRQL measures within the same time period, as well as the lagged correlation between changes in HRQL and the changes in ADHD symptoms that occurred in previous time periods. Changes in symptoms and HRQL that were most highly correlated when they occurred within the same time period would support the hypothesis that there is no lag between change in symptoms and change in HRQL. In contrast, if the lagged correlations between changes in HRQL and previously occurring changes in symptoms were stronger, then this would support the hypothesis that time must elapse between changes in symptom severity and for any resulting change in HRQL to be evident. The strength of the correlations were compared using a formula allowing a *t* test of the difference between 2 dependent correlations.[35] A *z* score transformation using baseline data was performed on all outcome measures so that changes over time could be compared on the same metric.

RESULTS

Disposition

There were 725 participants initially enrolled in the study. Of these, 23 did not take the study drug, leaving an ITT sample of 702. Of this sample, 18 were excluded from these analyses due to missing data on baseline variables, and 13 were excluded due to missing data on postbaseline measures to obtain an ITT sample with complete data on all measures of 671. Sample characteristics at baseline are reported in Table 1. For the analysis of the time course of the changes in ADHD symptoms and HRQL, complete data at all time periods were required, which reduced the sample size to 370 for those analyses.

Table 1. ITT Sample Characteristics at Baseline of Patients With ADHD Treated With MAS XR (N = 671)

Variable	
Sex, female, n (%)	345 (51.4)
Mean age[a], y	36.78
Race, white, n (%)	595 (88.7)
Mean ADHD-RS-IV total score	32.82
Mean ADHD-RS-IV inattentive score	19.37
Mean ADHD-RS-IV hyperactive/impulsive score	13.45
Mean CGI-S score	4.20
Clinical diagnosis	
Hyperactive/impulsive, n (%)	23 (3.4)
Combined, n (%)	375 (55.9)
Inattentive, n (%)	269 (40.1)
Not otherwise specified, n (%)	4 (0.6)

[a]Range, 18–78.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale for DSM-IV, investigator version; CGI-S = Clinical Global Impressions-Severity of Illness scale; ITT = intent to treat; MAS XR = mixed amphetamine salts extended release.

Patient Outcome

There was a robust and statistically and clinically significant improvement in ADHD inattentive symptoms ($t_{670} = 44.92$, $P < .001$), hyperactive/impulsive symptoms ($t_{670} = 35.19$, $P < .001$), total ADHD-RS-IV score ($t_{670} = 44.48$, $P < .001$), and SF-36v2 MCS ($t_{670} = 18.57$, $P < .001$). The mean change in ADHD-RS-IV symptoms was 63%, and the median change was 70%. The SF-36v2 Physical Component Summary (PCS) dropped 1 point—a change that was not clinically meaningful but did achieve statistical significance ($t_{670} = 3.47$, $P = .001$). The results are consistent with the interim analyses published earlier.[20] All 6 AIM-A subscales showed a statistically significant response to treatment (t_{670} = from −20.0 to −35.2; all $P < .001$). The effect size of change for each outcome variable is illustrated in Figure 1. Seventy-five percent of the sample was rated as responders on the CGI-I, defined as much or very much improved; 4.2% of the sample was rated as worse (n = 28).

Moderator analysis. Four patient characteristics had a statistically significant moderating effect of ADHD outcome. There was greater improvement in ADHD-RS-IV scores in those patients who were younger ($\beta = 0.09$, $P = .02$), female ($\beta = 0.14$, $P < .001$), and more severely ill at baseline ($\beta = 0.21$, $P < .001$). There was a trend to greater improvement in subjects who were treatment-naive ($\beta = 0.07$, $P = .059$). The model as a whole explained 7.8%

Table 2. Multiple Regression of the AIM-A Subscales

Measure	R^2	F**	ADHD-RS-IV Inattentive**	ADHD-RS-IV Hyperactive/Impulsive	Medication Satisfaction Scale**
Living with ADHD[a]	0.29	136.57	0.28	NA	0.34
General well-being[b]	0.35	119.17	0.25	0.11*	0.35
Performance and daily functioning[a]	0.43	249.76	0.39	NA	0.37
Relationships/communication[b]	0.18	48.15	0.24	0.11†	0.17
Bothersomeness[b]	0.27	83.93	0.24	0.19**	0.21
Interference in daily life[b]	0.34	115.26	0.26	0.22**	0.24

[a] $df = 2,668$.
[b] $df = 3,667$.
†$P < .05$.
*$P < .01$.
**$P < .001$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale for DSM-IV, investigator version; AIM-A = ADHD Impact Module for Adults; NA = not applicable; R^2 = coefficient of determination for multivariate analysis.

of the variance ($F_{4,667} = 14.12$, $P < .001$) in the change in total ADHD-RS-IV scores from baseline to termination.

The quality of life outcome for the treatment-naive subsample for quality of life was always slightly better. The AIM-A "living with ADHD" subscale measures the patient's perceived impact of ADHD and social stigma. Treatment-naive subjects showed moderately greater improvement on this scale than those who had prior treatment. The effect size of the difference between groups was moderate (.38).

Mediator analyses. The patient's satisfaction with medication ($\beta = 0.24$, $P < .001$) and improvement in both ADHD-RS-IV HI symptoms ($\beta = 0.15$, $P = .001$) and IA symptoms ($\beta = 0.20$, $P < .001$) were robust mediators of improvement on the SF-36v2 MCS. The model as a whole explained 23% of the variance of improvement in SF-36v2 MCS ($F_{3,668} = 66.81$, $P < .001$), indicating partial mediation.

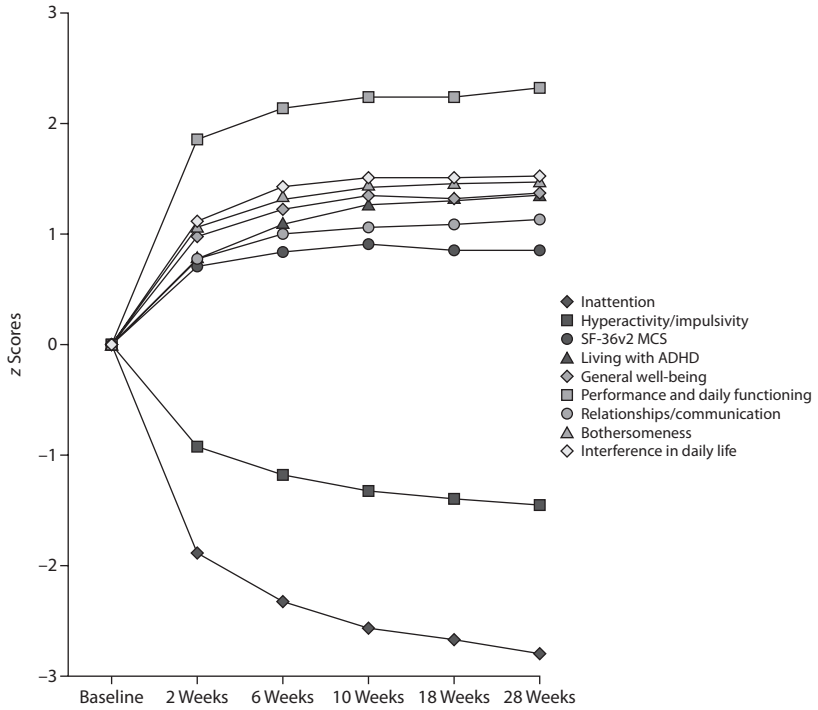
The results of the mediation analyses of the AIM-A are presented in Table 2. Improvement in attention and higher medication satisfaction on the MSS were consistently observed to be mediators of improvement in the AIM-A subscale scores. Improvements in hyperactivity/impulsivity did not mediate improvements in the daily functioning or living with ADHD subscale scores and were generally weaker than changes in the general well-being and relationships/communication subscale scores. The bothersomeness and interference subscales, which inquire about the impact of symptoms related to both inattention and hyperactivity/impulsivity, were predicted to a similar extent by inattention, hyperactivity/impulsivity, and MSS score. Mediation, in all cases, was partial, with the greatest degree of mediation occurring for the daily functioning subscale, in which mediators accounted for 43% of the variance, while the relationships/communication subscale showed the least mediation by MSS score and change in ADHD symptoms.

Temporal analyses. Figure 2 shows the mean scores for the ADHD-RS-IV, SF-36v2 MCS, and AIM-A subscales at each of the time periods during the course of the study for the 370 participants who had data on all relevant variables at each of the 6 visits. As can be seen, the majority of change in both HRQL and symptom scores occurred between the baseline and 2-week visits. The temporal correlation between changes in symptoms and HRQL is graphically represented by the symmetry of symptom and quality of life variables.

To examine whether the changes in symptoms and HRQL occurred at the same time or if there was a lag between symptom improvement and improvement in HRQL, the correlations between the changes in ADHD-RS-IV symptoms and both the SF-36v2 MCS and the subscales of the AIM-A within the same time period (eg, baseline to 2 weeks, 2 weeks to 6 weeks) were compared to the lagged correlations between changes in the HRQL variables and changes in ADHD-RS-IV symptoms occurring in previous time periods. As essentially the same pattern of results was found in all cases, the MCS results will be described in more detail to illustrate the general pattern, with data on the AIM-A subscales presented in eTable 1 (available at www.psychiatrist.com).

Improvements in ADHD-RS-IV scores were consistently significantly correlated with improvements in MCS scores within the same time period (Table 3), with the sole exception of the HI subscale at the 28-week time period. When all possible lagged correlations were examined, only one was significant, as change in MCS occurring between 2 to 4 weeks correlated with changes in ADHD-RS-IV IA occurring between baseline and 2 weeks. This was significantly different from the correlation between contemporaneous changes in the ADHD-RS-IV IA and SF-36v2 MCS both occurring during the 2-week to 4-week period ($t_{367} = 4.86$, $P < .001$). When variance accounted for by contemporaneous changes in ADHD-RS-IV IA was partialled out of the lagged correlation, it became nonsignificant ($r_{368} = -0.05$, $P > .05$). All other lagged correlations were both significantly below the contemporaneous correlations between changes in ADHD-RS-IV and nonsignificant. The same overall pattern held for the AIM-A subscales, with the difference that

Figure 2. Changes in ADHD-RS-IV, SF-36v2, and AIM-A *z* Scores Over Time



Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale for DSM-IV, investigator version; AIM-A = ADHD Impact Module for Adults; SF-36v2 MCS = Short Form-36 Health Survey questionnaire, version 2 Mental Component Summary.

Table 3. Contemporaneous and Lagged Correlations Between Changes in ADHD-RS-IV and SF-36v2 MCS[a]

	ADHD-RS-IV Inattentive Subscale				
SF-36v2 MCS	2 Weeks	6 Weeks	10 Weeks	18 Weeks	28 Weeks
2 Weeks	0.43**				
6 Weeks	−0.16*	0.33**			
10 Weeks	−0.07	−0.08	0.25**		
18 Weeks	0.02	0.07	−0.08	0.32**	
28 Weeks	−0.07	0.07	−0.03	−0.07	0.19**
	ADHD-RS-IV Hyperactivity/Impulsivity Subscale				
SF-36v2 MCS	2 Weeks	6 Weeks	10 Weeks	18 Weeks	28 Weeks
2 Weeks	0.34**				
6 Weeks	−0.04	0.26**			
10 Weeks	−0.09	−0.09	0.16**		
18 Weeks	0.09	0.05	−0.02	0.19**	
28 Weeks	−0.07	0.05	0.03	−0.04	0.08

[a]Higher scores indicate improvement. $df = 368$.
*$P < .01$.
**$P < .001$.
Abbreviations: ADHD-RS-IV = ADHD Rating Scale for DSM-IV, investigator version; MCS = Mental Component Summary; SF-36v2 = Short Form-36 Health Survey questionnaire, version 2.

the relationships between contemporaneous change in the ADHD-RS-IV and AIM-A variables were generally of a higher magnitude (see eTable 1). In no case was a lagged correlation of greater magnitude than the respective contemporaneous correlation, and in no case did a significant lagged correlation remain significant after partialling out contemporaneous change in the ADHD-RS-IV.

DISCUSSION

The Quality of Life, Effectiveness, Safety, and Tolerability study is the largest effectiveness study of outcome of a stimulant for treatment of ADHD in adults ever conducted to date. Mixed amphetamine salts extended release had previously been shown to be a safe and effective treatment, as compared to placebo,[36] that retained its efficacy for treatment of ADHD in a 2-year open-label extension.[37] These results were replicated in the QU.E.S.T. study, which further examined the relevance of these findings for actual effectiveness in community settings over time. Outcome of ADHD symptoms is moderated by age, female gender, and severity of illness. Our results replicate other studies[38] in which it has become apparent that patients who are treatment-naive are more likely to be responders, both in symptoms and in quality of life. Absence of prior treatment may select for a more responsive group of patients, as well as a group with higher pretreatment expectations.

The QU.E.S.T. study clearly demonstrates that ADHD in adults is associated with greatly diminished quality of life and that treatment of the disorder with long-acting amphetamine improves this important aspect of health. The improvement in HRQL was, as expected, greater for ratings of general emotional health as measured by the SF-36v2 as opposed to the PCS. The improvement in HRQL

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is largely accounted for by scales most relevant to psychiatric illness.

Improvement in ADHD-specific quality of life outcomes captured by the AIM-A is greater than improvement in generic quality of life as measured by the SF-36v2. Robust improvements were seen across all 6 subscales of the AIM-A, with performance and daily functioning showing a particularly large improvement. The greater degree of improvement on the AIM-A subscales, in contrast to the SF-36v2, illustrates the importance of measuring disease-specific quality of life and that quality of life outcomes are disease-specific. Generic measures may both fail to capture areas of impairment specific to ADHD and include areas of impairment irrelevant to ADHD.

This is the first psychopharmacologic study we know of that demonstrates that the patient's own reported satisfaction with medication is a mediator of outcome. It is hard to determine if improved outcome leads to improved satisfaction, or if comfort and satisfaction with medication made an independent contribution to ultimate outcome. Future research should consider the use of medication satisfaction questionnaires to explore this further, particularly in studies in which there are different treatment comparators.

The QU.E.S.T. study demonstrated that, following treatment initiation, improvement in ADHD symptoms took place concurrently with improvement in HRQL. This was an unexpected and clinically important observation. It is commonly assumed that an intermediate-term outcome study is needed to be able to identify improvement in quality of life or functioning, based on the idea that symptom improvement must ripen to allow the patient's daily experience to benefit from symptom remission. Earlier exploratory studies[39,40] of ADHD and quality of life were designed as intermediate-term studies for this reason, but it was never anticipated that ADHD symptoms and quality of life would improve at the same time. More recent research has demonstrated that change in quality of life for a range of disorders follows improvement fairly quickly, but this is the first study that demonstrates them to change simultaneously. This suggests that both symptoms and quality of life are direct and immediate results of treatment outcome. This is conceptually a new and important finding. Although quality of life and symptoms are overlapping but distinct concepts, the time course by which they evolve indicates that they are closely linked, and both represent valid and complementary outcomes sensitive to short-term change.

Inattention was a stronger mediator of ADHD-QoL outcome than hyperactivity/impulsivity. This was also an unexpected finding, since research in ADHD in childhood has consistently demonstrated that disruptive symptoms are associated with more social impairment, whereas attention deficits are associated with academic impairment.[41] It is well established that there is a shift in the relative prominence of attention difficulties as opposed to hyperactivity/impulsivity as patients with ADHD age.[42] The greater persistence of inattentive symptoms in adulthood could contribute to the greater impact of inattention on HRQL and impairment. It is also well established that the gender ratio for adults with ADHD includes relatively more women,[43,44] and this may also impact a relatively greater self-reported impact of attention versus deportment difficulties. Adults with ADHD may be more aware of, or more inconvenienced by, attention deficits as opposed to disruptive behaviors. It is possible that disruptive symptoms are more noticeable and bothersome to other people, whereas attention symptoms are less visible but more debilitating from the point of view of the patient. Future research is needed to determine if inattention remains a stronger mediator of outcome when the informant is a collateral observer. It is also possible that improvement in attention may have a differential impact on patient outcome, because while all adults with ADHD have problems with attention, problems with hyperactivity/impulsivity have attenuated in later life. Nonetheless, further research may replicate our finding that attention is not only more persistent in adults than hyperactivity/impulsivity, but also more disabling.

This study found that improvement in quality of life is as sensitive to the patient's satisfaction with medication as it is to whether or not ADHD symptoms actually improve. Factors related to the ease of use, side effects, and perceived effectiveness of the medication play an important role in HRQL and ADHD-QoL outcomes. This is the first study to demonstrate that patient satisfaction with medication is a major mediator of outcome. This suggests that whether or not pharmacotherapy actually translates into improved patient well-being is dependent on many variables, including the patient's view of medication and medication tolerability. Patients' self-report of satisfaction with medication tells us as much about whether their quality of life improves as objective ratings of symptoms. In short, when we treat ADHD, symptoms get better, quality of life gets better, and the patient's report of their satisfaction with treatment makes it clear that they are aware that pharmacotherapy helped.

Limitations

While the strength of this study is that it provides naturalistic, community-based effectiveness data, we are limited by the constraints inherent in any open-label study. Without a local normal control group, we do not know the extent to which the findings reported here compare with those for the population at large, except through the normative data provided with the SF-36v2, though this concern is attenuated somewhat, as the study was performed at investigational sites across the United States and Canada. Without a treatment-as-usual arm or other comparator arm, we do not know whether our results are specific to treatment with a long-acting amphetamine, MAS XR, or might vary with other types of intervention. The most salient results of this study then relate to the analyses of the correlations between different dimensions of outcome within the sample. Future

research should perhaps include patients who refuse treatment or a local normal control group as comparators.

Another limitation is that all the outcomes reported in this study are based on self-report, and the results might be different if collateral or objective outcome measures had been included. Patients may be more aware of how their illness impacts them than how it impacts others, which may in turn affect their relationships and daily functioning.

Clinical Implications

This study demonstrates that ADHD in adults is associated with quality of life ratings comparable to other disabling medical and psychiatric illness. More important is the finding that treatment targets go beyond symptoms. Improvement in ADHD symptoms is mirrored by an immediate and robust improvement in quality of life.

Future research on HRQL outcomes in adults with ADHD would provide us with a more accurate picture of the limitations of short-term symptom outcomes as a reflection of the actual impact of treatment on the patient's burden of illness.

Drug names: atomoxetine (Strattera), mixed amphetamine salts extended release (Adderall XR).

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Supplementary material: eTable 1 is available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Moderators and Mediators of Symptoms and Quality of Life Outcomes in an Open-Label Study of Adults Treated for Attention-Deficit/Hyperactivity Disorder

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List of Supplementary Material for the article

1. eTable 1 Contemporaneous and Lagged Correlations Between the ADHD-RS-IV and AIMA Change Scores at 2 and 6 Weeks

Disclaimer

This Supplementary Material has been provided by the author(s) as supporting information to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eTable 1: Contemporaneous and Lagged Correlations Between the ADHD-RS-IV and AIMA Change Scores at 2 and 6 Weeks

	Inattention		Hyperactivity/Impulsivity	
	2 Weeks	6 Weeks	2 Weeks	6 Weeks
Living with ADHD				
2 Weeks	.34**		.27**	
6 Weeks	.11†	.27**	–.06	.23**
General well-being				
2 Weeks	.42**		.31**	
6 Weeks	–.17**	.36**	–.06	.30**
Daily functioning				
2 Weeks	.54**		.31**	
6 Weeks	–.23**	.50**	–.06	.30**
Relationships/communications				
2 Weeks	.32**		.26**	
6 Weeks	.05	.21**	–.06	.24**
Symptom bothersomeness				
2 Weeks	.44**		.36**	
6 Weeks	–.12†	.35**	–.08	.31**
Symptom interference				
2 Weeks	.47**		.38**	
6 Weeks	–.11†	.36**	–.04	.26**

Note: Higher scores indicate improvement. $df = 368$.
†$P < .05$.
*$P < .01$.
**$P < .001$.