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Safety and Tolerability of Once Versus Twice Daily Atomoxetine in Adults with ADHD

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Background. *Attention-Deficit/Hyperactivity Disorder (ADHD) is a disorder characterized by hyperactivity, impulsiveness, and inattention that affects 4% of adults. Atomoxetine hydrochloride is an FDA-approved treatment for adult ADHD, but no studies have clarified whether there are advantages to once versus twice daily dosing.*
Methods. *This randomized, double-blind, multicenter study compared safety and tolerability of 80 mg atomoxetine QD versus 40 mg atomoxetine BID in 218 adults with ADHD. Treatment-emergent adverse events (TEAEs), laboratory values, vital signs, weight, electrocardiograms, scores on the Arizona Sexual Experiences Scale, and efficacy (using the Conners' ADHD Rating Scale-Investigator Rated: Screening Version) were assessed.*
Results. *The overall incidence for any one TEAE was low. There was no significant treatment group difference in likelihood of patients experiencing ≥1 of the four most commonly observed TEAEs (dry mouth, insomnia, nausea, and erectile dysfunction). Frequency of nausea was significantly lower in the 40 mg BID group (16.4%) than the 80 mg QD group (32.4%; p = .007). There were no unexpected safety results. Although both QD and BID treatments were efficacious, the reduction in scores was greater for BID treatment.*
Conclusions. *Data indicate both dosing strategies are safe, well tolerated, and efficacious in the treatment of adult ADHD. Changes in dosing strategy are unlikely to be accompanied by safety risks, implying that there is room for prescribers to use discretion and to base dosing strategies on individual factors.*

Keywords attention-deficit/hyperactivity disorder, atomoxetine, nonstimulants, adults

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a central nervous system disorder characterized by hyperactivity and difficulties controlling impulses and sustaining attention. It occurs in 3% to 7% of school-age children in the United States (1). As children with ADHD mature, functioning tends to improve, possibly as a result of developmental changes in the brain and/or because patients learn behaviors that help compensate for the deficits imposed by ADHD. However, about 60% of children with ADHD have symptoms that

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persist into adulthood (2). Thus, an estimated 4% of the US adult population (approximately 8 million adults) has ADHD. A variety of undesirable outcomes are associated with adult ADHD, leading to family dysfunction, social impairment, and academic, occupational, and driving difficulties (3,4).

Atomoxetine, a highly specific inhibitor of the presynaptic norepinephrine transporter is an FDA-approved treatment for ADHD in adults and children. Atomoxetine is not a psychostimulant, which sets it apart from other common medications used for ADHD, such as methylphenidate and amphetamine. Two large studies have shown the superiority of atomoxetine compared with placebo in reducing adult ADHD symptoms (5). Atomoxetine was administered in equal doses twice daily. Recent research suggests that a total daily adult dose of 80 mg is safe and efficacious; however, research has not yet clarified whether this dose is better tolerated in a single or a divided dose. While pediatric research shows that safety and efficacy of atomoxetine are comparable regardless of whether it was dosed once or twice daily (6), no similar comparison has been made in adults.

Optimization of dosing strategies at an individual level can influence compliance as well as tolerability and efficacy, potentially enhancing patient satisfaction and treatment effectiveness. Thus, the aim of this study was to compare safety and tolerability of once (80 mg QD) and twice (40 mg BID) daily atomoxetine treatment in adults with ADHD. In addition, the study provides an opportunity to compare clinical response between these dosing strategies.

METHODS

Patients

The trial included 218 adults, aged 18 to 50 years, from 14 study centers. At study entry, patients had to meet the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV™) (7) criteria for ADHD on the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) for childhood and current symptoms. Patients were excluded if they had significant medical and/or psychiatric illnesses. The pharmacokinetics of atomoxetine are influenced by the polymorphic expression of cytochrome P450 2D6 (CYP2D6); thus, concomitant use of drugs that inhibit CYP2D6 was prohibited to limit possible effects on atomoxetine metabolism.

Written informed consent was obtained from each participant. The study was approved by each site's institutional review board and conducted in accordance with the ethical principles originating in the Declaration of Helsinki and consistent with good clinical practices and applicable laws and regulations.

Study Design

This was a randomized, double-blind, multicenter study. Data presented in this article were from an initial, acute portion (Study Period II) of an expanded, 7-month study of atomoxetine treatment optimization. Study Period I was an assessment period to collect baseline measures prior to randomization. Study Period II was a 6-week, randomized, double-blind, acute treatment period with patient visits occurring every two weeks. Patients were randomized to receive either: 1) two equally divided daily doses (40 mg each) of atomoxetine in the morning and late afternoon/early evening (4:00–8:00 PM), or 2) one daily morning atomoxetine dose of 80 mg. At the investigator's discretion, patients could switch treatment arms once for tolerability reasons at Visit 4 (four weeks into the treatment period). Study Period II was followed by a double-blind extension period, then an optional, open-label extension phase.

Primary Objective

The primary objective of this portion of the study was to compare safety and tolerability of once (80 mg QD) and twice (40 mg BID) daily atomoxetine treatment in adults with ADHD as assessed by a comparison of the frequency of patients experiencing at least one of the four TEAEs most commonly observed in previous studies of BID atomoxetine therapy in adults (dry mouth, insomnia, nausea, and erectile dysfunction). Analyses of the following subgroups also were performed for TEAEs: gender, median age, ADHD subtype, and prior stimulant use.

Secondary Objectives

Safety and tolerability were further assessed using change from baseline data from laboratory values, vital signs, weight, electrocardiograms (ECGs), and scores on the Arizona Sexual Experiences Scale (ASEX; male and female versions) (9). Indicator variables were used to assess the clinical significance of changes from baseline in vital signs, weight, and ECG values or changes, as well as to evaluate serious AEs and TEAEs; discontinuations due to AEs; switching treatment arms for tolerability reasons; and use of concomitant medications. Patients were included in these analyses if they took at least one dose of the study drug and had a baseline and at least one post-baseline measure.

Efficacy

Although this study was not designed to maximize treatment effects, efficacy was evaluated by comparing clinical response between once-daily and twice-daily dosing strategies using 18 items of the Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version (CAARS-Inv:SV) (8). The mean change from baseline to endpoint in the 18-item Total ADHD Symptom score (the sum of the inattention and

hyperactivity/impulsivity subscales, hereafter referred to as CAARS-Inv ADHD score (5)) was the primary efficacy measure. The mean changes from baseline to endpoint in the inattention and hyperactivity/impulsivity subscales also were assessed.

Data Analysis

Power calculations were based on the primary endpoint of a third study period that followed this acute portion of the trial, results of which will be reported separately. Previous studies suggested the percentages of patients that would continue into the third study period, and these percentages were used to derive a sample size of 200 sufficient to detect a 30% difference between re-randomized treatment groups on the primary endpoint of Study Period III, with a power of at least 80%. In the study period being reported here, the sample size of 108 patients per arm provided over 80% power to detect differences in adverse event rates where one group had double the incidence of the other, provided the lesser incidence was at least 17%. Thus, there was 82% power to detect a difference of 34% versus 17%. However, when one group had less than double the rate of the other group, the power decreased substantially. Patients were analyzed according to their original randomization groups. For patients who switched, their change from baseline scores or TEAEs were based on all data prior to the switch. SAS versions 6.09 and 8.2 were used for the analyses.

Primary Endpoint

The primary endpoint, assessed by frequency of patients experiencing at least one of the four most commonly observed TEAEs (dry mouth, insomnia, nausea, and erectile dysfunction), was compared across treatment groups using logistic regression. The primary response variable was categorical and equal to 1 if the patient experienced one or more of these TEAEs and 0 otherwise. Treatment and gender were included as categorical effects, and time on treatment was included as a continuous covariate. Adverse events were included in this analysis if they occurred prior to a patient switching treatment arms (if any switch occurred).

Homogeneity of incidence of TEAEs was tested across gender, median age, ADHD subtype, and prior stimulant use subgroups using the Breslow-Day statistic. The Fisher's exact test was used to compare incidence across treatments within subgroups.

Secondary Variables

Treatment differences in reasons for discontinuation and categorical demographic measures were compared using Fisher's Exact test. Continuous demographic measures were compared across treatments using one-way ANOVA. The changes from baseline in laboratory values (ranked), vital signs, weight, and ECGs were analyzed across treatment groups using a fixed-effects ANOVA incorporating treatment and investigator effects. Changes from baseline in ASEX scores were analyzed across treatment groups using a fixed effects analysis of covariance (ANCOVA) model with terms for treatment and investigator and baseline. Adverse event data and abnormal laboratory, vital sign, weight, and ECG values, as well as incidence of switching dosing strategies for tolerability reasons and concomitant medication use were compared across treatments using Fisher's exact test. The chi-square test was used to test for differences between dose groups in incidence of emergent sexual dysfunction for all patients and by gender. Emergence of sexual dysfunction was defined as patients who met one of the following three conditions at any visit post-randomization: 1) ASEX total score ≥19; 2) any item score ≥5; or 3) any three items with scores ≥4 following the scale developer's documentation (9).

Efficacy

The efficacy endpoint was assessed by comparing the change from baseline to endpoint in the CAARS-Inv ADHD score, using a fixed-effects ANCOVA model with terms for baseline score, treatment, and investigator. The subscales were analyzed using the same ANCOVA model.

RESULTS

There were 273 patients screened; 218 met inclusion criteria and were randomized to treatment (110 atomoxetine 40 mg BID, 108 atomoxetine 80 mg QD; Figure 1). There was a similarly high rate of completion among enrolled patients in both the atomoxetine 40 mg BID and 80 mg QD treatment groups (approximately 75%). Among those who discontinued after enrollment, there were no statistically significant differences between treatment groups in reason for discontinuation.

Baseline characteristics for the atomoxetine 40 mg BID and 80 mg QD groups were similar and are summarized in Table 1.

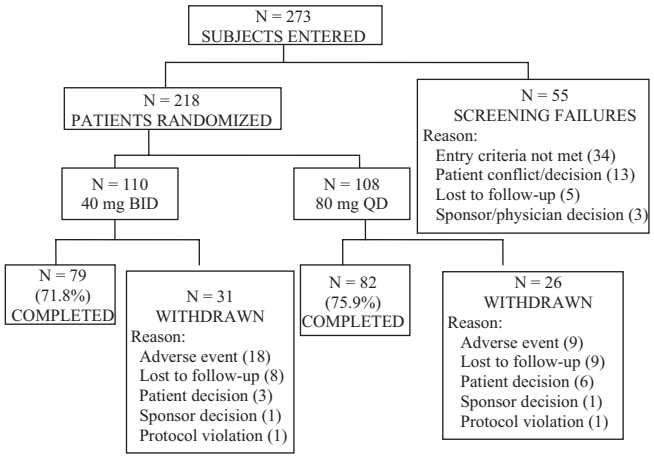

Figure 1 Overview of patient disposition.

Table 1 Summary of Demographics and Other Patient Characteristics for Randomized Patients

Characteristic[a]	ATX 40 mg BID (N = 110)	ATX 80 mg QD (N = 108)	Total (N = 218)
Female n (%)	33 (30.0)	33 (30.6)	66 (30.3)
Male n (%)	77 (70.0)	75 (69.4)	152 (69.7)
Origin n (%)			
Caucasian	102 (92.7)	99 (91.7)	201 (92.2)
Hispanic	2 (1.8)	6 (5.6)	8 (3.7)
Other	6 (5.5)	3 (2.8)	9 (4.1)
Mean Age in years (SD)	37.0 (7.66)	37.1 (8.69)	37.0 (8.17)
Mean Height in cm (SD)	173.8 (10.02)	173.0 (11.30)	173.4 (10.66)
Mean Weight in kg (SD)	83.9 (17.22)	84.4 (20.08)	84.2 (18.65)
DSM-IV ADHD Subtype n (%)			
Hyperactive/Impulsive	3 (2.7)	2 (1.9)	5 (2.3)
Inattentive	36 (32.7)	29 (26.9)	65 (29.8)
Combined	71 (64.5)	77 (71.3)	148 (67.9)
Prior Stimulant Exposure[b] n (%)			
No	60 (54.5)	56 (52.3)	116 (53.5)
Yes	50 (45.5)	51 (47.7)	101 (46.5)
CYP2D6 Phenotype n (%)			
Extensive	102 (92.7)	102 (94.4)	204 (93.6)
Slow	8 (7.3)	6 (5.6)	14 (6.4)

[a]There were no statistically significant between-group differences for any characteristic at baseline.
[b]One patient in the 80 mg QD treatment group did not specify.

Treatment compliance (defined as taking the prescribed medication at the prescribed dose on at least 70% of the days in the visit interval) was similarly high (>80%) for each treatment group throughout the study.

Discontinuations

There were no deaths or serious adverse events reported during this acute study. The incidence of discontinuation due to an AE throughout the study was low (12.4%). Although twice as many patients in the 40 mg BID group discontinued due to an AE compared with the 80 mg QD group (18 versus 9), this trend did not reach statistical significance. The majority (63%) of discontinuations due to an AE were related to nausea, feeling jittery, headache, erectile dysfunction, and irritability (Table 2). There were no statistically significant treatment group differences in the number of patients discontinuing due to any specific type of AE.

Treatment Emergent Adverse Events

The results of the logistic regression analysis showed no statistically significant difference between treatment groups in the primary endpoint, which was the likelihood of patients experiencing at least one of the four most commonly observed TEAEs including dry mouth, insomnia, nausea, and erectile dysfunction (odds ratio = 0.83; 95% CI = 0.48–1.42, p = .491). The lack of difference in tolerability between treatment groups is supported by further assessment of TEAE data. The overall incidence for any one TEAE was low. There were 6 TEAEs (nausea, insomnia, headache, dry mouth, decreased appetite, and dizziness) with an incidence of 10% or more in at least 1 of the 2 treatment groups (Table 3). Of these TEAEs, dry mouth, insomnia, and nausea were captured in the logistic regression.

Table 2 Discontinuations Due to Adverse Events

Reason for Discontinuation[a] n (%)	ATX 40 mg BID N = 110	ATX 80 mg QD N = 108
Nausea	4 (3.6)	2 (1.9)
Feeling jittery	3 (2.7)	1 (0.9)
Headache	3 (2.7)	0
Erectile dysfunction[b]	0	2 (2.7)
Irritability	2 (1.8)	0
Anger	0	1 (0.9)
Fatigue	1 (0.9)	0
Insomnia	0	1 (0.9)
Lethargy	1 (0.9)	0
Decreased libido	1 (0.9)	0
Sedation	1 (0.9)	0
Sexual dysfunction[c]	1 (0.9)	0
Increased sweating	0	1 (0.9)
Tachycardia[c]	1 (0.9)	0
Vomiting[c]	0	1 (0.9)
Total[d]	18 (16.4)	9 (8.3)

[a]There were no statistically significant between-group differences for any reason for discontinuation.
[b]Not otherwise specified, denominator based on males only.
[c]Not otherwise specified.
[d]p = 0.099.

Table 3 Treatment Emergent Adverse Events (TEAEs) with Overall Frequency of ≥5%

Adverse Event	ATX 40 mg BID N = 110 (n %)	ATX 80 mg QD N = 108 (n %)	Total N = 218 (n %)	p-value
Patients with ≥1 TEAE	97 (88.2)	88 (81.5)	185 (84.9)	0.189
Patients with no TEAEs	13 (11.8)	20 (18.5)	33 (15.1)	NA
Nausea	18 (16.4)	35 (32.4)	53 (24.3)	**0.007**
Insomnia	28 (25.5)	18 (16.7)	46 (21.1)	0.136
Headache	25 (22.7)	15 (13.9)	40 (18.3)	0.115
Dry mouth	19 (17.3)	19 (17.6)	38 (17.4)	1.000
Appetite decreased[a]	15 (13.6)	21 (19.4)	36 (16.5)	0.277
Dizziness	10 (9.1)	14 (13.0)	24 (11.0)	0.394
Sweating increased	9 (8.2)	10 (9.3)	19 (8.7)	0.814
Irritability	8 (7.3)	10 (9.3)	18 (8.3)	0.631
Feeling jittery	8 (7.3)	8 (7.4)	16 (7.3)	1.000
Libido decreased	8 (7.3)	8 (7.4)	16 (7.3)	1.000
Fatigue	7 (6.4)	8 (7.4)	15 (6.9)	0.795
Erectile dysfunction[b]	7 (9.1)	7 (9.3)	14 (9.2)	1.000
Constipation	10 (9.1)	3 (2.8)	13 (6.0)	0.083
Paraesthesia	8 (7.3)	3 (2.8)	11 (5.0)	0.215

[a]Not otherwise specified.
[b]Not otherwise specified; denominator includes only male patients for this AE type.

Most types of AEs occurred in fewer than 5% of patients and occurrences were dispersed among patients and across treatment groups such that the overall incidence of having at least one TEAE was similar between groups (88.2% for 40 mg BID versus 81.5% for 80 mg QD).

When incidences of each type of AE were compared, there was a significantly greater frequency of nausea in patients treated with atomoxetine 80 mg QD (32.4%) than in patients treated with 40 mg BID (16.4%; p = .007). There also was a trend toward a lower incidence of constipation in patients treated with atomoxetine 80 mg QD (2.8%) than with those treated with 40 mg BID (9.1%; p = .083). No other significant differences were found. Subgroup analyses showed no significant differences in the likelihood of experiencing one or more TEAEs regardless of gender, age group (≤38 or >38 years), ADHD subtype, or prior stimulant use.

Laboratory Values, Vital Signs, Weights, and ECGs

There were no mean laboratory value changes from baseline to endpoint that were unexpected, and there were no statistically significant treatment group differences. The only statistically significant difference in treatment-emergent abnormal laboratory values was a greater incidence of low bicarbonate for patients treated with atomoxetine 40 mg BID than for those treated with 80 mg QD (6 (8.3%) versus 0, respectively; p = .028). There also were very few abnormal values observed during the study, with no clinically significant differences between groups.

There were no unexpected mean vital sign changes from baseline to endpoint, nor were there any statistically significant differences between treatment groups in mean vital sign changes. Mean pulse rate increased in both treatment groups (6.32 and 7.16 bpm in the 40 mg BID and 80 mg QD groups, respectively), which is similar to what has been observed in previous studies of atomoxetine treatment (10). The incidence of potentially clinically significant changes in vital signs was very low and there were no statistically significant differences between treatment groups.

Similarly, there were no statistically significant differences between treatment groups in mean weight change over the course of the study. On average, patients in both the 40 mg BID and 80 mg QD groups lost about 1 kg during the course of the study. There was only one individual (in the 80 mg QD treatment group) who experienced a potentially clinically significant change in weight (loss of 8.9 kg). (However, this individual had gained 8.9 kg in the 2 weeks prior to randomization, thus the loss of 8.9 kg brought a return to his starting weight.) There were no statistically significant differences between treatment groups in incidence of potentially clinically significant weight change.

There were no statistically significant treatment group differences for mean change in ECG values from baseline to endpoint. There were no within group mean changes that were unexpected, and changes noted were similar to findings from previous studies; there were no clinically significant ECG findings.

Arizona Sexual Experiences Scale

ASEX scores can range from 5 to 30, with high scores associated with sexual dysfunction. Results showed no unexpected mean ASEX changes or differences between treatment groups for either males or females. Mean baseline to endpoint scores (and standard deviations) for females were 15.20 (4.46) to 14.67 (5.08) in the 40 mg BID group and 16.15 (4.33) to 15.52 (4.72) in the 80 mg QD group, indicating improvement within both groups. These improvements approached significance among females in the 40 mg BID treatment group (mean within group change of –0.53; p = .052), but were not statistically significant for the 80 mg QD group.

Mean baseline to endpoint scores (and standard deviations) for males were 11.59 (3.29) to 13.53 (5.42) in the 40 mg BID group and 11.18 (3.93) to 13.36 (4.46) in the 80 mg QD group. These increases are statistically significant (mean within group change of 1.95; p < .001 for the 40 mg BID group and 2.18, p = .002 for the 80 mg QD group). However, mean endpoint scores are still well below the average score of 20 among men with clinical sexual dysfunction (10). Categorical analyses showed that 5 (13.5%) females and 30 (27.8%) males experienced emergence of clinical sexual dysfunction during the course of the study, with no differences by treatment group for either males or females (p = .979 and p = .962 for females and males, respectively). Similarly, when analyzed within each gender, there were no differences by treatment group. Results are consistent with previous studies. There were low incidences of erectile dysfunction or other sexually related TEAEs.

Switching Dosing Strategies

Fewer than 10% of patients switched treatment arms and there was no statistically significant difference between treatment groups in the number of patients switched (9 (8.2%) versus 10 (9.3%) in the atomoxetine 40 mg BID and 80 mg QD groups, respectively).

Efficacy

The primary efficacy measure for this study was the mean change from baseline to endpoint in the CAARS-Inv ADHD score. Scores were significantly reduced in both the atomoxetine 40 mg BID group (mean baseline and endpoint values of 37.2 and 20.2; p < .001) and 80 mg QD group (mean baseline and endpoint values of 38.4 and 25.1; p < .001; Figure 2). However, the reduction was significantly greater in the atomoxetine 40 mg BID treatment group than in the 80 mg QD treatment group (mean reduction of 17 versus 13 points; p < .001).

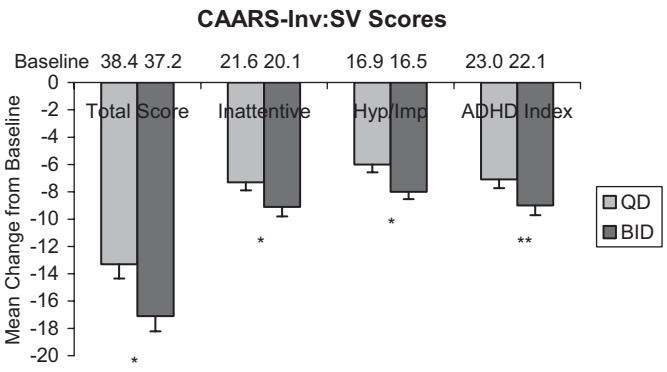

Figure 2 Comparison of the efficacy of QD and BID atomoxetine for treating ADHD as measured by the CAARS-Inv:SV Total score and the Inattentive, Hyperactive/Impulsive, and ADHD Index subscales. Mean change from baseline data are shown. * = $p < .001$, ** = $p < .01$ for QD versus BID comparisons.

Both dosing groups achieved significant improvement in scores in both the inattention and the hyperactivity/impulsivity subscales of the CAARS-Inv:SV. The improvement in scores was significantly greater in the atomoxetine 40 mg BID treatment group than in the 80 mg QD treatment group for each subscale.

DISCUSSION

Atomoxetine was approved for treatment of adult and pediatric ADHD in November of 2002. In adults there is a recommended initial dosing of 40 mg to be increased incrementally as needed over a period of weeks to a target dose of 80 mg daily and a maximum dose of 100 mg. A systematic evaluation of adults was needed to determine whether taking atomoxetine as a single daily dose offered advantages over taking it in evenly divided twice-daily doses. Data related to adverse events, laboratory values, vital signs, weight, ECG, sexual experience, switching treatment arms, and efficacy indicate that both dosing strategies are safe, well tolerated, and efficacious in the treatment of adult ADHD. The results of the current study are important in that they provide an opportunity to compare once daily (80 mg QD) and twice daily (40 mg BID) atomoxetine dosing in adults.

There were no unexpected safety results, and most notable changes were present in both the 40 mg BID and 80 mg QD treatment groups. For example, the increase in mean pulse rate of approximately 6–7 bpm is consistent with findings from previous studies (10). Similarly, the increase in ASEX scores among males during the course of treatment is comparable to previous observations, and in spite of the increase, the mean final score was still well below the average score for men with sexual dysfunction. There were no significant differences between dosing groups for individual ASEX item scores or total ASEX scores. The most common TEAEs reported in both treatment groups were nausea, insomnia, headache, dry mouth, decreased appetite, and dizziness. In contrast to previous studies, erectile dysfunction was not among the most common TEAEs in either treatment group. The ECG changes observed are consistent with previous findings.

There were a few notable safety and tolerability differences between the two dosing strategies. First, there was significantly less likelihood of experiencing nausea with twice daily dosing, while there was a trend toward reduced likelihood of constipation with once daily dosing. It should be noted that sample sizes for this portion of the study might be too small to produce enough power to detect statistically significant differences.

Second, while not statistically significant, discontinuations due to AEs were nearly twice as likely in the 40 mg BID treatment group (16.4%) than the 80 mg QD treatment group (8.3%). Additional studies are warranted using large sample sizes to thoroughly examine safety and tolerability differences between BID and QD dosing.

Finally, although both dosing strategies were efficacious, dosing at 40 mg BID yielded statistically greater efficacy than 80 mg QD dosing. This difference may be clinically significant. However, it should be noted that this study was not primarily designed to compare efficacy. The magnitude of the CAARS-Inv ADHD score improvement in both treatment arms of this study was larger than that found in previous studies (5). Because there was no placebo arm in this study, expectation bias cannot be ruled out. It is also possible that efficacy results in both treatment groups may be understated, however, because of the relatively short duration of this portion of the trial, and because dosage was held at 80 mg daily. In a recent 97-week interim analysis of another open-label, long-term trial where dose was titrated according to clinical response, the mean, median and maximum doses reported were 99, 120, and 160 mg/day (11).

Thus, while both dosing strategies are safe, tolerable, and efficacious, results provide preliminary evidence for basing dosing decisions on individual factors. Certain AEs were more common in one of the two treatment groups, implying results may be used to help prescribers individually tailor atomoxetine treatment by, for example, switching to BID dosing in a patient experiencing nausea with QD dosing, or switching to QD dosing in a patient experiencing constipation with BID dosing. In addition, results of this study support decisions to switch patients who are inconvenienced by BID dosing to QD dosing. Changes in dosing strategy are unlikely to be accompanied by safety risks, and both dosing strategies are associated with significant improvement in ADHD symptoms.

The overarching implication of this study is that there is room for prescribers to use discretion in dosing strategies. If a patient has difficulty tolerating atomoxetine with BID dosing, QD dosing may be a viable and effective alternative dosing strategy, or vice versa. Tailoring dosing strategies to patients' specific circumstances is likely to improve patient satisfaction and compliance, thus leading to enhanced effectiveness and quality of life.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 2000
2. Wender PH, Wolf LE, Wasserstein J: Adults with ADHD: An overview. *Ann N Y Acad Sci*. 2001; 931:1–16
3. Murphy K, Barkley RA: Attention deficit hyperactivity disorder adults: Comorbidities and adaptive impairments. *Comprehensive Psychiatry* 1996; 37:393–401
4. Biederman J, Faraone S, Spencer T, Wilens T, Norman D, Lapey K, Mick E, Lehman, B.K. Doyle A: Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *Am J Psychiatry* 1993; 150: 1792–1798
5. Michelson D, Adler L, Spencer T, Reimherr F, West S, Allen AJ, Kelsey D, Wernicke J, Dietrich A, Milton D: Atomoxetine in adults with ADHD: Two randomized placebo-controlled studies. *Biol Psychiatry* 2003; 53:112–120
6. Michelson D, Allen AJ, Busner J, Casat C, Dunn D, Kratochvil C, Newcorn J, Sallee FR, Sangal RB, Saylor K, West S, Kelsey D, Wernicke J, Trapp NJ, Harder D: Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. *Am J Psychiatry* 2002; 159:1896–1901
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed*., Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000
8. Conners C, Erhardt D, Sparrow E: Conners' adult ADHD rating scales technical manual. North Tonawanda, NY: Multi-Health Systems Inc. 1999
9. Arizona Board of Regents. *ASEX Scales: General Instructions for Clinicians Administering the Scale*. Tucson, AZ: University of Arizona, 1997
10. Strattera® [Package Insert]. Indianapolis, IN: Eli Lilly and Company; 2003
11. Adler LA, Spencer TJ, Milton DR, Moore RJ, Michelson D: Long-term, open-label study of the safety and efficacy of atomoxetine in adults with attention-deficit/hyperactivity disorder: An interim analysis. *J Clin Psychiatry* 2005; 66: 294–299