Attention-Deficit/Hyperactivity Disorder–Specific Quality of Life With Triple-Bead Mixed Amphetamine Salts (SPD465) in Adults: Results of a Randomized, Double-Blind, Placebo-Controlled Study

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Objective: To assess the quality of life (QOL) in adults with attention-deficit/hyperactivity disorder (ADHD) given triple-bead mixed amphetamine salts (MAS), a long-acting amphetamine formulation designed for a duration of action of up to 16 hours.

Method: 274 adults with ADHD (DSM-IV-TR criteria) were randomly assigned to 7 weeks of double-blind treatment with an optimal dose of triple-bead MAS (12.5 mg to 75 mg) (N = 137) or placebo (N = 137). As a secondary objective of this study, QOL was assessed on the basis of self-reported Adult ADHD Impact Module (AIM-A) scores, describing ADHD-specific QOL in 6 domains and global QOL (questions 1–4). To assess safety, data were collected on adverse events, vital signs, electrocardiograms, laboratory tests, and sleep quality. The trial was conducted from January 2005 to June 2005.

Results: Statistically significant improvement between triple-bead MAS and placebo was observed in all 6 ADHD-specific AIM-A subscales. In addition, statistically significant improvement in global QOL between triple-bead MAS and placebo was seen, based on AIM-A question 1 (p = .0006) and question 4 (p = .0001). Patients' age, gender, race, and prior use of stimulant medication were not found to significantly affect AIM-A subscale scores. The most common treatment-emergent adverse events with triple-bead MAS (insomnia, dry mouth, decreased appetite, headache, and weight decreased) were consistent with amphetamine treatment, and their incidence generally decreased with time.

Conclusions: Adults with ADHD showed significantly improved QOL for both ADHD-specific and global measures with triple-bead MAS in comparison to placebo, based on AIM-A scores. Treatment-emergent adverse events were mostly mild to moderate in intensity and were consistent with amphetamine treatment.

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Attention-deficit/hyperactivity disorder (ADHD) is estimated to affect 4.4% of adults (aged 18–44 years) in the United States.[1] As in pediatric patients, adults with ADHD may experience clinically significant impairments across many settings that negatively affect social, academic, and occupational functioning.[2] Adults with unrecognized and untreated ADHD have been reported to experience lower educational and/or occupational attainment, higher work impairment, greater interpersonal and emotional difficulties, and a higher incidence of comorbid illness than adults without ADHD.[3,4] Quality of life (QOL) impairments are commonly associated with adult ADHD.[4–6] Adler and colleagues[5] found that in adults with untreated ADHD, QOL based on a 36-item, validated, and well-recognized short health survey (SF-36) was impaired; all mental component subscores—vitality, role emotional, social function, and mental health—were below the U.S. norm. Similar QOL impairments have been described in untreated children with ADHD.[7] These findings indicate that a reduced QOL, likely related to ADHD symptoms, may occur across a variety of dimensions in patients with ADHD.[4]

Emerging evidence suggests that some treatments for ADHD may also help improve QOL.[5,8–12] In a study of untreated adults,[5] 6 weeks of double-blind treatment with atomoxetine was associated with significant improvement in the SF-36 mental component summary score. The Adult

Attention-Deficit/Hyperactivity Disorder Quality of Life Scale, consisting of 4 subscales (life productivity, psychological health, life outlook, and relationships), also has been shown to be a valid and responsive outcome measure of QOL in patients undergoing treatment for ADHD. Statistically significant improvement was observed on all 4 subscales after 8 weeks of treatment with atomoxetine ($p < .0001$).[13] Psychostimulants are a commonly employed pharmacologic treatment of ADHD in children and adults,[14,15] and similar positive effects on QOL have been seen with psychostimulant treatment. During a 10-week interim analysis of a 30-week, open-label trial of mixed amphetamine salts extended release (MAS XR) in adults with ADHD, significant improvements from baseline were observed in nearly all SF-36 subscales.[8]

Despite these encouraging findings, few trials have employed an instrument designed to rigorously measure the impact of ADHD on QOL. The Adult ADHD Impact Module (AIM-A) was developed to assess the impact of core ADHD symptoms on day-to-day functioning and QOL in adults and to assist clinicians in identifying and monitoring treatment targets.[11] This self-report tool comprises 6 multi-item scales that evaluate ADHD-specific impact on 6 distinct QOL domains, with most responses based on Likert-type rating scales. Global QOL is assessed by 4 separate questions and economic impact by 5 questions. For the multi-item subscales, ratings are summed and transformed so that higher scores indicate better QOL. The reliability and validity of the AIM-A were recently evaluated in a prospective, open-label trial of MAS XR treatment in 317 adults with ADHD.[11] The majority of participants in that study were Caucasian (87%) and were either married or remarried (54%), and 52% were female. Most had been diagnosed within the past 6 months with moderately (45%) or markedly (35%) severe ADHD, combined subtype (59%).

The AIM-A was sufficiently sensitive to discriminate (i.e., to detect a significant change in QOL) between those patients who were rated as markedly ill versus those who were mildly or moderately ill; those with the combined ADHD subtype versus those classified as inattentive; and those who were treatment-naive versus previously treated.[11] Item-scaling analysis showed that items in each of the 6 subscales had internal consistency reliability (Cronbach α range, 0.68–0.91), confirming that all items were grouped and scored appropriately.[11] While there were significant correlations between all AIM-A subscale scores and selected SF-36 subscales, the AIM-A outperformed the SF-36 in discerning ADHD symptom severity, subtype, and medication experience; this suggests that the disease-specific nature of the AIM-A has greater clinical accuracy and sensitivity than the more general SF-36.[11]

To date, a pediatric version of the AIM (the AIM-C [ADHD Impact Module-Child]) and the AIM-A have been used to assess QOL in open-label trials of psychostimulants in children and adults, respectively, with ADHD. In a separate analysis of the 30-week open-label study of MAS XR in adults with ADHD mentioned above, statistically significant improvements were seen in all 6 AIM-A subscales.[10] A more recent study in children with ADHD showed that 4 weeks after a switch from oral methylphenidate to transdermal methylphenidate, parent-rated family and child QOL had significantly improved, based on the AIM-C.[16] The findings from these open-label studies indicate that psychostimulants can help improve ADHD-specific QOL.

Currently available long-acting stimulants provide treatment for 10 to 12 hours, which is usually sufficient for a child's functional day; however, many adults require longer symptom control. As a secondary endpoint, this study sought to extend the examination of the effect of an ADHD medication of longer duration (triple-bead MAS) on QOL using the AIM-A.

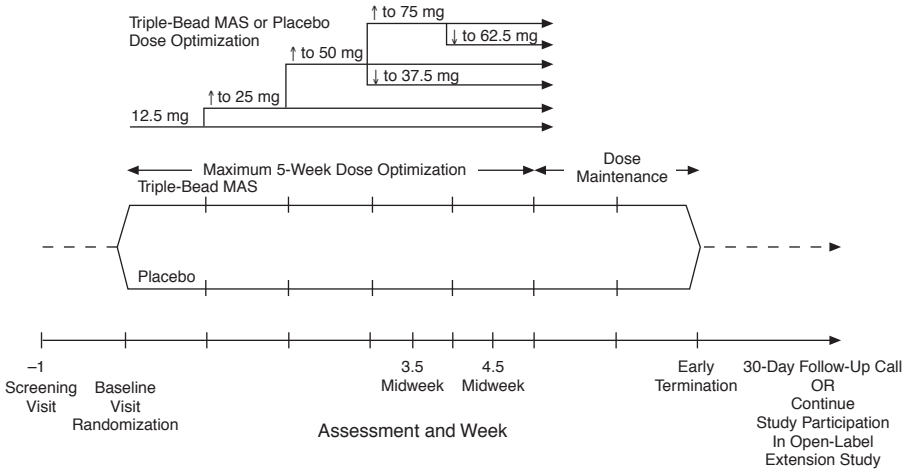
METHOD

Subjects

Inclusion criteria. Men or women between the ages of 18 and 55 years, inclusive, who met the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (DSM-IV-TR)[17] criteria for a primary diagnosis of ADHD, based on a psychiatric evaluation and administration of the Adult ADHD Clinical Diagnostic Scale, version 1.2, with at least 6 of the 9 subtype criteria exhibited,[18] were eligible for enrollment in the study; subjects were also required to have a baseline ADHD Rating Scale version IV (ADHD-RS-IV) score ≥ 24. Women were required to be nonpregnant and nonlactating; women of childbearing age must have agreed to use acceptable methods of contraception throughout the study. Subjects were also required to have a satisfactory medical assessment with no clinically significant or relevant abnormalities and to provide informed consent.

Exclusion criteria. Individuals with any of the following criteria at screening or baseline (if reassessed) were excluded from the study: current illness (chronic or acute) or an unstable medical condition; known cardiac structural abnormality or other cardiac condition that might affect cardiac performance; a history of controlled or uncontrolled hypertension or a resting, sitting, systolic blood pressure > 139 mm Hg or a diastolic blood pressure > 89 mm Hg at screening; body mass index < 18.5 kg/m^2 or morbid obesity; clinically significant electrocardiogram (ECG); or laboratory abnormalities at screening or baseline. Also excluded were individuals with a comorbid psychiatric diagnosis with significant symptoms or requiring pharmacologic treatment; seizure history, tic disorder, diagnosis or family history of Tourette's disorder; or mental retardation. Individuals who had used psychotropic

Figure 1. Study Design Flowchart for the 7-Week, Double-Blind, Randomized Controlled Study of the Efficacy and Safety of Triple-Bead MAS[a]



[a]Repinted with permission from Spencer et al.[24]
Abbreviation: MAS = mixed amphetamine salts.
Symbols: ↑ = upward titration to the indicated dose, ↓ = downward titration to the indicated dose.

medication that required more than a 28-day washout period, who had participated in an investigational drug trial within 30 days of screening, who had reported drug dependence or substance use disorder (excluding nicotine) within 6 months of screening, or who had a positive urine drug test result at screening or baseline were excluded from participation. Patients with a known allergy, intolerance, or nonresponse to methylphenidate or amphetamines were also excluded from participation. The concomitant use of psychoactive medications that might interfere with the efficacy, safety, or tolerability of triple-bead MAS was prohibited during the study.

Study Design

Overview. This was a 7-week, phase 3, randomized, double-blind, multicenter, placebo-controlled, parallel-group, dose-optimization study to evaluate the impact of triple-bead MAS treatment in adults with ADHD. A total of 39 sites in the United States participated in the study. Institutional review board approval was obtained, either through a central governing body (33 sites) or through a local board (6 sites). The trial was conducted from January 2005 to June 2005.

The study was conducted in accordance with the Declaration of Helsinki and its most recent amendment (http://www.wma.net/e/ethicsunit/Helsinki.htm). Subjects were required to provide written, personally signed, and dated informed consent to participate in the study in accordance with the International Conference on Harmonization, Good Clinical Practice Guidelines[19] and applicable regulations before completing any study-related procedures.

Figure 1 provides an overview of the investigational plan. The study comprised 3 phases: (1) screening, (2) washout and baseline, and (3) a 7-week, double-blind evaluation of triple-bead MAS and placebo. To determine eligibility, prospective subjects were screened for approximately 2 weeks. Subjects who were currently receiving stimulant treatment underwent a washout period of at least 7 days before baseline evaluations. Subjects receiving medications that resulted in receptor changes in the central nervous system, including but not limited to bupropion and atomoxetine, were required to undergo a 28-day prebaseline washout period. At baseline, subjects who continued to meet all eligibility requirements were randomly assigned in a 1:1 ratio to 7 weeks of double-blind treatment with a single morning dose of triple-bead MAS or placebo (Figure 1). Randomization was accomplished using a centralized, interactive, voice-response system.

During the first 5 weeks of the 7-week, double-blind treatment period, the dose could be adjusted weekly on the basis of clinical efficacy and tolerability; the final 2 weeks of double-blind treatment comprised a maintenance phase. All subjects who were randomly assigned to triple-bead MAS began treatment with a 12.5-mg dose that could be increased first to 25 mg, then to 50 mg, and finally to a maximum dose of 75 mg, until an optimal dose had been achieved. The optimal dose was determined by the investigators based on clinical improvement (a ≥ 30% decrease in baseline ADHD-RS-IV score) and tolerability. At the investigators' discretion, downward titration was permitted 2 times during the study. At the end of week 3 (visit 3), subjects could be down-titrated from 50 mg to a week 4 dose of 37.5 mg; at the end of week 4 (visit 4), subjects could be down-titrated from 75 mg to a week 5 dose of 62.5 mg. During the final 2 weeks of

double-blind treatment, all subjects were maintained at their clinically optimal dose (possible dose range: 12.5–75 mg) until the end of the study. Subjects visited the clinic once a week during double-blind treatment for evaluation of drug tolerability and effectiveness. If the subject had been titrated to a dose of 62.5 mg or 75 mg, a midweek visit to the clinic was required to assess vital signs.

Assessments

As a secondary efficacy outcome measure, the AIM-A was administered to assess ADHD-specific QOL. As previously discussed, the AIM-A, validated in adults, is a self-report instrument comprising 4 global QOL questions, 5 economic impact questions, and 6 multi-item scales that evaluate ADHD-specific impact on 6 distinct QOL domains: living with ADHD, general well-being, performance and daily functioning, relationships and communication, bothersomeness and concern, and daily interference.[11] For the multi-item subscales, Likert-type ratings for each item are summed and transformed; higher scores indicate a better QOL. This article reports on the change from baseline to endpoint for each of the AIM-A multi-item subscale scores and global QOL questions; changes in score for economic impact questions were not assessed.

The primary efficacy outcome measure was the clinician-administered ADHD-RS-IV, which consists of 18 items that reflect current ADHD symptoms.[20] Each item is scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms). In the current investigation, the ADHD-RS-IV was adapted to assess the impact of ADHD in adults,[18] using a semistructured format and an extensive list of examples. Other secondary outcome measures included the ADHD-RS-IV hyperactivity/impulsivity and inattention subscales, Clinical Global Impressions-Improvement scale (CGI-I),[21] Brown Attention-Deficit Disorder Scale,[22] and Time-Sensitive ADHD Symptom Scale.[23] Primary and secondary efficacy outcomes based on these measures are described in detail in separate reports.[24,25]

Safety was assessed based on treatment-emergent adverse events (TEAEs), vital signs, ECGs, clinical laboratory evaluations (clinical chemistry, hematology, pregnancy test, and routine urinalysis with urine drug screen), and physical examination results and are reviewed in detail elsewhere.[24] Only reported TEAEs will be presented here.

Schedule of Assessments

Baseline assessments included all defined measures of efficacy and QOL, except the CGI-I (the Clinical Global Impressions-Severity of Illness scale [CGI-S] was completed at baseline). At each weekly visit, the ADHD-RS-IV and CGI-I were completed, and ECG and drug-compliance tests were performed. At all study visits, subjects were queried for adverse events (AEs) and vital signs (blood pressure and pulse rate) were recorded. The AIM-A was completed at baseline and again at the final study visit. Physical examinations and clinical laboratory evaluations were performed at screening and final visit.

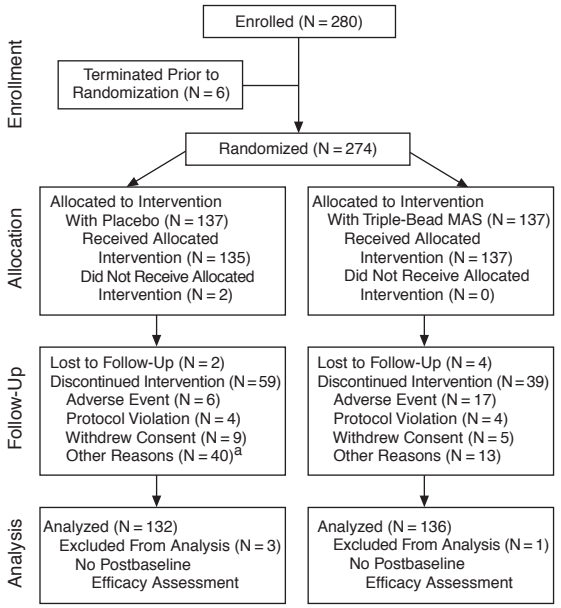
Statistical Analysis

The impact of triple-bead MAS on QOL was assessed based on analysis of change from baseline to endpoint in the intention-to-treat (ITT) population on (1) each of the 6 AIM-A multi-item subscale scores and (2) scores for global QOL questions 1 and 4. The ITT population was defined as all randomized subjects who had undergone baseline assessment, received at least 1 dose of study medication during the study, and had at least 1 postbaseline primary efficacy assessment. Endpoint score was defined as the last postbaseline study visit (either week 7 or early termination) when a valid score was obtained. A 1-way analysis of covariance (ANCOVA) model was used, with treatment as a fixed effect and baseline AIM-A score as the covariate; a type I error rate for rejecting the null hypothesis was set at an α level of .05. Summary descriptive statistics for each AIM-A subscale and global QOL questions 1 and 4 were calculated for baseline and endpoint by randomized treatment group. Shift tables were constructed to describe changes from baseline in response to global QOL questions 2 and 3, exploratory questions in which a significant shift in response was not expected in a short-term study. No inferential statistics were performed for questions 2 and 3. The 5 economic impact items were collected only at baseline.

A number of post hoc exploratory analyses were also carried out to further explore QOL differences between triple-bead MAS treatment and placebo for the 6 multi-item subscales. The possible effect of demographic/baseline characteristics on AIM-A outcomes was examined, based on type III tests from ANCOVA models that included terms for treatment, demographic/baseline variable (e.g., gender, age [$\leq$ 40 vs. $>$ 40 years], race, or prior stimulant-use status [naive, non-naive]), and treatment-by–demographic/baseline variable interaction as fixed effects and baseline value as a covariate.

Adverse events were coded using criteria from the *Medical Dictionary for Regulatory Activities*, version 7.1 (http://www.meddramsso.com/MSSOWeb/index.htm). Frequency of TEAEs was calculated for each body system and was recorded as the number and percentage of subjects reporting the adverse event. Descriptive statistics were provided for vital signs, ECG parameters, and laboratory test parameters. Pittsburgh Sleep Quality Index total scores, subscale scores, and the change from baseline were summarized using descriptive statistics. Inferential statistical comparisons of safety data were not conducted.

Figure 2. Subject Disposition



[a]Lack of efficacy was "other" reason for discontinuation in 30/40 subjects in the placebo group.
Abbreviation: MAS = mixed amphetamine salts.

RESULTS

Subject Disposition and Study Population

Subject disposition is summarized in Figure 2. Two hundred eighty subjects were enrolled into the study; 274 were randomly assigned to treatment (N = 137, triple-bead MAS; N = 137, placebo). The randomized safety population consisted of 272 subjects (N = 137, triple-bead MAS; N = 135, placebo); 2 subjects randomly assigned to the placebo group were excluded from the safety analysis because they did not take a dose. The ITT population consisted of 268 subjects, with 136 subjects in the triple-bead MAS group and 132 subjects in the placebo group. The study was completed by 170 subjects (triple-bead MAS group: 68.6%; placebo group: 55.5%). The most common reason for premature discontinuation in the triple-bead MAS group was adverse events (N = 17, 12.4%); in the placebo group, the most common reason for discontinuation was "other" (N = 35, 25.5%), mainly lack of efficacy (22.2%, compared with 7.3% in the triple-bead MAS group).

Table 1 summarizes baseline demographic and clinical characteristics for the study sample. The mean ± standard deviation (SD) age of all study subjects was 36.5 ± 10.2 years. Most subjects were white (84.9%), with equal proportions of men (50%) and women (50%). The combined ADHD subtype was seen in the majority of subjects (70.6%), and the most common CGI-S category reported at baseline was "markedly ill" (49.3%); the mean time since diagnosis of ADHD was 5.5 years. Approximately 25% of the subjects in each group had received previous pharmacotherapy for ADHD, most frequently MAS XR (15.1%). The AIM-A contains 5 questions assessing the economic impact of ADHD; at baseline, subjects in both treatment groups reported a similar number of motor vehicle infringements during the past year, number of jobs held to date, number of emergency department or physician visits due to injuries/accidents to date, number of visits to a physician regarding ADHD during the past year, and number of days missed from work/school during the past year.

AIM-A Quality-of-Life Analysis

Statistically significant improvements from baseline were seen on the primary AIM-A QOL measures following 7 weeks of triple-bead MAS treatment. Table 2 summarizes the mean baseline and endpoint scores on the primary AIM-A QOL measures. Changes from baseline to endpoint on all 6 multi-item subscales are illustrated in Figure 3. The triple-bead MAS treatment group was significantly better than placebo for all 6 multi-item subscales. The performance and daily functioning subscale showed the greatest magnitude of difference between triple-bead MAS and placebo (least squares mean change: 24.5 vs. placebo, 5.7; $p < .0001$).

Post hoc exploratory analyses did not detect significant effects of gender, age, race, or prior stimulant use (stimulant-naive vs. stimulant history) or significant treatment-by–demographic/baseline variable interactions on changes from baseline at endpoint for any of the 6 AIM-A subscale scores. The triple-bead MAS treatment group showed significantly greater improvement than placebo for global QOL questions 1 and 4 (Figures 4 and 5). For question 1 ("On a scale from 1 to 10, how would you rate the overall quality of your life right now?"), least squares mean changes from baseline to endpoint for triple-bead MAS and placebo were 1.1 and 0.3, respectively ($p = .0006$, triple-bead MAS vs. placebo). For question 4 ("How much do you agree with this statement: 'Over the past few weeks, I've had more good days than bad days'?" [on a scale of 1 = "strongly agree" to 5 = "strongly disagree"]), least squares mean changes from baseline to endpoint were –0.5 and 0.0 for the triple-bead MAS and placebo groups, respectively ($p = .0001$, triple-bead MAS vs. placebo).

For question 2 ("Has ADHD and its symptoms limited your ability to achieve what you want in life?"), "Yes, a lot" was the most common response with both triple-bead MAS (44.1%) and placebo (50.0%) at baseline. At endpoint, "Yes, a lot" was still the most common response in the placebo group (47.6%), while "Yes, some" was the most common response in the triple-bead MAS group (40.9%), with "Yes, a lot" decreasing to 37.0%. For question 3 ("Do you feel you are on the right track with your

Table 1. Demographic Characteristics of Subjects in the Randomized Controlled Trial of Triple-Bead MAS[a,b]

Variable	Placebo (N = 135)	Triple-Bead MAS (N = 137)	Total (N = 272)
Age, y			
Mean (SD)	37.0 (10.3)	36.1 (10.1)	36.5 (10.2)
Median	38.0	37.0	38.0
Range	18–55	18–55	18–55
Age group, N (%)			
18–25 y	24 (17.8)	26 (19.0)	50 (18.4)
26–35 y	29 (21.5)	36 (26.3)	65 (23.9)
36–45 y	48 (35.6)	50 (36.5)	98 (36.0)
46–55 y	34 (25.2)	25 (18.2)	59 (21.7)
Sex, N (%)			
Male	67 (49.6)	69 (50.4)	136 (50.0)
Female	68 (50.4)	68 (49.6)	136 (50.0)
Race, N (%)			
White	113 (83.7)	118 (86.1)	231 (84.9)
Black	12 (8.9)	9 (6.6)	21 (7.7)
Asian	3 (2.2)	4 (2.9)	7 (2.6)
Other	7 (5.2)	6 (4.4)	13 (4.8)
Weight at screening, lb[c]			
Mean (SD)	177.8 (41.1)	180.4 (43.6)	179.1 (42.3)
Median	176.0	173.0	175.0
Range	96–306	102–333	96–333
ADHD subtype, N (%)			
Inattentive	34 (25.2)	38 (27.7)	72 (26.5)
Hyperactive-impulsive	4 (3.0)	4 (2.9)	8 (2.9)
Combined	97 (71.9)	95 (69.3)	192 (70.6)
Duration since ADHD diagnosis, y			
Mean (SD)	5.3 (9.3)	5.7 (9.8)	5.5 (9.5)
Median	1.0	1.1	1.1
Range	0–46	0–44	0–46
Previous ADHD medications, N (%)			
Any	33 (24.4)	33 (24.1)	66 (24.3)
MAS immediate release	2 (1.5)	7 (5.1)	9 (3.3)
MAS extended release	24 (17.8)	17 (12.4)	41 (15.1)
Atomoxetine	3 (2.2)	0	3 (1.1)
Bupropion	3 (2.2)	2 (1.5)	5 (1.8)
Dextroamphetamine	1 (0.7)	1 (0.7)	2 (0.7)
Methylphenidate	3 (2.2)	8 (5.8)	11 (4.0)
CGI-S score at baseline, N (%)			
Normal, not at all ill	0	0	0
Borderline mentally ill	0	0	0
Mildly ill	0	2 (1.5)	2 (0.7)
Moderately ill	53 (39.3)	57 (41.6)	110 (40.4)
Markedly ill	72 (53.3)	62 (45.3)	134 (49.3)
Severely ill	9 (6.7)	15 (10.9)	24 (8.8)
Among the most extremely ill	1 (0.7)	1 (0.7)	2 (0.7)

[a]Reprinted with permission from Spencer et al.[24]
[b]Results are based on the number of subjects in the randomized safety population in each group.
[c]For this variable, data were available for only 136 subjects in the triple-bead MAS group.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGI-S = Clinical Global Impressions-Severity of Illness scale, MAS = mixed amphetamine salts.

life?"), the number of subjects responding "Yes, definitely" increased from baseline to endpoint with triple-bead MAS (19.7% to 37.0%) and with placebo (10.5% to 22.6%).

Safety and Tolerability Analysis

The TEAEs reported in the randomized safety population are discussed in greater detail in a previous report.[24] A total of 89.1% of triple-bead MAS–treated subjects and 63.7% of placebo-treated subjects reported at least 1 TEAE. The most common TEAEs reported by subjects in the triple-bead MAS group were those commonly associated with amphetamine treatment; these included insomnia (29.2%), dry mouth (22.6%), decreased appetite (19.7%), headache (18.2%), and weight decreased (13.1%).

DISCUSSION

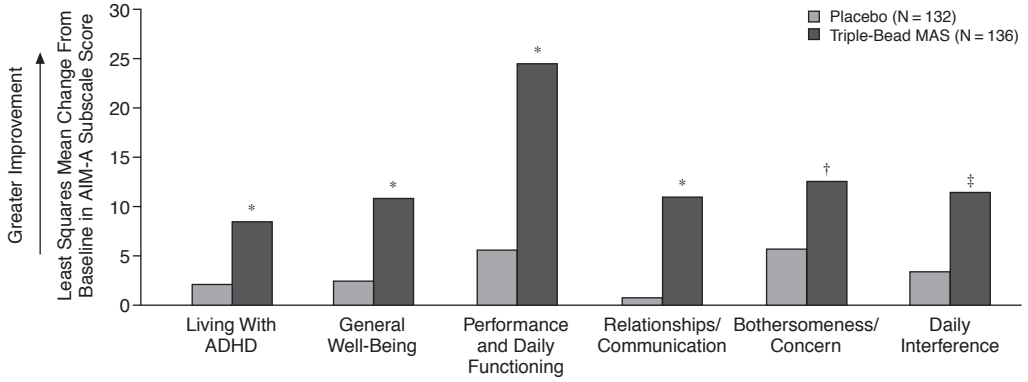
This is the first randomized, placebo-controlled, double-blind investigation describing the effects of stimulant treatment with triple-bead MAS on QOL in adults with ADHD. ADHD-specific and global AIM-A measures of QOL were significantly improved versus placebo with

Table 2. Baseline and Endpoint AIM-A Scores (ITT population)

	Placebo (N = 132)		Triple-Bead MAS (N = 136)	
Item	Baseline, Mean (SD)	Endpoint, Mean (SD)	Baseline, Mean (SD)	Endpoint, Mean (SD)
AIM-A global quality of life question				
Q1[a]	5.4 (2.15)	5.8 (2.13)	5.8 (2.09)	6.8 (1.95)
Q4[b]	2.7 (1.12)	2.6 (1.20)	2.5 (1.08)	2.0 (1.04)
AIM-A Multi-item subscale				
Living with ADHD	50.8 (12.22)	53.2 (13.01)	52.6 (12.30)	60.8 (13.41)
General well-being	47.5 (14.35)	50.7 (16.74)	50.2 (15.23)	60.7 (17.62)
Performance and function	28.6 (18.65)	35.3 (22.55)	32.0 (17.31)	55.7 (26.03)
Relationships/communication	62.1 (21.45)	62.5 (19.76)	59.9 (20.16)	71.4 (20.89)
Impact on daily life—bother/concern	39.2 (21.69)	46.3 (24.30)	40.8 (18.86)	53.3 (22.75)
Impact on daily life—interference	43.7 (23.12)	47.8 (24.32)	45.4 (20.12)	57.1 (23.31)

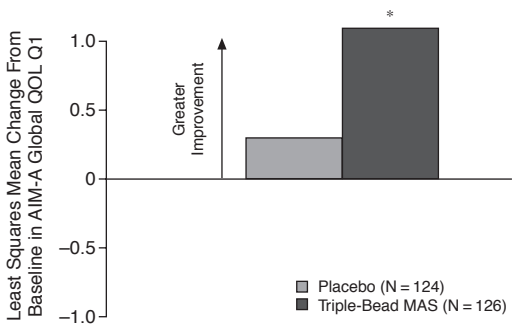
[a]Q1: "How would you rate the overall quality of your life right now?"
[b]Q4: "How much do you agree with this statement: 'Over the past few weeks, I've had more good days than bad days'?"
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, AIM-A = Adult ADHD Impact Module, ITT = intention-to-treat, MAS = mixed amphetamine salts.

Figure 3. Least Squares Mean Change From Baseline to Endpoint in AIM-A Multi-Item Subscales (ITT population)



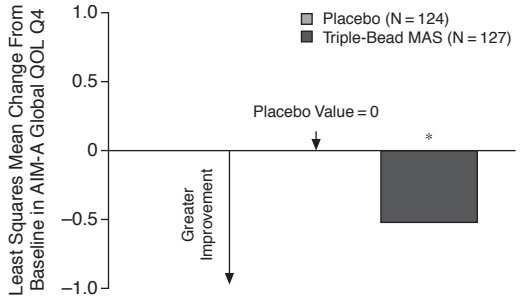
*p < .0001 vs. placebo; †p = .01 vs. placebo; ‡p = .003 vs. placebo. p Values are based on type III tests from an analysis of covariance model for the change from baseline, including treatment as a fixed effect and baseline value as a covariate.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, AIM-A = Adult ADHD Impact Module, ITT = intention-to-treat, MAS = mixed amphetamine salts.

Figure 4. Least Squares Mean Change From Baseline to Endpoint in AIM-A Global QOL, Question 1 (ITT population): "On a Scale From 1 to 10, How Would You Rate the Overall Quality of Your Life Right Now?"[a]



[a]A positive difference indicates a positive effect of triple-bead MAS vs. placebo on question 1.
*p = .0006 vs. placebo; p values are based on type III tests from an analysis of covariance model for the change from baseline, including treatment as a fixed effect and baseline value as a covariate.
Abbreviations: AIM-A = Adult ADHD Impact Module, ITT = intention-to-treat, MAS = mixed amphetamine salts, QOL = quality of life.

Figure 5. Least Squares Mean Change From Baseline to Endpoint in AIM-A Global QOL, Question 4 (ITT population): "How Much Do You Agree With This Statement: 'Over the Past Few Weeks, I've Had More Good Days Than Bad Days'?"[a]



[a]A negative difference indicates a positive effect of triple-bead MAS vs. placebo on question 4.
*p = .0001 vs. placebo; p values are based on type III tests from an analysis of covariance model for the change from baseline, including treatment as a fixed effect and baseline value as a covariate.
Abbreviations: AIM-A = Adult ADHD Impact Module, ITT = intention-to-treat, MAS = mixed amphetamine salts, QOL = quality of life.

clinically optimized doses of triple-bead MAS (12.5 mg/day to 75 mg/day) in this 7-week study. The most robust improvements were seen in the performance and daily functioning subscale. Exploratory analyses indicated that AIM-A subscale outcomes were unaffected by the demographic/baseline variables age, gender, race, or prior stimulant use. In addition, the differences between triple-bead MAS and placebo for the subscale outcomes were not affected by these demographic/baseline variables. The most frequently reported TEAEs (insomnia, dry mouth, headache, decreased appetite, and weight decreased) were generally mild to moderate in intensity, were consistent with amphetamine treatment, and generally decreased in frequency over time.

Safety and Tolerability

The most frequently reported AEs—which included insomnia, dry mouth, headache, decreased appetite, and weight decreased—were not unexpected as they are commonly reported with amphetamine treatment. The majority of these AEs were mild, occurred early during treatment, and generally decreased in frequency with continued treatment.

Clinical Implications of the Study

While treatment with an amphetamine formulation has been shown to improve ADHD symptoms, few studies have rigorously defined how patients' lives are affected by unmanaged ADHD and how they may improve after beginning treatment. Given evidence of QOL impairments in patients with ADHD,[4,5,12] it was of particular clinical interest to examine whether improvements in QOL occur with treatment. Previous reports from open-label trials indicated that QOL improvements may occur for some patients after beginning a medication regimen. The present investigation examined this question in the context of a randomized, placebo-controlled trial.

Economic impact data measured by the AIM-A would not be expected to change within the context of a short, randomized, controlled trial and were thus not assessed in this study. In line with open-label trial results, however, the present study showed that adults with ADHD who were treated with triple-bead MAS reported improvements in ADHD-specific QOL (evaluated as a secondary endpoint) in all 6 AIM-A subscales in comparison with placebo treatment, indicating the broad impact of treatment on multiple domains at endpoint. The performance and daily functioning subscale showed the greatest magnitude of difference between triple-bead MAS and placebo (least squares mean change: 24.5 vs. placebo, 5.7; least squares mean difference, 18.8).

Global AIM-A QOL measures (questions 1 and 4) showed that triple-bead MAS statistically improved QOL when compared with the largely unchanged global QOL response seen in patients receiving placebo. Perhaps most surprising, subjects in the active treatment group reported improvements in global QOL (questions 2 and 3), which were not specifically expected to improve during the brief time course of the study. It should be noted that the positive effects of triple-bead MAS on the QOL subscales were observed regardless of gender, age, race, or prior stimulant treatment.

The current findings provide the first controlled evidence of improvements in ADHD-specific QOL (based on AIM-A scores) following stimulant treatment, confirming reports from previous open-label or uncontrolled trials.[8,10,11] The improvements in QOL observed here occurred soon after initiation of stimulant treatment. In the investigation of Prasad and colleagues,[12] significant improvements in parent-reported QOL were reported for pediatric patients with ADHD after 10 weeks of treatment with atomoxetine. Yet, within 7 weeks of initiating stimulant treatment in this study, both ADHD-specific and global QOL measures had significantly improved in comparison to placebo. Further, while the most common reason for early study discontinuation among subjects treated with triple-bead MAS was the occurrence of AEs (12.4% vs. 4.4% in the placebo group), the most common reason for discontinuation among placebo-treated subjects was lack of efficacy (22.2% vs. 7.3% in the triple-bead MAS group). Although poor tolerability may contribute to compliance issues in stimulant-treated subjects—thus negatively affecting the potential QOL advantages treatment affords—these outcomes suggest that the lack of active treatment may have a greater impact on reduced compliance.

The recent development of another ADHD-specific QOL instrument[26] highlights the growing recognition of the importance of assessing, and therapeutically targeting, the impact of ADHD symptoms on daily functioning in multiple domains and environments. Investigators continue to recognize the unique symptom-management needs of adults that often extend into the evening hours.

Limitations of the Study

While the controlled nature of the current investigation allows firm conclusions to be drawn about the positive impact on disease-specific QOL by stimulant treatment with triple-bead MAS in adults with ADHD, the study nevertheless has limitations. The short duration of the study (7 weeks) does not permit determination of the impact on QOL of long-term triple-bead MAS treatment. The study population included adults aged 18 to 55 years; therefore, the impact of triple-bead MAS on ADHD-specific QOL was not determined for subjects in other age groups, such as adolescents or geriatric patients. The study also excluded patients with major medical or psychiatric comorbidities, and the current findings may not generalize to these patient populations. Further, while the study included analysis of the AIM-A items measuring global

QOL and the 6 multi-item subscales, the short study duration precluded assessment of the AIM-A items addressing ADHD economic impact—an important component of adult QOL. Lastly, this study did not include questionnaires from others close to the subjects (e.g., spouse, other family members) that could provide subjective opinions of QOL improvement to support the AIM-A outcomes.

CONCLUSIONS

Triple-bead MAS (vs. placebo) significantly improved ADHD-specific QOL in adults with ADHD in all areas measured by the AIM-A after 7 weeks of treatment. Scores for all 6 AIM-A subscales were significantly improved compared to placebo, as was global QOL on questions 1 and 4. Post hoc analyses did not detect significant effects on AIM-A scores based on the demographic/baseline characteristics of age, gender, race, or prior treatment with psychostimulants nor were interactions with treatment observed. TEAEs were generally mild to moderate in intensity, with the most frequently reported TEAEs consistent with those expected in subjects treated with amphetamine. This is the first controlled study of stimulant treatment in adults using this advanced QOL scale. It will be important to further study QOL in 12-hour and longer-acting preparations to test for differential response in adult ADHD, evaluate QOL over a longer time-frame that would allow for accurate measurement of economic impact, and analyze these QOL outcomes by ADHD subtypes and symptom severity.

Drug names: atomoxetine (Strattera), bupropion (Aplenzin, Wellbutrin, and others), dextroamphetamine (Dexedrine, Dextrostat, and others), methylphenidate (Daytrana, Ritalin, and others).

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REFERENCES

1. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry 2006;163:716–723
2. Biederman J, Faraone SV, Spencer TJ, et al. Functional impairments in adults with self-reports of diagnosed ADHD: a controlled study of 1001 adults in the community. J Clin Psychiatry 2006;67(4):524–540
3. Adler LA. Clinical presentations of adult patients with ADHD. J Clin Psychiatry 2004;65(suppl 3):8–11
4. Able SL, Johnston JA, Adler LA, et al. Functional and psychosocial impairment in adults with undiagnosed ADHD. Psychol Med 2007; 37:97–107
5. Adler LA, Sutton VK, Moore RJ, et al. Quality of life assessment in adult patients with attention-deficit/hyperactivity disorder treated with atomoxetine. J Clin Psychopharmacol 2006;26:648–652
6. de Graaf R, Kessler RC, Fayyad J, et al. The prevalence and effects of adult attention-deficit/hyperactivity disorder (ADHD) on the performance of workers: results from the WHO World Mental Health Survey Initiative [published online ahead of print May 27, 2008]. Occup Environ Med
7. Sawyer MG, Whaites L, Rey JM, et al. Health-related quality of life of children and adolescents with mental disorders. J Am Acad Child Adolesc Psychiatry 2002;41:530–537
8. Goodman DW, Ginsberg L, Weisler RH, et al. An interim analysis of the Quality of Life, Effectiveness, Safety, and Tolerability (QUEST) evaluation of mixed amphetamine salts extended release in adults with ADHD. CNS Spectr 2005;10:26–34
9. Perwien AR, Kratochvil CJ, Faries DE, et al. Atomoxetine treatment in children and adolescents with attention-deficit hyperactivity disorder: what are the long-term health-related quality-of-life outcomes? J Child Adolesc Psychopharmacol 2006;16:713–724
10. Landgraf JM. ADHD-specific quality of life with mixed amphetamine salts extended release in adults with ADHD. Presented at the 159th annual meeting of the American Psychiatric Association; May 24, 2006; Toronto, Ontario, Canada
11. Landgraf JM. Monitoring quality of life in adults with ADHD: reliability and validity of a new measure. J Atten Disord 2007;11:351–362
12. Prasad S, Harpin V, Poole L, et al. A multi-centre, randomised, open-label study of atomoxetine compared with standard current therapy in UK children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Curr Med Res Opin 2007;23:379–394
13. Matza LS, Johnston JA, Faries DE, et al. Responsiveness of the Adult Attention-Deficit/Hyperactivity Disorder Quality of Life Scale (AAQoL). Qual Life Res 2007;16(9):1511–1520
14. Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry 2002;41:26S–49S
15. Goksoyr PK, Nottestad JA. The burden of untreated ADHD among adults: the role of stimulant medication. Addict Behav 2008;33:342–346
16. Landgraf JM, Arnold LE, McKay MJ. Treatment satisfaction after conversion from oral methylphenidate to transdermal methylphenidate. Presented at the 160th annual meeting of the American Psychiatric Association; May 19–24, 2007; San Diego, Calif
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision: DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000
18. Adler L, Cohen J. Diagnosis and evaluation of adults with attention-deficit/hyperactivity disorder. Psychiatr Clin North Am 2004;27:187–201
19. Center for Drug Evaluation and Research. Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance. Rockville, Md: Center for Drug Evaluation and Research; 1996
20. DuPaul GJ, Power TJ, Anastopoulos AD, et al. ADHD Rating Scale-IV. New York, NY: Guilford Press; 1998
21. Guy W. Clinical Global Impression (CGI). ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare

publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health, Psychopharmacology Research Branch; 1976:218–222
22. Brown TE. Brown Attention-Deficit Hyperactivity Disorder Scales for Adolescents and Adults. Toronto, Ontario, Canada: The Psychological Corporation, Harcourt Assessment Canada; 1996
23. Adler LA, Sitt D, Faraone S, et al. Reliability and validity of the Time-Sensitive ADHD Symptom Scale (TASS) in adults. Presented at the 53rd annual meeting of the American Academy of Child and Adolescent Psychiatry; Oct 27, 2006; San Diego, Calif
24. Spencer TJ, Adler LA, Weisler RH, et al. Triple-bead mixed amphetamine salts (SPD465), a novel, enhanced, extended-release amphetamine formulation for the treatment of adults with ADHD: a randomized, double-blind, multicenter, placebo-controlled study. J Clin Psychiatry 2008;69(9):1437–1448
25. Brown TE, Spencer TJ, Youcha SH, et al. Improved executive functions with triple-bead mixed amphetamine salts (SPD465), a novel, enhanced extended-release amphetamine formulation, in adults with ADHD [poster]. Presented at the 47th annual New Clinical Drug Evaluation Unit; June 12, 2007; Boca Raton, Fla
26. Brod M, Johnston J, Able S, et al. Validation of the Adult Attention-deficit/Hyperactivity Disorder Quality-of-Life Scale (AAQoL): a disease-specific quality-of-life measure. Qual Life Res 2006;15:117–129