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Clinical Consequences of Initial Duloxetine Dosing Strategies: Comparison of 30 and 60 mg QD Starting Doses

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ABSTRACT

Background: To reduce the risk for treatment-emergent adverse events and increase patient compliance, clinicians frequently prescribe a suboptimal starting dose of antidepressants, with the goal of increasing the dose once the patient has demonstrated tolerability.

Objective: The aim of this study was to examine the tolerability and effectiveness associated with an initial week of duloxetine hydrochloride treatment at 30 mg QD and subsequent dose increase to 60 mg QD, compared with a starting dose of 60 mg QD.

Methods: In this open-label study, all patients met the criteria for major depressive disorder (MDD) described in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.* Patients were required to wash out from previous antidepressant medications for 21 days, and were then randomized to receive duloxetine 30 or 60 mg QD for 1 week. After 1 week, patients receiving duloxetine 30 mg QD had their dose increased to 60 mg QD. Patients returned for assessments at weeks 2, 4, 6, 8, and 12. During the remainder of the 12-week study period, the duloxetine dose could be titrated based on the degree of response from 60 mg QD (minimum) to 120 mg QD (maximum), with 90 mg QD as an intermediate dose. Tolerability was assessed by means of discontinuation rates, spontaneously reported adverse events, changes in vital signs, and laboratory tests. Effectiveness measures included the 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$) total score, $HAMD_{17}$ core and Maier subscales, individual $HAMD_{17}$ items, the Hamilton Rating Scale for Anxiety total score, and the Clinical Global Impression of Severity.

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Results: One hundred thirty-seven patients were enrolled (82 women, 55 men; mean age, 42 years; duloxetine 30 mg QD, 67 patients; duloxetine 60 mg QD, 70 patients). The rate of discontinuation due to adverse events did not differ significantly between patients starting duloxetine at 30 mg QD and 60 mg QD (13.4% vs 18.6%). The most frequently reported adverse events across both treatment groups were nausea, headache, dry mouth, insomnia, and diarrhea. In the first week of treatment, patients receiving duloxetine 30 mg QD had a significantly lower rate of nausea compared with patients receiving 60 mg QD (16.4% vs 32.9%; $P = 0.03$). Over the 12-week acute-treatment phase, patients starting duloxetine treatment at 30 mg QD had a significantly lower rate of nausea compared with patients initiating treatment at 60 mg QD ($P = 0.047$). Although between-group differences in the $HAMD_{17}$ total score were not statistically significant at any visit, patients starting at 30 mg QD experienced significantly less improvement in $HAMD_{17}$ core and Maier subscales at week 1 compared with patients starting at 60 mg QD (core, $P = 0.044$; Maier, $P = 0.047$). After 2 weeks of treatment, the magnitude of improvement among patients starting at 30 mg QD did not differ significantly from that observed in patients who started treatment at 60 mg QD, and there were no significant between-group differences in effectiveness at any subsequent visit.

Conclusions: Results from this open-label study in patients with MDD suggest that starting duloxetine treatment at 30 mg QD for 1 week, followed by escalation to 60 mg QD, might reduce the risk for treatment-emergent nausea in these patients while producing only a transitory impact on effectiveness compared with a starting dose of 60 mg QD. (*Curr Ther Res Clin Exp.* 2005;66:522–540)

Key words: duloxetine, tolerability, safety, efficacy.

INTRODUCTION

Major depressive disorder (MDD) is a common and debilitating condition. In the United States, MDD affects >20 million people, with a lifetime prevalence of approximately 16%.[1] In addition to the considerable morbidity associated with MDD, the risk for suicide in these patients is ~20-fold that of the general population.[2]

Effective treatment of MDD is essential. Potential consequences of undertreatment include prolonged suffering, suicide, occupational impairment, and impairment in interpersonal and family relationships.[3] Current guidelines recommend that antidepressant treatment be administered at a therapeutic dose for at least 4 to 6 months,[4] and emphasize that the primary goal of treatment should be the achievement of remission (ie, the virtual absence of depressive symptoms, usually defined as a 17-item Hamilton Rating Scale for Depression [$HAMD_{17}$][5,6] total score ≤7). Although MDD is a potentially chronic and recurring illness, achievement of remission of all depressive symptoms during the initial treatment episode might reduce the risk for future episodes.[7]

Selective serotonin reuptake inhibitors (SSRIs) currently represent the first line of pharmacotherapy in the treatment of MDD. However, some adverse events associated with initiating SSRI or serotonin/norepinephrine reuptake inhibitor (SNRI) therapy continue to represent a potential barrier to effective treatment. For example, treatment-emergent nausea is reported at rates between 20% and 31%.[8] Strategies designed to mitigate the risk for adverse events might improve patient compliance, and play an important role in ensuring that patients receive effective treatment of depression.

One strategy frequently used by antidepressant prescribers is to initiate medications at a dose less than the recommended starting dose to minimize potential adverse effects experienced by the patient. If the patient tolerates the initial dose over a period of several days, the dose is then increased into the therapeutic range. However, this strategy also has some potential drawbacks for the patient. First, the initial period of suboptimal dosing would be expected to be associated with reduced efficacy. Even after the dose is increased into the therapeutic range, efficacy might continue to lag behind that of patients who initiated treatment at the recommended starting dose. The second, and considerably greater, concern is that patients might not receive a dose increase, although this problem is seen more frequently with tricyclic antidepressants (TCAs) than with SSRIs or SNRIs.[9] If treatment is continued at the initial suboptimal dose, a degree of improvement in depressive symptoms might be expected, but the patient is unlikely to achieve an outcome equivalent to that associated with the therapeutic dose.

Duloxetine hydrochloride is a dual reuptake inhibitor of serotonin and norepinephrine that has been shown to be tolerable and effective in the acute treatment of MDD.[10–14] The recommended therapeutic dose of duloxetine is 60 mg QD.[15] The rationale underlying this recommendation, namely that duloxetine 60 mg QD provides an optimal combination of efficacy and tolerability, has been discussed previously.[16] In placebo-controlled clinical trials, the most common adverse event associated with duloxetine 60 mg QD dosing was nausea, which was reported by 38% of patients.[10,17] Although the rate of discontinuation due to nausea in these studies was relatively low (0.8% at 60 mg QD; 1.4% across a dose range of 40–120 mg/d),[17] treatment-emergent adverse events such as nausea might have a greater impact on patient compliance in day-to-day clinical practice, where patients are often less motivated to continue treatment compared with clinical trial participants. Thus, starting doses of medications as derived from clinical trials are sometimes higher than those deemed tolerable in clinical practice. Furthermore, given the heterogeneity of MDD and of the patients with this condition, it is unrealistic to believe that a single starting dose would be best in all patients. The objective of the present investigation was to compare the merits of 2 initial dosing regimens for duloxetine in the treatment of MDD (30 and 60 mg QD), and to establish whether a lower starting dose would reduce the incidence of adverse events such as nausea.

PATIENTS AND METHODS

Study Design

This was an open-label, multicenter trial involving 27 investigative sites in the United States. This study was part of a larger study comparing treatment outcomes in currently untreated patients initiating duloxetine (at 30 or 60 mg QD) with those of patients switching from SSRI/venlafaxine to duloxetine. Comparisons of treatment outcomes between switching and untreated patients are reported in a separate publication.[18] The present analyses focus on currently untreated patients initiating duloxetine treatment at 30 or 60 mg QD—patients in the "switching" arm were excluded. The study protocol was approved by the institutional review board at each site, in accordance with the principles of the Declaration of Helsinki and its amendments,[19] and all patients provided written informed consent prior to participation in any study-related procedures.

Patients could have received previous antidepressant treatment or were treatment naive. Patients who had received previous treatment were required to wash out from antidepressant medications for a period of 21 days (30 days in the case of fluoxetine) and were then considered to be untreated. All patients then entered a 1-week screening period. At the conclusion of the screening period, patients meeting study criteria were randomly assigned within each investigative site (1:1 ratio) to receive duloxetine 30 or 60 mg QD. All patients were required to remain at their assigned initial duloxetine dose for a 1-week initial treatment phase. Patients unable to tolerate duloxetine treatment during this period were withdrawn from the study. At the end of this initial treatment phase, all patients receiving 30 mg QD had their duloxetine dose increased to 60 mg QD. During the remainder of the 12-week study period, each patient's duloxetine dose could be titrated based on the degree of response within a range from 60 mg QD (minimum) to 120 mg QD (maximum), with 90 mg QD as an intermediate dose. The duloxetine dose could be increased or decreased only at scheduled visits (weeks 2, 4, 6, 8, and 12), and could be increased by the investigator only if the patient's $HAMD_{17}$ total score was ≥7 at the scheduled visit.

Patients

Patients were adult males and females (≥18 years of age) meeting criteria for MDD defined in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*.[20] Patients were required to have a $HAMD_{17}$ total score ≥15 and a Clinical Global Impression of Severity (CGI-S)[21] score ≥4 at visits 1 and 2. Exclusion criteria included a diagnosis of bipolar disorder, schizophrenia, or other psychotic disorder; the presence of a primary and current Axis II disorder; a serious medical illness; serious suicidal risk; treatment with fluoxetine within 30 days prior to visit 1; treatment with a monoamine oxidase inhibitor within 14 days prior to visit 1; lack of response of the current episode to 2 or more adequate courses of antidepressant treatment at a clinically appropriate dose for a minimum of 4 weeks, or treatment-refractory

depression; any anxiety disorder as a primary diagnosis within the previous 6 months; a history of substance dependence within the previous 6 months; and/or a positive urinary drug screening result. Use of concomitant medications with primarily central nervous system activity was not allowed during the study. The use of β-blockers, diuretics, angiotensin-converting enzyme inhibitors, antiarrhythmics, anticoagulants, 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.

Tolerability Measures

Tolerability was assessed by means of discontinuation rates, spontaneously reported adverse events, changes in vital signs, and laboratory tests (hematology, urinalysis, and clinical chemistry). Abnormal vital sign values were defined as follows: high supine systolic (diastolic) blood pressure (BP): ≥140 (≥90) mm Hg and ≥10 mm Hg greater than baseline; low supine systolic (diastolic) BP: ≤90 (≤50) mm Hg and ≥10 mm Hg lower than baseline; elevated (low) heart rate: ≥100 (≤50) bpm and ≥10 bpm greater (less) than baseline; weight gain (loss): body weight increase (decrease) ≥7% from baseline. A patient was considered to have sustained hypertension if criteria for elevated systolic or diastolic BP were met at 3 consecutive visits.

Effectiveness Measures

Effectiveness measures included the $HAMD_{17}$ total score, $HAMD_{17}$ subscales (core: items 1, 2, 3, 7, and 8; Maier: items 1, 2, 7, 8, 9, and 10; anxiety: items 10, 11, 12, 13, 15, and 17; retardation: items 1, 7, 8, and 14; sleep: items 4, 5, and 6), individual $HAMD_{17}$ items, the Hamilton Rating Scale for Anxiety (HAMA)[22] total score, and the CGI-S (all measures were assessed at each study visit). *Response* was defined a priori as a ≥50% reduction from baseline in $HAMD_{17}$ total score. *Remission* was defined as a $HAMD_{17}$ total score ≤7.

Statistical Analysis

All analyses were conducted on an intent-to-treat basis unless otherwise specified. All patients who received study drug were included in tolerability analyses unless otherwise specified. Patients with at least 1 postbaseline observation were included in the effectiveness analyses.

The primary outcome of the larger study was a comparison of stabilized doses for switching versus untreated patients. Using $\alpha = 0.05$, and assuming that 50% of currently untreated patients stabilized at duloxetine 60 mg QD, compared with 30% in switch patients, the study was estimated to have 86% power for the primary end point. For the present investigation, with ~70 patients per arm, power to detect a difference between true rates of 20% versus 40% was 68%, and power to detect a difference in true rates of 10% versus 20% was 30%. Therefore, this investigation was underpowered to detect clinically important differences in common adverse events between the 30 and 60 mg groups, and

did not have adequate power to detect between-group differences in rare events such as discontinuation due to adverse events and effectiveness.

Baseline scores on $HAMD_{17}$, HAMA, and CGI-S were compared using a 1-way analysis of variance (ANOVA). Patient demographic characteristics were compared using the ANOVA model for continuous outcomes (age) and with the Fisher exact test for comparing percentages of categorical outcomes (sex, race).

Longitudinal changes in effectiveness outcomes were assessed using a likelihood-based, mixed-effects model, repeated-measures approach. The model included the fixed categorical effects of group and investigator. Time of assessment was modeled as a continuous effect by including linear and quadratic terms for days on treatment, as well as the interaction of the linear and quadratic terms with group. Time was included as a continuous effect because the visit intervals had more flexibility than often seen in acute phase trials. Thus, fitting time as continuous accounted for the unequal visit timing. Baseline severity was also included as a continuous covariate. Within-patient errors were modeled using an unstructured covariance matrix. The Kenward-Roger method was used to estimate denominator degrees of freedom.

Mean changes from baseline to last observation in effectiveness measures were compared using ANOVA with a model that includes group, investigator and baseline severity. Probabilities of response and remission were compared using the Fisher exact test.

The incidence of serious adverse events, discontinuations due to adverse events, and treatment-emergent adverse events were compared using the Fisher exact test. Mean changes from baseline to last observation in BP and heart rate were compared using ANOVA with a model that includes group, investigator, and baseline severity. The percentages of the patients who had abnormal values for vital signs at end point were compared using the Fisher exact test.

RESULTS

Patients

A total of 137 currently untreated patients with MDD were randomized to receive duloxetine 30 mg QD for the first week of treatment (67 patients), or duloxetine 60 mg QD during the first week (70 patients) (82 women, 55 men; mean age, 42 years). There were no significant between-group differences in baseline demographic characteristics or psychiatric profile (**Table I**).

Final Prescribed Dose

Following the initial week of fixed dosing, patients could receive flexible dosing based on the degree of response within a range from 60 to 120 mg QD, with 90 mg QD as an intermediate dose. Within the group starting duloxetine treatment at 30 mg QD, the proportions of patients receiving each of these doses as their final dose at study end point were as follows: 60 mg QD, 21/66 (31.8%) patients; 90 mg QD, 18/66 (27.3%); 120 mg QD, 19/66 (28.8%); and other dose

Table I. Baseline demographic and clinical characteristics of the study patients.*

Baseline Characteristic	Duloxetine 30 mg QD (n = 67)	Duloxetine 60 mg QD (n = 70)
Age, mean (SD), y	42.3 (13.5)	42.0 (12.6)
Age range, y	19–72	18–83
Sex, no. (%)		
Female	38 (56.7)	44 (62.9)
Male	29 (43.3)	26 (37.1)
Weight, mean (SD), kg	79.5 (20.7)	82.6 (21.1)
Race, no. (%)†		
White	59 (88.1)	59 (84.3)
Hispanic	5 (7.5)	4 (5.7)
Black	3 (4.5)	5 (7.1)
East Asian	0 (0.0)	2 (2.9)
$HAMD_{17}$ total score, mean (SD)	20.9 (3.7)	20.2 (3.2)
HAMA score, mean (SD)	16.9 (5.7)	16.8 (5.6)
CGI-S score, mean (SD)	4.36 (0.51)	4.28 (0.52)
VAS overall pain score, mean (SD)‡	28.2 (24.1)	25.6 (22.1)
Atypical features, no. (%)§	7 (10.4)	3 (4.3)
Melancholic features, no. (%)§	43 (64.2)	45 (64.3)
Number of previous episodes, mean (median)	9 (4)	6 (4)
Duration of current episode, mean (median), wk	81 (26)	64 (29)

$HAMD_{17}$ = 17-item Hamilton Rating Scale for Depression[5]; HAMA = Hamilton Rating Scale for Anxiety[22]; CGI-S = Clinical Global Impression of Severity[21]; VAS = visual analog scale.

*There were no significant between-group differences in any aspect of baseline demographic or clinical characteristics.

†Percentages may not total 100% due to rounding.

‡Patients' rating of their overall pain at baseline, using a 100-mm VAS (0 = none to 100 = as severe as I can imagine).

§The presence of melancholic or atypical features (using criteria defined in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*[20]) was determined using results from the Mini International Neuropsychiatric Interview.[23]

(0 or 30 mg QD), 8/66 (12.1%). Within the group starting duloxetine at 60 mg QD, the proportions of patients receiving each dose at study end point were as follows: 60 mg QD, 15/62 (24.2%) patients; 90 mg QD, 22/62 (35.5%); 120 mg QD, 18/62 (29.0%); other dose, 7/62 (11.3%). In comparisons between the 30 and 60 mg QD starting groups, there were no significant differences in the proportions of patients receiving each of the doses at study end point.

Tolerability

Adverse Events

Five of 137 (3.6%) patients reported serious adverse events during the study. Two of these patients started duloxetine at 30 mg QD, and 3 patients started at 60 mg QD (3.0% and 4.3%, respectively). Events reported by patients initiating treatment at 30 mg QD were pneumonia and postoperative fever (1 patient each), whereas events reported by patients starting at 60 mg QD were appendicitis; superficial thrombophlebitis; and a combination of bacteremia, nephrolithiasis, pyelonephritis, pneumonia, and congestive heart failure (1 patient each).

During the first week of treatment, the rates of discontinuation due to adverse events in patients receiving duloxetine 30 or 60 mg QD were 3 (4.5%) patients and 9 (12.9%) patients, respectively; this difference was not statistically significant. Events leading to discontinuation in the first week in patients receiving duloxetine 30 mg QD were somnolence, disturbance in attention, and blurred vision (1 patient each). Among patients receiving duloxetine 60 mg QD, adverse events leading to discontinuation in the first week were nausea (2 patients) and vomiting, abdominal pain, somnolence, fatigue, insomnia, choking, and balance disorder (1 patient each). Over the 12-week acute-treatment period, the rate of discontinuation due to adverse events did not differ significantly between patients starting duloxetine at 30 mg QD and those starting at 60 mg QD (9 [13.4%] vs 13 [18.6%] patients). Furthermore, the rates of discontinuation due to individual adverse events did not differ significantly between treatment groups. The adverse events leading to discontinuation in >1 patient in either treatment group were nausea and insomnia, each of which led to discontinuation in 2 patients starting duloxetine at 60 mg QD. Events leading to discontinuation in 1 patient in each treatment group were headache and somnolence. Other adverse events reported as reasons for discontinuation in a single patient were abdominal pain, agitation, balance disorder, bruxism, choking, diarrhea, disturbance in attention, fatigue, increased heart rate, hot flash, rash, blurred vision, and vomiting. Discontinuation due to adverse events generally occurred early in treatment, with more than two thirds of all discontinuations occurring in the first 2 weeks of treatment.

In the first week of treatment, patients starting duloxetine treatment at 30 mg QD reported a significantly lower rate of nausea compared with patients initiating treatment at 60 mg QD (11 [16.4%] vs 23 [32.9%] patients; $P = 0.03$) (**Table IIA**). No other event occurred at significantly different rates in the 2 treatment groups during the first week of treatment (fixed dose). During the 12-week acute-treatment phase, the overall rate of treatment-emergent adverse events in patients starting at 30 mg QD did not differ significantly from that observed in patients starting at 60 mg QD (62 [92.5%] vs 63 [90.0%] patients) (**Table IIB**). The most frequently reported treatment-emergent adverse event in patients initiating duloxetine at 30 mg QD was headache (19 [28.4%] patients), whereas patients starting at duloxetine 60 mg QD most frequently reported nausea (28 [40.0%] patients) (**Table IIB**). Patients starting at 30 mg QD reported a signifi-

Table IIA. Incidence of treatment-emergent adverse events* during the first week of treatment (tolerability population). Values are no. (%) of patients.

Parameter	Duloxetine 30 mg QD (n = 67)	Duloxetine 60 mg QD (n = 70)	*P*
Patients with ≥1 event	45 (67.2)	53 (75.7)	0.344
Adverse Event			
Headache	13 (19.4)	11 (15.7)	0.655
Dry mouth	12 (17.9)	10 (14.3)	0.645
Nausea	11 (16.4)	23 (32.9)	0.03
Diarrhea	9 (13.4)	5 (7.1)	0.267
Insomnia	8 (11.9)	5 (7.1)	0.392
Somnolence	7 (10.4)	4 (5.7)	0.359
Fatigue	5 (7.5)	9 (12.9)	0.400
Dyspepsia	5 (7.5)	3 (4.3)	0.487
Disturbance in attention	4 (6.0)	1 (1.4)	0.202
Dizziness	4 (6.0)	5 (7.1)	1.00
Upper abdominal pain	4 (6.0)	0	0.055
Decreased libido	3 (4.5)	4 (5.7)	1.00
Hyperhidrosis	3 (4.5)	4 (5.7)	1.00
Decreased appetite	2 (3.0)	5 (7.1)	0.442
Vomiting	1 (1.5)	4 (5.7)	0.366
Restlessness	0	4 (5.7)	0.120

*Events reported by >5% of patients in either treatment group.

cantly lower rate of nausea (16 [23.9%] vs 28 [40.0%] patients; $P = 0.047$) and a significantly higher rate of upper abdominal pain (6 [9.0%] vs 0 patients; $P = 0.012$) compared with patients initiating duloxetine treatment at 60 mg QD.

Vital Signs

During the first week of treatment, there were no significant between-group differences in mean changes in vital sign measurements (**Table IIIA**). During the 12-week acute-treatment phase, mean changes in supine systolic and diastolic BP were ≤2 mm Hg in patients initiating duloxetine treatment at 30 mg QD or 60 mg QD, with no significant differences between treatment groups (**Table IIIB**). Patients starting duloxetine treatment at 30 mg QD had a significantly greater baseline–to–end point increase in supine heart rate compared with those initiating treatment at 60 mg QD ($P = 0.01$). Both treatment groups had a similar mean decrease in body weight.

The incidence of abnormal vital sign values at any postbaseline visit is presented in **Table IV**. The only significant between-group difference was in the

Table IIB. Incidence of treatment-emergent adverse events* during the acute phase (12 weeks) (tolerability population). Values are no. (%) of patients.

Parameter	Duloxetine 30 mg QD Start (n = 67)	Duloxetine 60 mg QD Start (n = 70)	*P*
Patients with ≥1 event	62 (92.5)	63 (90.0)	0.765
Adverse event			
Headache	19 (28.4)	19 (27.1)	1.00
Nausea	16 (23.9)	28 (40.0)	0.047
Dry mouth	15 (22.4)	18 (25.7)	0.693
Insomnia	12 (17.9)	12 (17.1)	1.00
Diarrhea	12 (17.9)	9 (12.9)	0.481
Hyperhidrosis	10 (14.9)	10 (14.3)	1.00
Constipation	8 (11.9)	7 (10.0)	0.789
Somnolence	8 (11.9)	9 (12.9)	1.00
Fatigue	7 (10.4)	13 (18.6)	0.228
Dyspepsia	7 (10.4)	5 (7.1)	0.556
Back pain	7 (10.4)	3 (4.3)	0.201

*Events reported by >10% of patients in either treatment group.

Table IIIA. Changes in vital signs and weight from baseline to week 1 (first week of treatment). Values are mean (SD).

Vital Sign	Duloxetine 30 mg QD (n = 67)	Duloxetine 60 mg QD (n = 65)	*P*
Supine heart rate, bpm	0.3 (11.1)	–1.7 (8.9)	0.074
Supine systolic BP, mm Hg	3.1 (10.5)	2.4 (9.7)	0.535
Supine diastolic BP, mm Hg	1.2 (8.1)	0.8 (7.5)	0.949
Weight, kg	–0.5 (1.3)	–0.6 (1.2)	0.950

BP = blood pressure.

incidence of high supine systolic BP: the incidence in patients starting duloxetine at 60 mg QD was significantly higher than that observed in patients starting duloxetine treatment at 30 mg QD (14/56 [25.0%] vs 6/58 [10.3%] patients; $P = 0.05$). The incidence of abnormal weight gain or weight loss did not differ significantly between the 2 treatment groups (**Table IV**).

Two patients starting duloxetine at 60 mg QD met criteria for sustained hypertension during the course of the study, whereas none of the patients starting at duloxetine 30 mg QD met criteria for sustained hypertension.

Table IIIB. Changes in vital signs and weight from baseline to end point. Values are mean (SD).

Vital Sign	Duloxetine 30 mg QD Start (n = 67)	Duloxetine 60 mg QD Start (n = 65)	*P*
Supine heart rate, bpm	4.5 (11.3)	1.1 (11.8)	0.01
Supine systolic BP, mm Hg*	1.8 (12.3)	0.6 (11.6)	0.390
Supine diastolic BP, mm Hg*	0.6 (9.6)	–0.6 (9.1)	0.526
Weight, kg†	–1.0 (2.5)	–0.5 (3.0)	0.168

BP = blood pressure.
*30 mg QD start (n = 66); 60 mg QD start (n = 65).
†30 mg QD start (n = 65); 60 mg QD start (n = 65).

Effectiveness

Although the between-group differences at week 1 in $HAMD_{17}$ total score, HAMA, and CGI-S did not achieve statistical significance, patients initiating duloxetine treatment at 60 mg QD showed significantly greater improvement on the $HAMD_{17}$ core and Maier subscales at week 1 compared with patients initiating treatment at 30 mg QD (core, $P = 0.044$; Maier, $P = 0.047$) (**Table VA**). From week 2 onward (when patients could receive flexible dosing), between-group differences in effectiveness measures progressively diminished (**Figure 1**), and no significant differences were observed at any subsequent visit. Baseline–to–end point mean changes in $HAMD_{17}$ total score, $HAMD_{17}$ subscales, HAMA, and CGI-S did not differ significantly between patients initiating duloxetine treatment at 30 or 60 mg QD (**Table VB**).

Estimated probabilities of response (≥50% reduction in $HAMD_{17}$ total score) at week 1 and week 12 in patients starting duloxetine treatment at 30 mg QD were similar to those observed in patients initiating treatment at 60 mg QD (week 1: 30 mg QD, 13.8%; 60 mg QD, 12.3%; week 2: 30 mg QD start, 23.2%; 60 mg QD start, 21.8%; week 12: 30 mg QD start, 81.5%; 60 mg QD start, 80.4%). Estimated probabilities of remission ($HAMD_{17}$ total score, ≤7) at week 12 were 67.3% in patients starting duloxetine treatment at 30 mg QD and 66.8% in those starting at 60 mg QD.

At early visits (weeks 1 and 2), patients initiating duloxetine at 60 mg QD showed a similar increase (worsening) in $HAMD_{17}$ item 12 score (somatic symptoms–gastrointestinal) compared with patients starting at 30 mg QD (**Figure 2A**). At weeks 1 and 2, patients initiating duloxetine treatment at 60 mg QD had a significant increase (worsening) in $HAMD_{17}$ item 16 (loss of weight) compared with patients starting at 30 mg QD ($P < 0.01$) (**Figure 2B**). At subsequent visits, there were no significant between-group differences on $HAMD_{17}$ item 16.

Table IV. Incidence of abnormal vital sign values and abnormal weight at any time during the 12-week study period. Values are no. (%) of patients.

Vital Sign	Duloxetine 30 mg QD Start	Duloxetine 60 mg QD Start	*P*
Supine pulse			
High*	6 (9.1)	3 (4.6)	0.492
Low*	0	1 (1.5)	0.496
Supine systolic BP			
High†	6 (10.3)	14 (25.0)	0.050
Low‡	1 (1.8)	0	1.00
Supine diastolic BP			
High§	7 (12.3)	10 (18.2)	0.438
Low‡	2 (3.6)	1 (1.8)	1.00
Weight			
Gain‖	1 (1.5)	1 (1.5)	1.00
Loss‖	5 (7.7)	3 (4.6)	0.718

BP = blood pressure.
*30 mg QD start (n = 66); 60 mg QD start (n = 65).
†30 mg QD start (n = 58); 60 mg QD start (n = 56).
‡30 mg QD start (n = 56); 60 mg QD start (n = 55).
§30 mg QD start (n = 57); 60 mg QD start (n = 55).
‖30 mg QD start (n = 65); 60 mg QD start (n = 65).

Table VA. Changes in efficacy from baseline to the end of the first week of treatment. Values are mean (SE).*

Efficacy Measure	Duloxetine 30 mg QD (n = 67)	Duloxetine 60 mg QD (n = 65)	*P*
$HAMD_{17}$ total score	–4.46 (0.59)	–5.33 (0.60)	0.287
$HAMD_{17}$ subscale scores			
Core	–1.98 (0.29)	–2.79 (0.29)	0.044
Maier	–2.56 (0.34)	–3.50 (0.34)	0.047
Anxiety	–1.25 (0.24)	–1.53 (0.24)	0.415
Retardation	–1.51 (0.26)	–1.94 (0.26)	0.237
Sleep	–0.58 (0.19)	–0.83 (0.19)	0.342
HAMA score	–3.36 (0.59)	–4.78 (0.60)	0.085
CGI-S score	–0.45 (0.09)	–0.63 (0.10)	0.174

$HAMD_{17}$ = 17-item Hamilton Rating Scale for Depression[5]; HAMA = Hamilton Rating Scale for Anxiety[22]; CGI-S = Clinical Global Impression of Severity.[21]
*Mixed-effects model for repeated measures analysis.

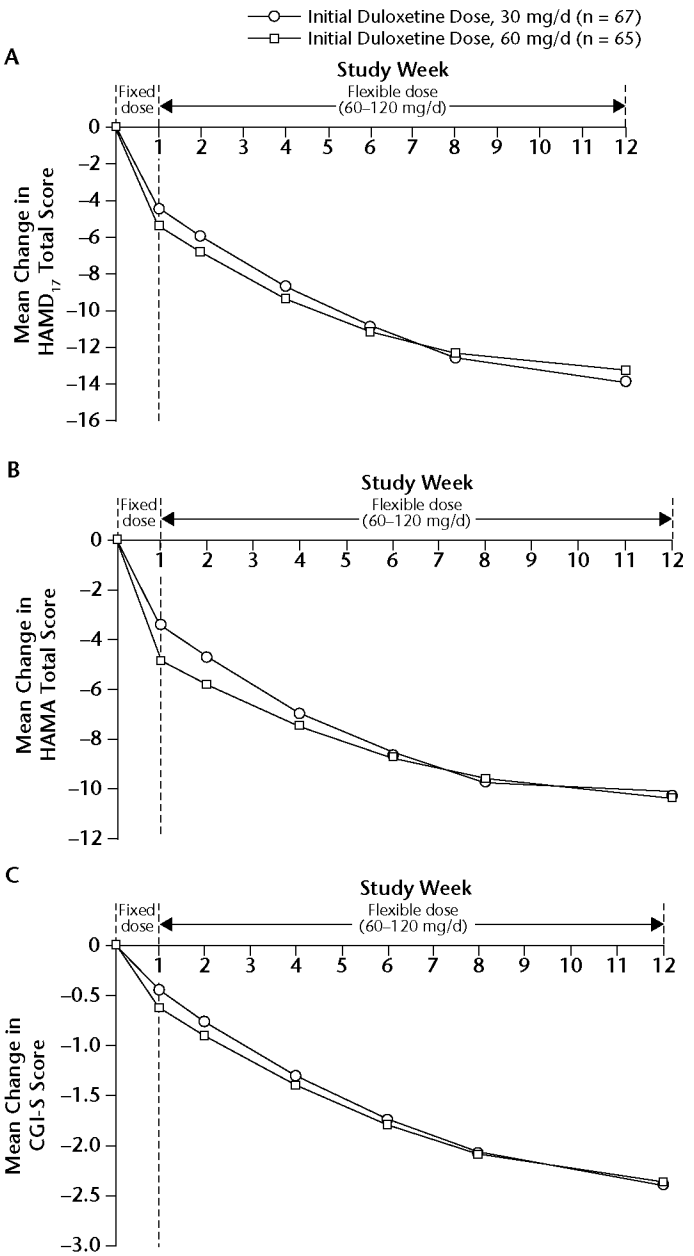

Figure 1. Mean changes in efficacy rating scale scores in patients initiating duloxetine treatment at 30 or 60 mg QD. (A) 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$)[5] total score; (B) Hamilton Rating Scale for Anxiety (HAMA)[22] total score; and (C) Clinical Global Impression of Severity (CGI-S)[21] score. There were no significant between-group differences.

Table VB. Changes in efficacy from baseline to the end of the study (week 12). Values are mean (SE).*

Efficacy Measure	Duloxetine 30 mg QD Start (n = 67)	Duloxetine 60 mg QD Start (n = 65)	*P*
$HAMD_{17}$ total score	–13.8 (0.9)	–13.3 (0.8)	0.648
$HAMD_{17}$ subscale scores			
Core	–6.64 (0.42)	–6.39 (0.39)	0.659
Maier	–7.92 (0.48)	–7.58 (0.45)	0.598
Anxiety	–4.14 (0.31)	–3.86 (0.28)	0.508
Retardation	–5.44 (0.36)	–5.07 (0.34)	0.450
Sleep	–1.98 (0.21)	–2.08 (0.20)	0.731
HAMA score	–10.2 (0.81)	–10.2 (0.75)	0.958
CGI-S score	–2.39 (0.17)	–2.37 (0.16)	0.942

$HAMD_{17}$ = 17-item Hamilton Rating Scale for Depression[5]; HAMA = Hamilton Rating Scale for Anxiety[22]; CGI-S = Clinical Global Impression of Severity.[21]
*Mixed-effects model for repeated measures analysis.

DISCUSSION

Two initial dosing regimens of duloxetine were compared in this open-label study: (1) a starting dose of 30 mg QD for 1 week followed by escalation to the therapeutic dose of 60 mg QD and (2) starting directly at 60 mg QD. The results suggest that a 30 mg QD starting dose of duloxetine during the initial week of treatment was associated with a significantly lower risk for nausea compared with a 60 mg QD starting dose. However, the magnitude of improvement in some measures of depressive symptoms during week 1 was significantly smaller in patients starting at 30 mg QD compared with those starting at 60 mg QD (core subscale, $P = 0.044$; Maier subscale, $P = 0.047$).

During the first week of treatment, a 30 mg QD dose of duloxetine produced a similar overall rate of treatment-emergent adverse events compared with a 60 mg dose (67.2% vs 75.7%). Furthermore, patients receiving 30 mg QD reported a significantly lower rate of nausea during the first week of treatment compared with patients receiving 60 mg QD (16.4% vs 32.9%; $P = 0.03$). However, certain other adverse events such as insomnia, diarrhea, and somnolence were reported at similar rates during the first week of treatment by patients receiving duloxetine 30 mg QD compared with the 60 mg dose. Thus, an initial week of duloxetine dosing at 30 mg QD appears to be associated with a significantly lower risk of nausea compared with a 60 mg starting dose. It should also be noted that the present study focused on patients who had washed out from their previous antidepressant medication and were not receiving treatment at the beginning of the study. The incidence and pattern of adverse events might differ in patients switching from another antidepressant to duloxetine.

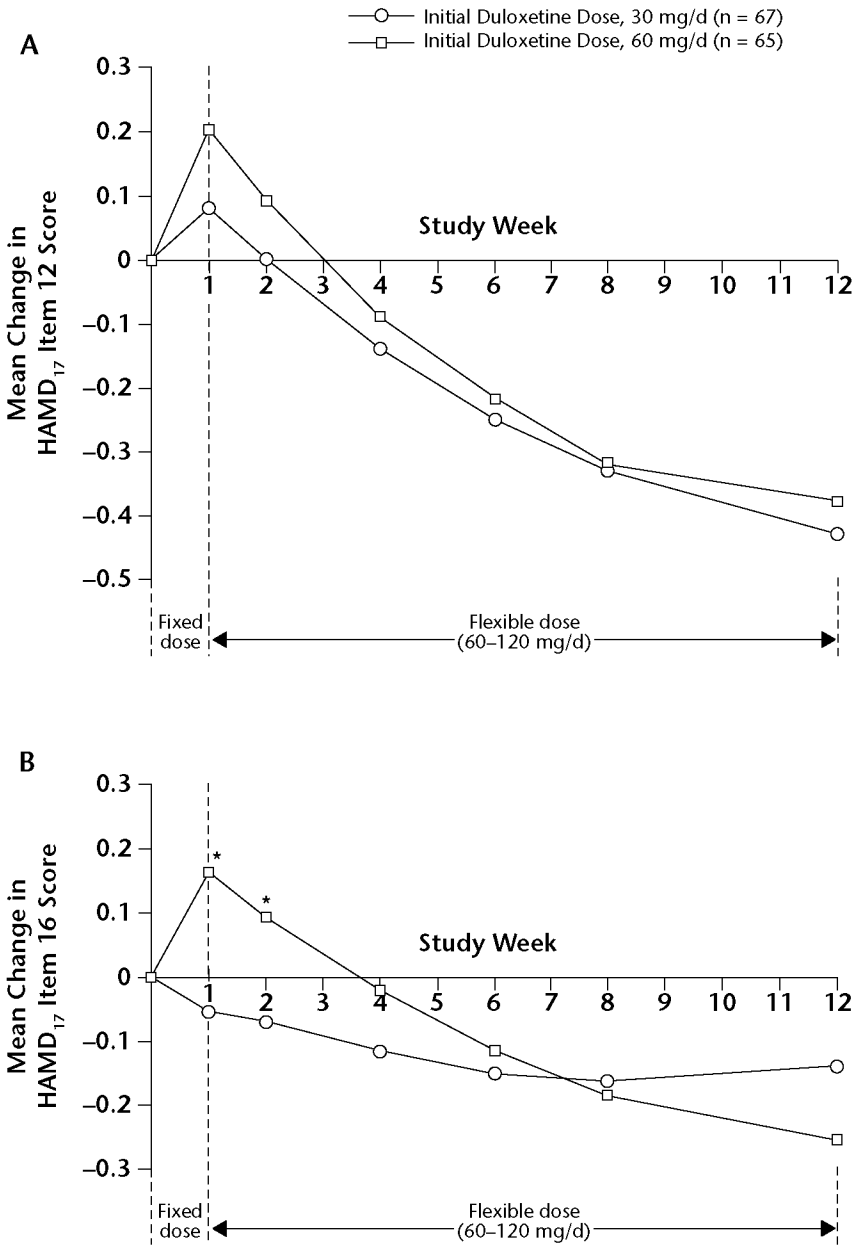

Figure 2. Mean changes in (A) 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$)[5] item 12 (somatic symptoms–gastrointestinal) and (B) $HAMD_{17}$[5] item 16 (loss of weight) scores in patients initiating duloxetine treatment at 30 mg QD or 60 mg QD. *$P < 0.01$ versus duloxetine 30 mg QD start.

Although the results of this study suggest that a 30 mg QD starting dose of duloxetine appears to reduce the risk for certain treatment-emergent adverse events, most notably nausea, this lower starting dose might only be required in some proportion of patients. In most patients, initiating duloxetine treatment directly at the therapeutic dose of 60 mg QD is well tolerated. In 2 placebo-controlled studies of duloxetine using a fixed dose of 60 mg QD, in which the protocol allowed a dose reduction to 40 mg QD during the first 3 weeks of the study, 11% of patients required a dose reduction for tolerability reasons.[10,11] Similarly, in the acute open-label phase of a relapse-prevention study, in which the protocol allowed a dose reduction from 60 to 30 mg QD during the first 4 weeks, 15% of patients required a dose reduction for tolerability reasons.[24] In a typical outpatient setting, physicians might exercise clinical judgment on a case-by-case basis to determine which patients could benefit from a lower starting dose.

Results from previous studies have shown that duloxetine doses could be escalated rapidly.[12] In a study of the tolerability and effectiveness of duloxetine at 120 mg/d (administered 60 mg BID), patients received duloxetine 20 mg BID for 3 days, followed by 3 days at 40 mg BID, and then the final dose of 60 mg BID.[12] In this study, the proportion of patients discontinuing treatment due to adverse events did not differ significantly between the duloxetine and placebo treatment groups (3.2% vs 3.2%). Results from the present study suggest that patients initiating duloxetine treatment at 30 mg QD did not experience a substantial incidence of new-onset adverse events on dose escalation to 60 mg QD at the end of week 1. For example, the incidence of nausea among patients starting at 30 mg QD was 16.4% in the first week, compared with 23.9% for the entire 12-week study period.

In the initial 2 to 4 weeks of treatment, the magnitude of depressive symptom improvement in patients starting duloxetine at 30 mg QD was similar to that observed in patients starting at 60 mg QD; between-group difference in $HAMD_{17}$ total score, HAMA total score, or CGI-S score was not statistically significant. After 1 week of treatment, the mean change in $HAMD_{17}$ total score in patients receiving duloxetine 30 mg QD was 83.7% of that observed in patients receiving 60 mg QD. Similarly, mean changes at week 1 in HAMA total score and CGI-S score among patients receiving 30 mg QD were 70.3% and 71.4%, respectively, of those observed in patients receiving duloxetine 60 mg QD. On measures of core emotional symptoms ($HAMD_{17}$ core and Maier subscales) patients starting at 30 mg QD experienced significantly less improvement at week 1 compared with patients starting at 60 mg QD ($P < 0.05$). However, following the dose escalation from 30 to 60 mg QD at the end of week 1, the lag in effectiveness began to diminish. After 4 weeks of treatment, mean changes in patients who started duloxetine treatment at 30 mg QD were similar to those observed in patients who had started at 60 mg QD. Thus, the results of this study suggest that the reduction in efficacy associated with an initial week of 30 mg duloxetine dosing appeared to be transitory and was no longer evident within 3 weeks of a dose escalation to 60 mg QD.

Mean changes in weight and vital signs were generally similar in the 2 treatment groups. The only significant between-group difference occurred in the comparison of mean changes in supine heart rate from baseline to end point. Patients starting duloxetine at 30 mg QD had a significantly greater increase in supine heart rate compared with those starting at 60 mg QD (4.5 bpm vs 1.1 bpm, respectively; $P = 0.01$). The magnitude of increase in heart rate observed in patients starting treatment at 30 mg QD is not consistent with observations from previous studies. Analyses of pooled safety data from several placebo-controlled studies have revealed increases in supine heart rate among duloxetine-treated patients of <2 bpm at doses up to 120 mg/d.[16] Given the atypical nature of the present result, and the fact that the observed increase was <5 bpm, it is not considered to be a clinically relevant finding.

The incidences of abnormal increases or decreases in weight and vital signs were also similar between patients receiving 30 or 60 mg starting doses. However, during the 12-week study period, the incidence of abnormal high supine systolic BP was significantly higher in patients receiving a 60 mg QD starting dose compared with those receiving a 30 mg QD starting dose ($P = 0.05$). Furthermore, 2 patients in the 60 mg QD starting group met criteria for sustained hypertension, compared with none in the 30 mg QD group. Although these results appear to suggest a dose response effect, it should be noted that after week 1, all patients could have their duloxetine dose titrated in a range from 60 to 120 mg QD. In addition, the lack of a placebo arm makes interpretation of these results difficult. In an analysis of pooled data from placebo-controlled studies, the incidence of sustained hypertension among duloxetine-treated patients (40–120 mg/d) did not differ significantly from the rate in the placebo group.[16]

A number of limitations of the current study should be noted. First, this was an open-label study. In the absence of a placebo group, interpretation of results should be approached with a degree of caution.[25] For this reason, the discussion of effectiveness has been limited to a comparison of the magnitude of improvement in each treatment group. Furthermore, the open-label nature of the study could also influence the rates of reporting of adverse events. Second, the study design allowed flexible dosing of duloxetine after the first week of treatment (in a range of 60–120 mg/d), and thus the 2 study groups were not receiving identical treatment after week 1. However, a flexible dosing regimen might provide a more naturalistic setting in which to assess treatment effects, and provide a more accurate reflection of results typically encountered in day-to-day clinical practice. Furthermore, during the first week of treatment, which is perhaps the most important period with regard to treatment-emergent adverse events, each treatment group received a fixed dose of duloxetine (30 or 60 mg QD). Third, this study was powered to compare treatment outcomes in patients initiating duloxetine (pooled 30 and 60 mg starting groups) with those of patients switching from SSRI/venlafaxine to duloxetine (results from the switching group have been published elsewhere[18]). Thus, contrasts between

the 30 and 60 mg starting groups might have been underpowered, although these analyses were specified a priori in the protocol. Fourth, this was a 12-week study and therefore the results and conclusions are relevant only to the acute treatment of MDD. Finally, this is the first study to closely examine a QD duloxetine dose of 30 mg. Therefore, results from this open-label investigation should be considered preliminary. Additional double-blind studies, involving larger treatment arms, will be required to more fully validate our initial findings with regard to this dose.

CONCLUSIONS

The results from this open-label study in patients with MDD suggest that initiating duloxetine dosing at 30 mg QD for 1 week, followed by escalation to 60 mg QD, significantly reduced the risk for nausea, while producing only a transitory impact on effectiveness, compared with starting at 60 mg QD.

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