A Comparison of Initial Duloxetine Dosing Strategies in Patients With Major Depressive Disorder

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Objective: To compare the effects of starting doses of duloxetine taken with or without food on tolerability and efficacy in patients with major depressive disorder (MDD).

Method: This double-blind, concurrent-dose–controlled, parallel-design trial contained a variable expected-duration placebo lead-in period and was conducted in adult outpatients with DSM-IV-TR–defined MDD at psychiatric outpatient sites between October 2004 and January 2006. In actuality, patients received placebo for 1 week and then were randomly assigned to duloxetine 30 mg once daily in the morning (q.a.m.) (N = 219), 30 mg twice daily (b.i.d.) (N = 213), or 60 mg q.a.m. (N = 215) for 1 week along with 1 of 2 instructions about food: take study drug with food or do not take within 1 hour of eating. For the remaining 5 weeks of acute treatment, all patients received 60 mg once daily. The primary objective was to compare incidence of treatment-emergent nausea at 30 mg q.a.m. versus 60 mg q.a.m. using item 112 (nausea) of the Association for Methodology and Documentation in Psychiatry adverse event scale (AMDP-5). Secondary outcome measures included mean change on AMDP-5 item 112, discontinuations due to adverse events, mean changes in AMDP-5 items and subscales, spontaneously reported treatment-emergent adverse events, and vital signs. Efficacy was evaluated by the 17-item Hamilton Rating Scale for Depression (HAM-D-17).

Results: The primary analysis, which combined data from both food groups, showed no significant difference in the incidence of nausea between starting doses of 30 mg q.a.m. and 60 mg q.a.m. (23% vs. 29%, respectively; p = .207). However, mean changes on the AMDP-5 nausea item revealed a significant main effect of food (p = .010) and a significant interaction between food and starting dose (p = .033). The food-by-dose interaction indicated that the benefit from taking drug with food was greatest in patients started at 60 mg q.a.m., and the benefit of starting at 30 mg q.a.m. was greatest in patients taking drug without food. In patients who took study drug without food, there was a significant difference across initial-dose groups for discontinuation due to adverse events (30 mg q.a.m. = 3.6%, 30 mg b.i.d. = 14.0%, 60 mg q.a.m. = 10.2%; 30 mg q.a.m. vs. 30 mg b.i.d., p = .008; 30 mg q.a.m. vs. 60 mg q.a.m., p = .066); however, in patients who took study drug with food, discontinuations due to adverse events did not significantly differ (30 mg q.a.m. = 5.4%, 30 mg b.i.d. = 7.5%, 60 mg q.a.m. = 7.4%; all p values > .50). Patients who started at 30 mg b.i.d. or 60 mg q.a.m. without food did not differ regarding mean changes (i.e., increases) in the common adverse events score after 1 week of treatment but had significantly greater mean changes than patients who started at 30 mg q.a.m. without food (0.87, 0.82, and 0, respectively; p < .05 vs. 30 mg b.i.d. and 60 mg q.a.m.). No significant differences were found between initial-dose groups in vital signs.

Conclusions: These data imply that starting duloxetine at 30 mg q.a.m. for 1 week with or without food or starting duloxetine at the therapeutic dose of 60 mg q.a.m. with food can improve the initial tolerability of the medication. Adding this information to existing knowledge of duloxetine will enable the clinician to tailor therapy most appropriately for the individual patient.

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Starting antidepressant medication in clinical practice may reflect more art than science. Nausea, the most common adverse event (AE) associated with initiating a selective serotonin reuptake inhibitor (SSRI), is reported in about 26% of patients in clinical trials.[1] Rates are similar among serotonin-norepinephrine reuptake inhibitors (SNRIs). Based on a review of 46 head-to-head randomized, controlled trials of SSRIs and SNRIs, Hansen and colleagues[2] report rates of nausea ranging from 4.3% to 31.0%. The most common AEs associated with duloxetine treatment in double-blind, placebo-controlled trials have been nausea (20%), dry mouth, fatigue, somnolence,

constipation, insomnia, dizziness, and sweating.[3] In trials with a mixed-age sample population (mean age of 43 years) in which patients started duloxetine at a dose of 60 mg once daily (q.d.), the rate of nausea was 38%.[4,5] In these studies, nausea usually occurred early and appeared to be short-lived and dose-related. In 4 studies comparing duloxetine 40 to 120 mg/day to paroxetine 20 mg/day, the rate of nausea was 14.4% and 12.0%, respectively.[6]

Initial AEs are a common cause of premature discontinuation. In a study of compliance with antidepressant treatment in a primary care setting, Demyttenaere and colleagues[7] found that 53% of patients had discontinued antidepressant treatment within 6 months, with 23% of these due to AEs. Among those patients who discontinued due to AEs, the mean period before discontinuation was 6.5 weeks, with lack of efficacy and AEs as the main reasons for discontinuation during the initial treatment period.

Strategies for minimizing discontinuations have been based largely on anecdotal evidence. Initiating treatment at a lower (potentially subtherapeutic) dose or suggesting that patients take medication with food has been reported anecdotally to reduce the incidence of nausea among patients treated with an SSRI. However, objective evaluations of these practices across a broad spectrum of clinical outcomes, including their effects on efficacy, are lacking.

Results from various investigations have suggested that the tolerability of duloxetine is more closely linked to starting dose than to highest or final dose.[3,8] Most notably, a flexible-dose, open-label study suggested that starting duloxetine at 30 mg q.d. for 1 week, followed by escalation to 60 mg q.d., may lessen the risk of initial nausea, relative to starting at 60 mg q.d. On the other hand, patients who started at 30 mg q.d. had significantly less improvement on the Core and Maier subscales of the 17-item Hamilton Rating Scale for Depression (HAM-D-17) at week 1 compared to patients who started at 60 mg q.d.[9]

The present study is a prospectively powered, double-blind, randomized, concurrent-dose–controlled study to confirm the results of the open-label study and to expand on that study by examining the effect of food and comparing a once-daily dose with a split dose. The primary objective was to compare incidence of treatment-emergent nausea at 30 mg q.a.m. versus 60 mg q.a.m. using item 112 of the Association for Methodology and Documentation in Psychiatry adverse event scale (AMDP-5). The most comprehensive measure of overall tolerability was the rate of discontinuations due to AEs. Additional secondary objectives used to explain and describe the results from the primary analysis and from the discontinuations due to AEs included comparisons between groups of common adverse events from the AMDP-5 items, spontaneously reported treatment-emergent adverse events (TEAEs), discontinuations, vital signs, and various efficacy measures. This study included an 8-week extension period to assess the effect of maintaining versus raising the dose in those patients who had an inadequate initial response to duloxetine treatment. The longer-term study results and other secondary analyses of comparative safety and efficacy will be the focus of future publications.

METHOD

Study Design

The protocol for this study (F1J-US-HMDR) was filed with the United States Food and Drug Administration prior to study initiation. It included all of the methodology presented here in addition to a complete statistical analysis plan. The study protocol was approved in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent after the procedure(s) and possible side effects were fully explained. Patients and investigative sites were blinded to certain details of the study design. The full protocol was provided to the investigators' ethical review boards as part of the initial protocol review.

This was a randomized, parallel, double-blind, variable expected-duration, placebo lead-in study conducted at 33 sites (psychiatric clinical settings) in the United States. Patients were enrolled in the study from October 2004 to January 2006.

Patients meeting entry criteria began a 7-week period of double-blind treatment during which study drug was dosed twice daily (b.i.d.) and with regard to meals for the first 3 weeks. At entry, patients were randomly assigned in a 3×2 complete factorial arrangement to 1 of 3 starting doses of duloxetine—30 mg q.a.m., 30 mg b.i.d., or 60 mg q.a.m.—and to 1 of 2 food groups, by instruction to take study drug with food or not to take within 1 hour of eating. The study design incorporated a 2-week, double-blind, variable expected-duration placebo lead-in period in which both patients and investigators were blind to the start of active therapy. Such a design may provide more accurate data on the timing of the onset of the true treatment effects, since lack of knowledge of when therapy starts may decrease any effects caused by expectation of side effects or efficacy. In actuality, all patients received placebo for the first week of the acute treatment phase, followed by 1 week on the duloxetine starting dose to which they were randomly assigned and then 5 weeks on 60 mg q.d. of duloxetine. Clinic visits were scheduled at weeks 1, 2, 3, 5, and 7 during acute treatment. Interviews were conducted by the physician, psychiatric nurse, or study coordinator.

Study drug was provided as 30-mg and 60-mg capsules of duloxetine. Placebo capsules and matching duloxetine capsules were utilized in a double-dummy fashion to maintain the integrity of the blind during the study. All patients received 4 capsules of study drug to be taken orally, b.i.d. (2 capsules each in the morning and evening)

during the first 3 weeks of the acute phase and q.d. (taken together at any time) during the remaining 4 weeks.

Concomitant medications with primarily central nervous system activity were not allowed. Chronic use of cough and cold medications containing pseudoephedrine or the sedating antihistamine diphenhydramine was not allowed. Chronic use of certain prescription medications such as angiotensin-converting enzyme inhibitors, α- and β-blockers, antiarrhythmics, and calcium channel blockers was permitted provided the patient had been on a stable dose for a minimum of 3 months prior to study enrollment. Patients were encouraged not to alter their intake of nicotine or caffeine during the course of the study. Narcotic use was allowed only on an episodic basis and upon approval of the Lilly physician. Alcohol consumption was not monitored.

Selection of Patients

Study participants were adult outpatients at least 18 years of age. All patients met diagnostic criteria for major depressive disorder (MDD) as defined by the *Diagnostic and Statistical Manual for Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR).[10] The diagnosis of MDD was confirmed by the Mini-International Neuropsychiatric Interview (MINI).[11] Patients were required to have a HAM-D-17[12,13] score > 15 at the screening and baseline study visits.

Patients were excluded for the following reasons: any current Axis I disorder other than MDD, dysthymia, or any anxiety disorder (however, obsessive-compulsive disorder was excluded); any previous diagnosis of mania, bipolar disorder, or psychosis; serious suicidal risk; serious medical illness or clinically significant laboratory abnormalities that, in the judgment of the investigator, would be likely to require intervention, hospitalization, or an excluded medication during the course of the study; lack of response of the current depressive episode to 2 or more adequate courses of antidepressant therapy at a clinically appropriate dose for a minimum of 4 weeks, or treatment-resistant depression; a history of a lack of response, at any time, to an adequate trial of duloxetine (≥ 60 mg/day for ≥ 4 weeks); a current Axis II disorder that could interfere with compliance with the study protocol; a history of substance abuse or dependence within the past 6 months, excluding nicotine and caffeine; a positive urine drug screen for any substances of abuse; electroconvulsive therapy or transcranial magnetic stimulation within the past year; initiating, stopping, or changing psychotherapy after study entry; treatment with a monoamine oxidase inhibitor within 14 days prior to baseline; and treatment with fluoxetine within 30 days prior to baseline.

Safety Measures

The primary objective of the study was to compare the incidence of treatment-emergent nausea for patients initially dosed at duloxetine 30 mg q.a.m. versus those dosed at duloxetine 60 mg q.a.m. This objective was evaluated by comparing the increase from baseline to any acute phase visit in the score of item 112 (nausea) of the AMDP-5,[14] a solicited adverse event scale. The scale consists of 47 items, each rated on a scale of 0 (not present) to 3 (severe), and it was administered at every visit.

As a secondary objective, the incidence of treatment-emergent nausea (as defined for the primary objective) for patients initially dosed at duloxetine 30 mg b.i.d. was also compared to the other 2 doses. Other secondary assessments of the primary objective were derived from the AMDP-5 and included mean changes in the nausea item score (112), the gastric events score and the common adverse events score. The gastric events score was defined as the mean of items 112 (nausea) and 113 (vomiting). The common adverse events score used items from the AMDP-5 to create a composite measure of the AEs from previous duloxetine trials for which the incidence was > 5% and twice the placebo rate. These AEs were nausea, dry mouth, constipation, insomnia, dizziness, fatigue, somnolence, increased sweating, and decreased appetite. The common adverse events total score was defined as the sum of the following 8 components: mean of items 112 (nausea) and 113 (vomiting), item 111 (dry mouth), item 115 (constipation), mean of items 101 through 104 (insomnia), item 118 (dizziness), item 105 (drowsiness), item 122 (increased perspiration), and item 106 (decreased appetite). To determine incidence rates of insomnia and gastric events, a patient was considered to have insomnia if the mean of the insomnia items was greater than zero and to have a gastric event if the mean score of the nausea and vomiting items was greater than zero. In addition to contrasting dose groups across food groups (taking study drug with or without meals), food groups were contrasted across dose groups.

It was believed a priori that mean scores from the AMDP-5 would be more sensitive to group differences than the corresponding incidence rates, because the mean changes incorporated both the incidence and severity of the event. Mean change was not specified as the primary analysis, however, because clinical relevance is hard to establish from mean changes. An increase of 1 unit on the outcome scale corresponded to an increase in 1 category (from absent to mild, mild to moderate, or moderate to severe). However, a mean change of 1, while a very useful summary of both incidence and severity, does not specifically tell us which severity category a patient falls into at a given point in time.

Other safety measures recorded at every visit included spontaneously reported TEAEs, blood pressure, and heart rate. Spontaneous AEs were collected before the administration of the AMDP-5, and AEs were not transferred between the 2 reports. Blood for chemistry and hematology laboratories was collected at baseline and after 4

weeks of active drug treatment. Treatment-emergent elevated pulse was defined as ≥ 100 beats per minute (bpm) and at least 10 bpm greater than baseline.

Changes in sexual function were assessed at every visit by means of the self-rated Patient Global Impressions of Sexual Function (PGI-SF) scale.[15] The PGI-SF is a 4-question instrument that assesses sexual interest/desire, erection (for men) or vaginal lubrication (for women), ability to achieve orgasm, and an overall rating of sexual function. Each question is rated on a 5-point scale ranging from 1 (no impairment) to 5 (severely impaired).

Efficacy Measures

Efficacy measures included the HAM-D-17[12,13] total score; the 30-item Inventory of Depressive Symptoms, Clinician Rated (IDS-C-30)[16]; the 16-item Quick Inventory of Depressive Symptomatology, Clinician Rated (QIDS-C)[17]; the Brief Pain Inventory, Short Form (BPI-SF)[18]; the Visual Analog Scales for pain (VAS)[19]; the Clinical Global Impressions-Severity of Illness scale (CGI-S)[20]; and the Patient Global Impression of Improvement scale (PGI-I).[20]

The aforementioned efficacy measures were assessed at the regularly scheduled clinic visits, except for the PGI-I, which was assessed at postbaseline visits only. Analyses included comparing the 3 initial-dosing groups in regard to mean changes from baseline (postbaseline means for the PGI-I), both on total scores and various subscales of the measures.

Statistical Analyses

Patient demographics and baseline illness characteristics were compared by dose groups using pairwise t tests for continuous variables and Fisher exact test for categorical variables. The frequency of solicited and spontaneous TEAEs as well as the incidence of TEAEs leading to discontinuation was compared by dose and food group. The proportion of patients achieving response (≥ 50% reduction in a patient's HAM-D-17 total score from baseline) and remission (HAM-D-17 total score ≤ 7) as well as those reporting improved, same, or worse sexual function (PGI-SF) were compared by initial-dose group. Fisher exact test was used to compare frequencies at the $\alpha = .05$ significance level.

Mean changes in the AMDP-5 nausea item score, gastric event score, and common adverse event score were analyzed using a restricted maximum likelihood–based mixed-model repeated measures (MMRM) approach. Analyses included the fixed, categorical effects of initial-dose group, food group, visit, all 2-way and the 3-way interactions between these effects, and investigator, as well as the continuous, fixed covariate of baseline score. Mean changes in the HAM-D-17 total score, IDS-C-30 total score, the QIDS-C total score, and vital signs were analyzed using an MMRM approach with fixed, categorical effects of initial-dose group, visit, the 2-way interactions between these effects, and investigator, as well as the continuous, fixed covariate of baseline score. In each case, the within-patient errors were modeled using an unstructured (co)variance structure. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Significance tests were based on least-squares means and Type III sum-of-squares, using a 2-sided $\alpha = .05$ (2-sided 95% confidence intervals). Mean changes from baseline in laboratory analytes were analyzed using a last-observation-carried-forward approach. An analysis of covariance was conducted on rank-transformed data with investigator, baseline value, and initial-dose group in the model.

Several outcomes were used to assess the tolerability and safety of duloxetine in patients participating in this study. In a study of this size, and even in the largest of studies, an adjustment of p values for multiple comparisons to maintain a nominal familywise type I error rate across this array of outcomes would render minimal power to detect clinically meaningful differences. Typically, multiplicity adjustments are used to prevent false positive results for efficacy outcomes in which an incorrect conclusion would result in belief that a drug was noneffective when it was effective. For safety outcomes, patient risk lies in false negative results–failing to find a more tolerable alternative when one exists. Therefore, rigid controls for multiplicity in declaring statistical significance were not enforced in this study. However, adjusted p values for key outcomes are presented for reference. The described approach is consistent with guidelines followed in studies supporting regulatory approvals. Specifically, a Bonferroni-type correction was used in which 9 treatment contrasts were of interest: with food versus without food for each of the 3 doses and the 3 pairwise dose contrasts within each of the food groups. Therefore, when comparing dose groups for any particular outcome, the Bonferroni adjusted p value for declaring significance would be .05/9 = .006.

RESULTS

Patient Disposition

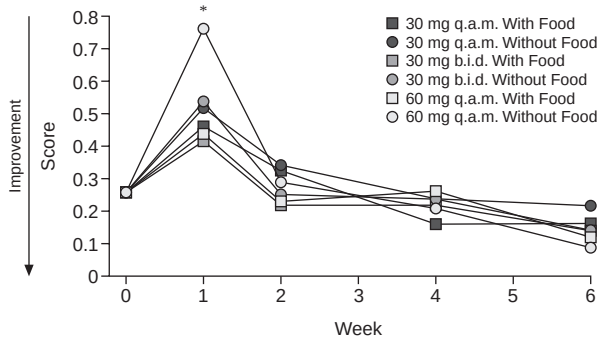
A total of 916 patients were screened, of whom 269 failed to meet entry criteria or declined to participate in the study. The remaining 647 patients were randomly assigned by initial dose (219 to duloxetine 30 mg q.a.m., 213 to duloxetine 30 mg b.i.d., 215 to duloxetine 60 mg q.a.m.) and by food groups (326 with food, 321 without food). The number of completers in each study arm was as follows: duloxetine 30 mg q.a.m. = 80 with food, 85 without food; duloxetine 30 mg b.i.d. = 79 with food, 68 without food; duloxetine 60 mg q.a.m. = 75 with food, 77 without food.

Table 1. Baseline[a] Characteristics of Enrolled Patients With Major Depressive Disorder

Characteristic	Starting Dose: Duloxetine 30 mg q.a.m. (N = 219)	Duloxetine 30 mg b.i.d. (N = 213)	Duloxetine 60 mg q.a.m. (N = 215)
Sex			
Female, N (%)	136 (62.1)	145 (68.1)	134 (62.3)
Age, mean (SD), y	42.2 (13.0)	42.8 (12.8)	43.9 (13.5)
Age range, y	18.9–80.1	18.7–82.7	18.6–77.5
Ethnic origin, N (%)			
White	169 (77.2)	162 (76.1)	174 (80.9)
African American	28 (12.8)	26 (12.2)	15 (7.0)
Hispanic	15 (6.8)	20 (9.4)	19 (8.8)
Other	7 (3.2)	5 (2.3)	7 (3.3)
HAM-D-17 total score, mean (SD)	21.6 (3.3)	21.7 (3.7)	21.2 (3.9)
IDS-C-30 total score, mean (SD)	35.5 (7.1)	35.9 (7.2)	35.1 (7.3)
QIDS-C total score, mean (SD)	18.1 (3.9)	18.2 (4.1)	17.8 (3.8)
CGI-S score, mean (SD)	4.4 (0.6)	4.3 (0.5)	4.3 (0.6)
AMDP-5 item 112 score, mean (SD)	0.3 (0.6)	0.3 (0.6)	0.2 (0.6)

[a]Defined as visit 3, when patients completed the placebo lead-in and were placed on active therapy.
Abbreviations: AMDP-5 = Association for Methodology and Documentation in Psychiatry adverse event scale; b.i.d. = twice daily; CGI-S = Clinical Global Impressions-Severity of Illness scale; HAM-D-17 = 17-item Hamilton Rating Scale for Depression; IDS-C-30 = 30-item Inventory of Depressive Symptomology, Clinician Rated; q.a.m. = once daily in the morning; QIDS-C = 16-item Quick Inventory of Depressive Symptomatology, Clinician Rated.

Figure 1. Weekly Mean on AMDP-5 Nausea Score by Starting Dose and Food[a]



[a]Baseline score (week 0) reflects mean score at the end of the placebo lead-in. After week 1, all patients were dosed at 60 mg q.d. p = .01 for main effect of food; MMRM analysis.
*p = .006 (60 mg q.a.m. without food vs. 60 mg q.a.m. with food); MMRM analysis.
Abbreviations: AMDP-5 = Association for Methodology and Documentation in Psychiatry adverse event scale, b.i.d. = twice daily, MMRM = mixed-model repeated measures, q.a.m. = once daily in the morning, q.d. = once daily.

Baseline Characteristics

The overall patient cohort was predominantly female (64.1%) and white (78.1%), with a mean age of 43 years and HAM-D-17 mean total baseline score of 21.5. There were no statistically significant between–dose group differences in baseline characteristics (Table 1). When patients were considered by food group instead of dose group, there were statistically significant differences in ethnicity between with-food and without-food groups. In particular, 13.5% (N = 44) of patients in the with-food group were of African descent, while 7.8% (N = 25) in the without-food group were of African descent (p = .008).

Safety and Tolerability: Adverse Events

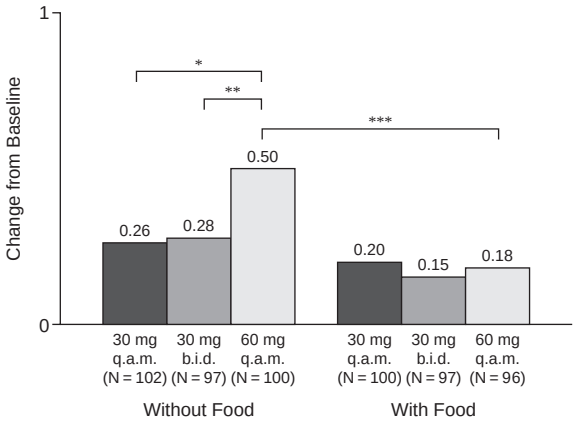
Results from the primary analysis showed no significant differences in the incidence of treatment-emergent nausea (AMDP-5 item 112) between the duloxetine 30 mg q.a.m. and duloxetine 60 mg q.a.m. initial-dose groups after 1 week of treatment (30 mg q.a.m. = 23%, N = 46/202; 60 mg q.a.m. = 29%, N = 56/196; p = .207). The incidence of treatment-emergent nausea in the 30 mg b.i.d. group (27%, N = 52/194) also did not differ from either of the other 2 groups. Across the entire 6-week acute active treatment period, nausea rates were similar in each starting-dose group (32%).

The weekly mean scores on AMDP-5 item 112 (nausea) by starting dose and food group are shown in Figure 1, and a detailed examination of week 1 mean change scores is summarized in Figure 2. The baseline score (week 0) reflects the mean score at the end of the placebo lead-in period. The highest mean nausea scores were reported at week 1 on all 6 treatment arms. Mean scores decreased after week 1 and approached or were lower than baseline nausea levels at weeks 2 through 6.

Regarding scores at week 1, there was a significant main effect of food (p = .010) and a significant food-group–by–dose-group interaction (p = .033). The interaction results are particularly important in that this result demonstrates a significant difference between dosing approaches without the need for adjustments for multiple comparisons, as only one p value is involved.

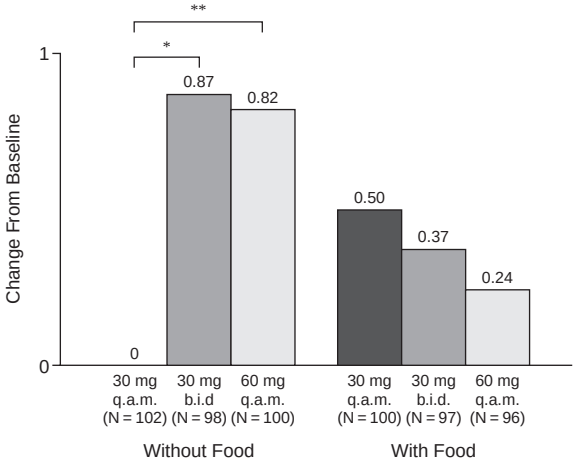
The nature of this interaction was such that the benefit from taking drug with food was greatest in patients started at 60 mg q.a.m., and the benefit of starting at 30

Figure 2. Mean Changes in AMDP-5 Nausea Score by Initial Starting Dose and by Food Group After 1 Week of Duloxetine Treatment[a]



[a]p = .01 for main effect of food; MMRM analysis.
*p = .034 (without food: 60 mg q.a.m. vs. 30 mg q.a.m.); MMRM analysis.
**p = .057 (without food: 60 mg q.a.m. vs. 30 mg b.i.d.); MMRM analysis.
***p = .006 (60 mg q.a.m. without food vs. 60 mg q.a.m. with food); MMRM analysis.
Abbreviations: AMDP-5 = Association for Methodology and Documentation in Psychiatry adverse event scale, b.i.d. = twice daily, MMRM = mixed-model repeated measures, q.a.m. = once daily in the morning.

Figure 3. Mean Changes in AMDP-5 Common Adverse Events Score by Initial Starting Dose and by Food Group After 1 Week of Duloxetine Treatment[a]



[a]p = .35 for main effect of food; MMRM analysis.
*p = .014 (without food: 30 mg b.i.d. vs. 30 mg q.a.m.); MMRM analysis.
**p = .021 (without food: 60 mg q.a.m. vs. 30 mg q.a.m.); MMRM analysis.
Abbreviations: AMDP-5 = Association for Methodology and Documentation in Psychiatry adverse event scale, b.i.d. = twice daily, MMRM = mixed-model repeated measures, q.a.m. = once daily in the morning.

mg q.a.m. was greatest in patients taking drug without food. For example, the highest mean change in nausea score reported at week 1 was for the 60 mg q.a.m. without-food arm, which differed significantly from both the 60-mg q.a.m. with-food group (p = .006, significant with or without regard to the Bonferroni multiplicity adjustment) and the 30-mg q.a.m. without-food group (p = .034, not significant if applying the Bonferroni multiplicity adjustment). Comparing the 3 initial-dose groups who were instructed to take drug with food showed no significant differences in the mean change of nausea between the dose groups after 1 week of active treatment. Similar results were seen for the gastric events score.

The importance of the mean change results was reinforced by rates of discontinuations due to AEs. In patients who took study drug without food, there was a significant difference across initial-dose groups for discontinuations due to AEs (30 mg q.a.m. = 3.6%, 30 mg b.i.d. = 14.0%, 60 mg q.a.m. = 10.2%; p = .008 for 30 mg q.a.m. vs. 30 mg b.i.d., p = .066 for 30 mg q.a.m. vs. 60 mg q.a.m., no differences significant if applying the Bonferroni multiplicity adjustment); however, in patients who took study drug with food, discontinuations due to AEs did not significantly differ (30 mg q.a.m. = 5.4%, 30 mg b.i.d. = 7.5%, 60 mg q.a.m. = 7.4%; all p values > .50). Rates of discontinuation for other reasons (lack of efficacy, protocol violation, patient decision, loss to follow-up, or sponsor decision) did not differ significantly between groups.

A shift analysis that assesses the frequency and magnitude of changes in the AMDP-5 nausea score among patients with treatment-emergent nausea at 1 week of active treatment was conducted to assess the individual roles of incidence and severity in driving the mean change results. Among patients who started at 60 mg q.a.m. without food, 14.0% reported a 1-point increase in nausea score, 16.0% reported a 2-point increase (the largest in any study arm), and 3.0% reported a 3-point increase. When patients started at 60 mg q.a.m. with food, 14.6%, 7.3%, and 2.1% of patients reported a 1, 2, or 3-point increase, respectively.

Figure 3 shows the week 1 mean score on the common adverse event score, by starting dose and food group. Patients who started at 30 mg b.i.d. or 60 mg q.a.m. without food did not differ regarding mean changes in the common adverse events score after 1 week of duloxetine therapy (0.87 and 0.82, respectively) but had significantly greater mean changes (worsening) than patients who started at 30 mg q.a.m. without food (0 vs. 30 mg b.i.d. and 60 mg q.a.m., p < .05). None of the pairwise contrasts between with-food and without-food groups within starting-dose groups were statistically significant for the common adverse events score.

To better understand the factors driving the difference in results between the common adverse events score and the nausea score for the 30-mg b.i.d. dose, the incidence of the individual AMDP-5 TEAEs comprising the

common adverse events score was calculated after 1 week of treatment on the starting dose of duloxetine. A slightly higher incidence of many AEs in the 30-mg b.i.d. arm explains the overall similarity in the common AE score between 30 mg b.i.d. and 60 mg q.a.m., despite lower nausea rates in the 30-mg b.i.d. arm.

The spontaneously reported TEAE profile of this study was similar to that of previous studies of duloxetine. The most common TEAEs (≥ 5%) experienced by all initial-dose groups during the 6-week acute therapy phase, in decreasing order, were nausea, headache, dry mouth, diarrhea, dizziness, hyperhidrosis, insomnia, somnolence, constipation, and fatigue.

Over the entire acute therapy phase, AEs led to discontinuation of treatment in 8.0% (N = 52) of patients. The majority (92.3%) were due to nonserious events, and the most common (≥ 1%) event leading to discontinuation was nausea (1.9%, N = 12). No other AEs were reported as a reason for discontinuation at a rate greater than 1%.

No deaths occurred during the acute therapy phase. Nine patients (1.4%) of the 647 randomly assigned patients had a total of 13 serious adverse events (SAEs) during the acute therapy phase (chest pain, concussion, depression, fall, head injury, psychotic disorder, rib fracture, road traffic accident, 2 suicidal ideations, tympanic membrane perforation, upper limb fracture, and vaginal hemorrhage). Two (psychosis and 1 suicidal ideation) of the 13 events were considered by the investigator to be possibly related to duloxetine.

Safety and Tolerability: Sexual Functioning

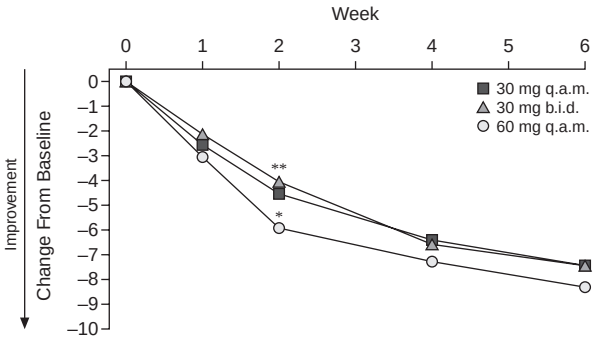
On the PGI-SF overall score, the majority of patients (54.5%) reported same sexual function, relative to their baseline function, while 23.7% reported worsened function and 21.8% reported better function. No significant differences were observed between initial-dose groups on the overall score or any of the individual items. On the AMDP-5, 20.1% of patients reported decreased libido and 11.3% of males reported decreased ejaculation.

Safety and Tolerability: Laboratory Analyses, Vital Signs, and Weight

Some statistically significant differences between initial-dose groups in laboratory values were seen. The duloxetine 30-mg q.a.m. group had significant mean increases in basophils (0.01 vs. –0.01; p = .010) and mean cell volume (1.13 vs. –1.63; p = .022) and a significant decrease in uric acid (–13.63 vs. –5.43; p = .038) compared with the duloxetine 60-mg q.a.m. group. The duloxetine 60-mg q.a.m. group had a significantly greater decrease in low-density lipoprotein cholesterol compared with the duloxetine 30-mg b.i.d. initial-dose group (–0.35 vs. 0.06, respectively; p = .043).

No statistically significant differences were seen between initial-dose groups in vital signs (least-squares mean change at endpoint for 30 mg q.a.m., 30 mg b.i.d., and 60 mg q.a.m. heart rate in bpm: 1.1, 2.1, and 1.8, respectively; weight in kg: –1.0, –0.5, and –0.7, respectively; systolic blood pressure in mm Hg: 1.8, 1.4, and 0.7, respectively; diastolic blood pressure in mm Hg: 1.6, 1.0, and 0.5, respectively).

Figure 4. Weekly Mean Change in HAM-D-17 Total Score by Starting Dose [a]



[a]After week 1, all patients were dosed at 60 mg q.d. Baseline mean score = 17.55 (after placebo lead-in).
*p = .01 (60 mg q.a.m. vs. 30 mg q.a.m.); MMRM analysis.
**p < .001 (60 mg q.a.m. vs. 30 mg b.i.d.); MMRM analysis.
Abbreviations: b.i.d. = twice daily, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MMRM = mixed-model repeated measures, q.a.m. = once daily in the morning.

Efficacy

Patients within each starting dose had statistically significant improvement in depressive symptoms at endpoint as measured by the HAM-D-17 total score, IDS-C-30 total score, and the QIDS-C score. However, patients who started at duloxetine 60 mg q.a.m. versus both other starting doses had statistically significantly greater improvement in the HAM-D-17 total scores at week 2 (Figure 4) and in the IDS-C-30 score at weeks 1 and 2 (p ≤ .05 vs. both groups). On the QIDS-C, patients who started at duloxetine 60 mg q.a.m. had statistically significantly greater improvement at weeks 2 and 3 versus the 30-mg q.a.m. group and at weeks 1 and 2 versus the 30-mg b.i.d. group (p ≤ .05). Additional a priori–specified secondary objectives to measure efficacy outcomes after 6 weeks of active treatment are summarized in Table 2.

The proportion of patients who achieved treatment response (≥ 50% reduction in a patient's HAM-D-17 total score from baseline) after 6 weeks of active treatment did not differ between initial-dose groups: 47.7% (N = 94/197) for the 60-mg q.a.m. group, 42.6% (N = 83/195) for the 30-mg b.i.d. group, and 46.0% (N = 93/202) for the 30-mg q.a.m. group. There were also no significant between-dose group differences in the proportion of patients achieving remission (HAM-D-17 total score ≤ 7) at week 6: 60 mg q.a.m. = 42.1% (N = 83/197), 30 mg

Table 2. Summary of Efficacy Measures

Measure	Mean Change (SE)		
	Duloxetine 30 mg q.a.m. (N = 202)	Duloxetine 30 mg b.i.d. (N = 195)	Duloxetine 60 mg q.a.m. (N = 198)
HAM-D-17 total score	–7.43 (0.45)	–7.46 (0.46)	–8.26 (0.46)
HAM-D-17 subscale score			
Anxiety	–2.08 (0.16)	–2.05 (0.16)	–2.25 (0.16)
Core	–3.83 (0.21)	–3.86 (0.22)	–4.05 (0.22)
Maier	–4.79 (0.26)	–4.76 (0.27)	–5.00 (0.27)
Retardation	–3.08 (0.19)	–3.35 (0.19)	–3.43 (0.19)
Sleep	–1.01 (0.13)	–0.90 (0.14)	–1.20 (0.14)
IDS-C-30 total score	–12.68 (0.74)	–13.11 (0.77)	–13.98 (0.77)
QIDS-C total score	–5.90 (0.39)	–6.25 (0.40)	–6.82 (0.40)
CGI-S score	–1.32 (0.08)	–1.28 (0.09)	–1.48 (0.09)
PGI-I score[a]	2.46 (0.08)	2.67 (0.08)	2.44 (0.08)*
VAS pain score	–6.79 (1.42)	–6.31 (1.48)	–6.90 (1.48)
BPI average pain score	–0.80 (0.11)	–0.86 (0.12)	–0.70 (0.12)

[a]Mean scores reported.
*$p \leq .05$ vs. 30 mg b.i.d.
Abbreviations: b.i.d. = twice daily; BPI average pain = Brief Pain Inventory, average pain severity; CGI-S = Clinical Global Impressions-Severity of Illness scale; HAM-D-17 = 17-item Hamilton Rating Scale for Depression; IDS-C-30 = 30-item Inventory of Depressive Symptomatology, Clinician Rated; PGI-I = Patient Global Impression of Improvement; q.a.m. = once daily in the morning; QIDS-C = 16-item Quick Inventory of Depressive Symptomatology, Clinician Rated; VAS Pain = Visual Analog Scale for pain.

b.i.d. = 35.9% (N = 70/195), and 30 mg q.a.m. = 39.6% (N = 80/202).

DISCUSSION

The primary analysis, which combined data from both food groups, showed no significant difference in the incidence of nausea between starting doses of 30 mg q.a.m. and 60 mg q.a.m. However, mean changes on the AMDP-5 nausea item, which captured both incidence and severity, revealed a significant main effect of food and a significant interaction between food and starting dose. The food-by-dose interaction indicated that the benefit from taking drug with food was greatest in the patients who started at 60 mg q.a.m., and the benefit of starting at 30 mg q.a.m. was greatest in patients taking drug without food. In patients who took study drug without food, there was a significant difference across initial-dose groups in discontinuations due to AEs (30 mg q.a.m. = 3.6%, 30 mg b.i.d. = 14.0%, 60 mg q.a.m. = 10.2%); however, in patients who took study drug with food, discontinuations due to AEs did not significantly differ (30 mg q.a.m. = 5.4%, 30 mg b.i.d. = 7.5%, 60 mg q.a.m. = 7.4%). No significant differences were found between initial-dose groups in vital signs. Differences in efficacy outcomes favoring the 60-mg q.a.m. group were observed at early weeks, but differences at endpoint were not significant.

The recommended therapeutic dose of duloxetine is 60 mg q.d. The present results show that either starting at 60 mg with food or starting at 30 mg without food improved tolerability. Each of these strategies resulted in a similar magnitude of reduction in nausea relative to starting at 60 mg q.a.m. without food, but adopting both at the same time—starting at 30 mg q.a.m. and taking with food—did not appear to result in an additional benefit in tolerability. The improved tolerability was the result of both reduced incidence and severity of AEs. That is, if a patient started at either 30 mg without food or 60 mg with food, the patient was less likely to experience an AE such as nausea, and it was even more likely that, if the patient did experience nausea, the nausea would be less severe than it would have been otherwise. This result is consistent with the finding that patients who either took study drug without food or started at 60 mg q.a.m. were more likely to discontinue due to an AE.

On efficacy measures, there were no significant differences between treatment arms in mean change scores or remission rates at endpoint. However, there were differences during the first few weeks of the study, with a significantly greater improvement in mean score on the HAM-D-17, IDS-C-30, and QIDS-C at time points ranging from week 1 to week 3. This result is not surprising given that efficacy of a 30-mg dose has not been established, and the minimally effective dose of duloxetine is 40 mg/day.[21,22] Therefore, one must consider the efficacy costs as well as the tolerability benefits when choosing a strategy for starting depressed patients on duloxetine.

Instructions to take study drug either with food or not within an hour of eating were left vague by design. For example, there was no specific guidance about the amount of food, so there may have been wide variability, which may have led to variability in effect on tolerability. Although patients were asked about compliance with these instructions, compliance was not enforced in this study. The manipulation was designed to mimic a minimal clinical intervention. Nevertheless, even this simple

intervention had an important impact on initial tolerability for patients starting at 60 mg q.a.m.. It is unknown whether a stronger intervention, such as instructing patients to take study drug with their largest meal, would have enhanced tolerability further.

There are no previous studies of duloxetine comparing q.a.m. with b.i.d. dosing in MDD. Although patients who started duloxetine at 30 mg b.i.d. reported reduced incidence and severity of nausea, the overall tolerability of the 30-mg b.i.d. start was no better than the 60-mg q.a.m. dose, either with or without food, thereby providing no compelling evidence to use split dosing as a strategy for starting duloxetine. There did not appear to be any particular AE that increased with the 30-mg b.i.d. dose and that served as a "trade-off" with nausea. Rather, various AEs occurred at rates slightly higher than in the 60-mg q.a.m. group, so that overall the 2 doses were similar in tolerability. Furthermore, patients starting at 30 mg b.i.d. had significantly less improvement in depressive symptoms during the first weeks of the study than patients starting at 60 mg q.a.m., so split dosing improved neither efficacy nor tolerability in this study. In a meta-analysis of 3 studies, Yyldyz and Sachs[23] reported decreased efficacy when medications with half-lives from 12 to 24 hours were given as split doses compared to the same medications given once daily, though they did not find a similar difference in drugs with half-lives less than 12 hours. The half-life of duloxetine is approximately 12 hours.[24]

Potentially in contrast to the conclusion that food is an important factor in tolerability, pharmacokinetic studies of duloxetine dosed at 40 mg q.d. in 12 healthy volunteers suggested that food did not influence plasma concentration of duloxetine, although food did seem to extend the time until maximum concentration.[25] It is difficult, however, to draw conclusions about the clinical findings from the current study based on the pharmacokinetic findings of Skinner and colleagues.[25] This is in part due to the limitation of the pharmacokinetic study that it was difficult a priori to ensure adequate power to find concentration differences. Further complicating the issue is the finding in the current study of no clear association between concentration (initial dose) and the frequency of adverse reactions. Accordingly, we do not conclude that the findings of Skinner and colleagues are inconsistent with the conclusions we have drawn from these data.

Limitations

The primary analysis did not reveal a significant difference between incidence of nausea among patients started at 30 mg q.a.m. and those started at 60 mg q.a.m. This article reports a number of secondary analyses without statistical corrections in all cases, and we base our conclusions on what appear to be consistent trends in the data. It would be useful to confirm these results by including these starting strategies in another prospective trial. In particular, it would be worthwhile to compare the 30-mg start with and without food, to consider whether there is in fact no additional benefit of starting at 30 mg with food, and to reexamine the numerically worse common AE score found among patients who started at 30 mg with food.

Since the median duration of treatment-emergent nausea was reported to be 7 days,[26] it is possible that many patients' nausea had resolved by the visit at week 1, and nausea was accordingly underreported. However, this effect would have presumably been distributed evenly across arms and so should not have affected comparisons.

There was no placebo control. Some AEs could have resulted from multiple pills, though the placebo lead-in should have controlled for this possibility to some extent. More importantly, the evaluation of week 1 changes on the AMDP-5 is limited by the omission of a placebo arm. This omission is particularly salient for events that might have been features of the disease, such as insomnia, and even some of the physical symptoms, which were common. This is also a limitation on the interpretation of efficacy results.

No time of dosing was specified for the second dose during the b.i.d. dosing period. It is possible that patients who took study drug with meals took drug at a different time than those who did not take study drug with food (e.g., bedtime vs. dinner time), which could confound the data. However, one might have expected the without-food group to then "sleep through" their nausea, reducing the reported incidence.

CONCLUSION

These data imply that starting duloxetine at 30 mg q.a.m. for 1 week with or without food, or starting duloxetine at the therapeutic dose of 60 mg q.a.m. with food, can improve the initial tolerability of the medication. Adding this information to existing knowledge of duloxetine will enable the clinician to tailor therapy most appropriately for the individual patient.

Drug names: diphenhydramine (Benadryl and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others).

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