Efficacy and Safety of Duloxetine 60 mg and 120 mg Daily in Patients Hospitalized for Severe Depression: A Double-Blind Randomized Trial

Stephan Brecht, MD, PhD; Durisala Desaiah, PhD; Elisete S. Marechal, MS; Ambra M. Santini, BS; Jana Podhorna, MD, PhD; and Julien D. Guelfi, MD

Objective: To assess whether hospitalized patients with severe depression and potential suicidal ideation/behavior have earlier and better response to duloxetine 120 mg daily than 60 mg daily.

Method: Adults from 34 sites in 4 countries with severe major depressive disorder, defined by *DSM-IV* criteria, who were demonstrating Montgomery-Asberg Depression Rating Scale (MADRS) scores ≥ 30, 6-item Hamilton Depression Rating Scale (HDRS-6) scores ≥ 12, and Clinical Global Impressions-Severity of Illness scale (CGI-S) ≥ 4 and hospitalized ≥ 2 weeks underwent double-blind treatment with either duloxetine 60 mg (n = 167) or 120 mg (n = 171) daily for 8 weeks. Patients treated with 60 mg/d who did not respond had their doses titrated up to 120 mg/d. Primary outcome was the difference in baseline to week 4 change in MADRS scores between the groups. Secondary outcomes were baseline to week 8 changes in MADRS and HDRS-6 scores, response and remission, CGI-S scores, CGI-Improvement scores, Patient Global Impressions-Improvement, Hamilton Anxiety Rating Scale scores, and Reasons For Living inventory results. Safety was also assessed. The study was conducted between February 9, 2007, and August 26, 2008.

Results: There was no significant difference in mean baseline to week 4 MADRS score change between the 60-mg (−20.1) and 120-mg (−19.9) groups ($P = .88$). At week 4, 96/166 (60 mg) and 106/170 (120 mg) patients responded and maintained responses at week 8 by further decreasing mean MADRS scores to 5.8 (60 mg) and 5.6 (120 mg). At week 8, 226/336 (67.3%) patients achieved remission, with no difference demonstrated between groups. Most secondary efficacy measures were significantly reduced from baseline to week 8 within each group and did not differ between groups. Treatment-emergent adverse events observed with > 10% frequency in both groups were headache and nausea.

Conclusions: Duloxetine 60-mg and 120-mg doses were equally effective and demonstrated no significant differences in treating severe depressive symptoms in hospitalized patients. The safety and tolerability profile of duloxetine in both dosages did not differ and was similar to those reported in previous duloxetine studies.

Trial Registration: clinicaltrials.gov Identifier: NCT00422162

J Clin Psychiatry 2011;72(8):1086–1094

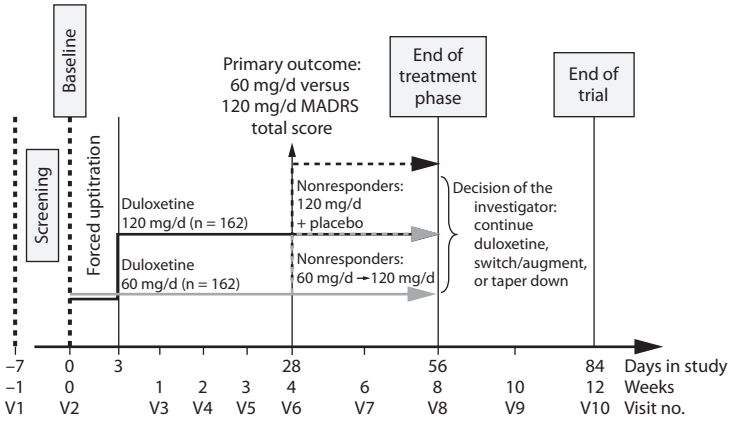
Submitted: *September 28, 2009; accepted January 28, 2010.*
Online ahead of print: *September 21, 2010 (doi:10.4088/JCP.09m05723blu).*
Corresponding author: *Stephan Brecht, MD, PhD, CDep Medical Affairs, Boehringer Ingelheim GmbH, 55216 Ingelheim am Rhein, Ingelheim, Germany (stephan.brecht@boehringer-ingelheim.com).*

Major depressive disorder (MDD) is a highly prevalent, disabling, chronic, and recurrent disorder often associated with significant morbidity and mortality.[1] Major depressive disorder is predicted to be the second leading cause of disability on the basis of disability-adjusted life-years.[2] In Western countries, the lifetime MDD prevalence rate is estimated to be 17%.[1] The impact of MDD on general health is enormous because it contributes to the development of other chronic illnesses such as diabetes and heart diseases.[3] Disability due to MDD and its comorbid disorders increases health resource utilization and cost to both society and patients.[4] Patients with severe illnesses due to MDD add an interesting dimension to the public health domain because these patients present complex symptoms including suicidal behavior[5,6] and increased risk of suicide.[7] Patients with severe depression with or without suicidal behavior who require hospitalization represent a critically ill population, and the treatment goal should be to achieve early response and remission for these patients.

The classification of MDD severity as mild, moderate, or severe is arbitrary because there are no universally accepted criteria.[8] However, the most common and widely used criteria for severe depression include the cut-off scores ≥ 25 on the Hamilton Depression Rating Scale (HDRS)[9] and ≥ 30 on the Montgomery-Asberg Depression Rating Scale (MADRS).[10] Severe depression is not a separate entity; epidemiologic, biologic, and clinical efficacy studies indicate that all levels of depression—mild, moderate, and severe—are part of the same disorder.[11]

A number of pharmacologic agents—including tricyclic antidepressants (TCAs),[12–15] selective serotonin reuptake inhibitors (SSRIs),[15,16] serotonin and norepinephrine reuptake inhibitors (SNRIs),[15–19] and other drugs[8]—have been studied for their efficacy in treating severe depression defined by hospitalization criteria. Literature reviews conducted on the efficacy of different classes of antidepressants showed that efficacy was similar across TCAs and SSRIs in treating severe depression.[20,21] Some reports show that venlafaxine, an SNRI, was superior to fluoxetine in reducing severe depression.[21–24] Although it is difficult to establish a dose relationship for antidepressants in the treatment of depression, it is clinically relevant to seek fast response with higher doses of antidepressants in patients with severe depression. It is important for both patients and society at large that, in treating patients with MDD, regardless of the disease severity, physicians have the objective of achieving remission. The risk of suicide has been shown to reduce significantly in patients diagnosed with

Figure 1. Study Design



Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

MDD achieving partial or full remission as compared with those patients who did not achieve remission.[25] Other than suicide reduction, the aspect of mental well-being has not been well studied in patients with severe depression.

Duloxetine, an SNRI approved for the treatment of MDD in more than 70 countries, has demonstrated efficacy in several clinical trials,[26–28] and the data confirming duloxetine efficacy have been reviewed.[29–32] However, these studies mostly excluded patients with severe depression leading to hospitalization and/or suicidal ideation/behavior. The meta-analysis of 4 similar studies showed that duloxetine was effective (in terms of remission and response rates) at a 60-mg once-daily dosage in the treatment of patients with MDD regardless of baseline disease severity.[19] So far, no data have shown whether a duloxetine dosage higher than 60 mg once daily results in a better outcome; such a finding would be helpful in the management of severe depression.

Patients with severe depression, hospitalized with or without suicidal behavior, are critically ill and require treatment to achieve fast response. To test this hypothesis, the present study was developed to treat hospitalized patients with severe depression using a higher starting dose of duloxetine (120 mg/d) compared with the approved therapeutic dose (60 mg/d). Further, this study tested the hypothesis that using a higher starting dose might improve severe depression over a shorter period of treatment—that is, within 4 weeks of treatment as compared with 8 weeks, which is the endpoint normally used in most acute depression trials.

METHOD

Study Design

This multicenter, randomized, double-blind, parallel-group trial was conducted at 34 investigational sites: 13 in France, 4 in Italy, 12 in Russia, and 5 in South Africa to assess the efficacy of duloxetine 60 mg/d (once daily) compared with 120 mg/d (60 mg twice daily, in the morning and evening) for 8 weeks in patients hospitalized for severe depression (clinicaltrials.gov Identifier: NCT00422162). The study was conducted between February 9, 2007, and August 26, 2008. The primary objective of this study was to test whether duloxetine 120 mg/d provides a better response to treatment than duloxetine 60 mg/d after 4 weeks in patients with severe MDD. The primary endpoint assessment was the difference in mean change in the MADRS total score from baseline to week 4 between the 2 treatment groups. Week 4 was chosen as the primary endpoint for the following reasons: (1) to assess whether the higher dose (120 mg/d) of the study drug would help patients faster and better than the usual 8 weeks of acute treatment using the therapeutic dose (60 mg/d) and (2) to provide an adequate length of time for the required 2-week hospitalization period to have some therapeutic effect on these patients. For ethical reasons, this study did not include a placebo group because the patients were severely depressed and had potential suicidal behavior. To assure blinding, assignment to treatment was determined by a computer-generated random sequence using an interactive voice response system (Fisher Clinical Services GmbH, Allschwil, Switzerland).

Each clinical study site's institutional review board approved the protocol, which was developed in accordance with the ethical standards of Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent before the commencement of any study procedures. Additional operational information about this study is disclosed under clinicaltrials.gov.

This clinical trial included 4 study periods (Figure 1). Study period I was a maximum 1-week screening phase during which patients were screened for entry eligibility and admitted to a hospital. Study period II started as treatment phase 1 from week 0 to week 4. At week 0, eligible patients were randomly assigned to 8 weeks of double-blind treatment with duloxetine 60 mg/d or duloxetine 120 mg/d in a 1:1 ratio. Randomization was stratified by country and pretreatment. Before switching to the study drug, the investigator ensured that the last dose of a patient's current antidepressant medication was taken 1 day prior to baseline. Study period III began after week 4 of treatment and ended at week 8. At week 4, nonresponders who were receiving duloxetine 60 mg daily had their doses uptitrated to receive an additional 60 mg daily in a blinded manner. Nonresponding patients who were receiving 120 mg daily were given an additional placebo dose to (1) maintain blinding of the initial treatment dose and (2) remain within the prescribing dose range described as being safe and effective in previous duloxetine studies. Responders were defined as those having a ≥ 50% improvement on MADRS total score and/or 6-item HDRS (HDRS-6) from baseline. Patients who completed the 8 weeks of therapy or who discontinued earlier had 3 options: at the investigator's discretion, patients could continue on duloxetine treatment, switch to any other antidepressant therapy, or, in rare cases, enter a 2-week taper-down phase (study period IV).

Patients: Inclusion and Exclusion Criteria

Male or female patients at least 18 years of age at screening who met the criteria for severe MDD, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*),[33] and had their diagnoses confirmed by the Mini-International Neuropsychiatric Interview,[34] a total score of ≥ 30 on the MADRS, a score of ≥ 12 on the HDRS-6,[35] and a score of ≥ 4 on the Clinical Global Impressions-Severity of Illness scale (CGI-S)[36] were included in this study. Eligible patients had to be willing to be hospitalized for at least 2 weeks from the baseline visit. Patients presenting with suicidal behavior at baseline were not excluded from this study. However, active suicidal behavior was not a mandatory inclusion criterion.

Patients were excluded if they met any of the following criteria: more than 2 previous episodes of MDD that did not respond to 2 or more adequate antidepressant therapies; symptoms of Axis I and II disorders other than anxiety disorder; any bipolar, schizophrenia, or obsessive-compulsive disorders; depression with psychotic features requiring neuroleptic treatment; *DSM-IV*–defined history of substance abuse; a history of seizure disorders; acute hepatitis or severe liver cirrhosis; at risk for narrow-angle glaucoma; end-stage renal disease or any other serious medical illnesses requiring medical intervention; abnormal thyroid-stimulating hormone levels; pregnancy in women; hypersensitivity to current or previous treatment with duloxetine at screening; treatment with any monoamine oxidase inhibitors during the 14 days before baseline screening; or treatment with fluoxetine during the 30 days before baseline screening.

Patients were generally not allowed to take any centrally acting drugs during the study. Episodic use of benzodiazepines or hypnotics was allowed. Investigators were given a list of allowed drugs during the treatment phase of this study; the daily dose of any given medication was not to exceed the stated maximum. Exceeding the daily allowed dose by a patient was rated as a protocol violation. Initiation of an individualized form of psychotherapy before or during the course of study drug treatment was not allowed. Pain medication with acetaminophen at a maximum dosage of 3 g/d was allowed for other medical conditions. At the discretion of the investigators, patients were allowed to take nonsteroidal anti-inflammatory drugs.

Efficacy Measures

Primary endpoint. The mean change from baseline to week 4 in MADRS total score was the primary endpoint of this study. The MADRS has been used extensively in clinical trials assessing antidepressants' efficacy; it comprises 10 items representing core depression symptoms, each scored 0 to 6 to constitute a maximum score of 60. Reduction in the total score is interpreted as improvement in depression.[10,37] To minimize interrater variability, investigators were trained in MADRS rating, and the same evaluator conducted the MADRS evaluations throughout the study.

Secondary endpoints. The secondary efficacy measures included mean changes in both MADRS total score and HDRS-6 total score from baseline to each visit during the study. The HDRS-6 is a 6-item rating instrument for assessing the core symptoms of depression[38] and has been shown to be more sensitive than the standard HDRS-17, a 17-item depression rating scale.[39]

Percentage of responders on MADRS or HDRS-6 total scores was evaluated, and responders were defined as patients with ≥ 50% improvement on the respective scales from baseline to each visit. Patients reaching remission were also assessed, remission being defined as reaching a total score ≤ 12 on MADRS.

Patients' perceived improvement as measured by the Patient Global Impressions-Improvement (PGI-I) scale[36] and the severity of illness as assessed by the CGI-S[36] were also included as secondary endpoints. Because anxiety symptoms usually accompany MDD, these symptoms were assessed using the Hamilton Anxiety Rating Scale (HARS).[36] Evaluations using the HARS were completed every 4 weeks.

The Reasons For Living (RFL) inventory[40] was used to assess patient reasons for not committing suicide. This instrument requires patients to rate how important each item would be for living if suicide were contemplated, using a 6-point rating scale in which 1 is "not at all important" and 6 is "extremely important." The full 48-item RFL inventory consists of the following domains: survival and coping beliefs, responsibility to family, children-related concerns, fear of suicide, fear of social disapproval, and moral objections. It was administered at baseline and endpoint, whereas the short 8-item RFL inventory, which considers coping beliefs only, was administered at all other visits.

Safety Measures

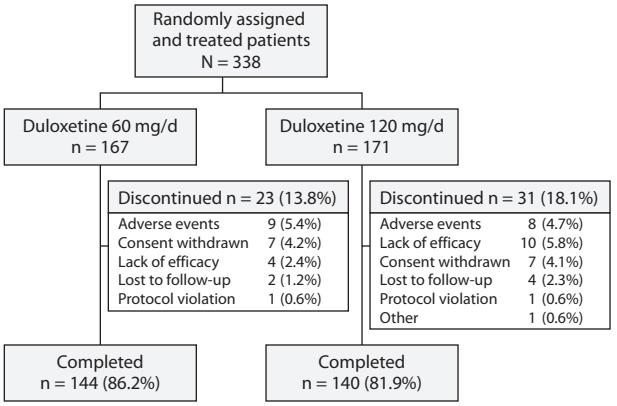
The safety and tolerability of duloxetine were assessed during the treatment phase and were based on discontinuation rates due to adverse events, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory analytes, weight, and vital signs.

Statistical Analyses

At week 4, the primary efficacy outcome and the other continuous endpoints were assessed by covariance analysis, with stratification factors (country and pretreatment) and baseline score as covariates. Least squares means were calculated to compare treatment means with 0 and with each other. The responder rate at week 4 was compared between treatment groups using a logistic regression model, with stratification factors (country and pretreatment) and baseline MADRS total score or HDRS-6 score as covariates. To evaluate the rescue option from week 4 to week 8, all endpoints were described according to 4 patient groups: 60-mg responders, 60-mg nonresponders, 120-mg responders, and 120-mg nonresponders. Within-group comparisons were performed using the signed rank test.

For other continuous variables, within-group comparisons were performed using a Student *t* test. For ordinal variables, treatment groups were compared using the Cochran-Mantel-Haenszel test with stratification by country. Within-group

Figure 2. CONSORT Diagram Showing the Patient Disposition



comparisons were performed for 60-mg responders and 60-mg nonresponders using the signed rank test.

Efficacy analyses were based on the full-analysis set (FAS) population (ie, patients who were randomly assigned to and received at least 1 dose of study medication and who had at least 1 baseline value and 1 postbaseline value), with data imputed using the last-observation-carried-forward (LOCF) method.

Safety was assessed by evaluating the percentage of patients withdrawn because of adverse events, the incidence and intensity of adverse events, laboratory assessments, vital signs, and weight. Safety analyses were based on the treated population (ie, patients who entered the treatment phase of the study and received at least 1 dose of duloxetine). No formal statistical testing was planned for the safety parameters; only descriptive analyses were intended.

A sample size of 162 randomly assigned eligible patients in each group was calculated to have 80% power to detect a difference in means of 2.5 (effect size = 0.313), assuming that the common standard deviation (SD) was 8.0, using a 2-group *t* test with a 2-sided α of .05. Assuming a dropout rate of 20%, it was determined that a total of 405 patients needed to be screened.

RESULTS

Patient Disposition

Most patients were from the Russian Federation (n = 165, 48.5%) and France (n = 128, 37.9%), followed by South Africa (n = 32, 9.2%) and Italy (n = 13, 3.8%). A total of 339 patients were randomly assigned (including 1 patient in the group assigned to duloxetine 120 mg not taking the study medication); hence 338 patients were randomly assigned and treated. The study groups comprised 167 patients treated with duloxetine 60 mg once daily (hereafter called the 60-mg group) and 171 treated with 60 mg twice daily (hereafter called the 120-mg group). Two patients were excluded from the FAS because of the lack of postbaseline efficacy data (1 per group of treatment): N = 336 in the FAS, including 166 patients in the 60-mg group and 170 patients in the 120-mg group. A total of 284 patients completed the study with 144 (86.2%) from the 60-mg group and 140 (81.9%) from the 120-mg group (Figure 2). A total of 54 (16.0%) patients discontinued the study, 23 (13.8%) in the duloxetine 60-mg group and 31 (18.1%) in the duloxetine 120-mg group; reasons for discontinuation included adverse events (5%), lack of efficacy (4.1%), and others reasons (6.8%). At week 4, the time for assessment of primary endpoint, 133 patients remained hospitalized. Mean hospital stay was 42 days for the 60-mg daily treatment arm and 41.8 days for the 120-mg daily treatment arm.

Table 1. Baseline Demographics and Clinical Characteristics in Treated Set Population

Variable	Duloxetine 60 mg/d (n = 167)	Duloxetine 120 mg/d (n = 171)
Age, mean (SD), y	45.7 (13.9)	43.9 (12.7)
Sex, n (%)		
Female	118 (70.7)	133 (77.8)
Male	49 (29.3)	38 (22.2)
Ethnicity, n (%)		
White	161 (96.4)	163 (95.3)
Other	6 (3.6)	8 (4.7)
Weight, mean (SD), kg	70.4 (16.7)	70.6 (15.2)
Body mass index, mean (SD), kg/m^2	25.2 (5.5)	25.5 (5.5)
Previous MDD episodes, n (%), yes	144 (86.2)	150 (87.7)
No. of previous episodes, mean (SD)	3.2 (2.7)	3.1 (3.0)
Duration of previous episodes, mean (SD), wk	16.4 (19.0)	13.7 (11.3)
No. of previous hospitalizations, mean (SD)	1.3 (1.6)	1.5 (2.3)
MADRS total score, mean (SD)	36.1 (4.0)	36.0 (4.6)
MADRS item 10 score ≥ 4, n (%)	32 (19.3)	29 (17.1)
HARS total score, mean (SD)	26.0 (6.4)	27.0 (7.0)
HDRS-6 total score, mean (SD)	15.4 (1.7)	15.4 (1.8)
RFL total score, mean (SD)	3.8 (1.1)	3.7 (1.0)

Abbreviations: HARS = Hamilton Anxiety Rating Scale, HDRS-6 = 6-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, RFL = Reasons For Living inventory.

Patient Baseline Demographics and Clinical Characteristics

Patients' baseline demographics and clinical characteristics are presented in Table 1. There were no differences between the 2 duloxetine treatment groups, and all the variables were well balanced. A majority of patients were white (95.9%) and female (74.3%), with a mean age of 44.8 years. The MADRS total score was 36, indicating severe depression in both treatment groups at baseline. At baseline, 32 (19.3%) patients in the duloxetine 60-mg group and 29 (17.1%) patients in the 120-mg group scored at baseline at least a 4 on the MADRS item 10, indicating common suicidal thoughts.

Efficacy Measures

Primary endpoint. The mean (SD) change in total MADRS score in the 60-mg group was −20.1 (10.6) compared with −19.9 (10.0) in the 120-mg group, and the difference between the 2 treatment groups was not significant ($P = .88$).

Secondary endpoints. MADRS total scores. Changes in mean total scores of MADRS from baseline to all visits up to week 8 (endpoint) in both the duloxetine 60-mg and 120-mg groups are presented in Figure 3A. A significant reduction in MADRS score was observed from baseline to endpoint

Figure 3. (A) Montgomery-Asberg Depression Rating Scale Total Score Over Time From Baseline to Endpoint in Duloxetine 60-mg/d and 120-mg/d Treatment Groups and (B) Montgomery-Asberg Depression Rating Scale Total Score From Baseline to Week 4 and in Responders and Nonresponders From Week 4 to Endpoint in 60-mg/d and 120-mg/d Treatment Groups (last observation carried forward, full-analysis set population)

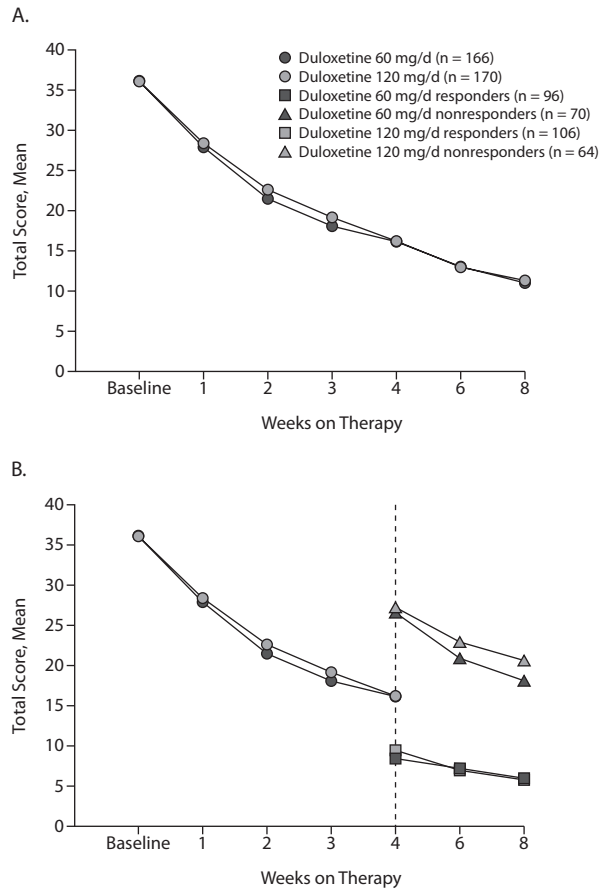
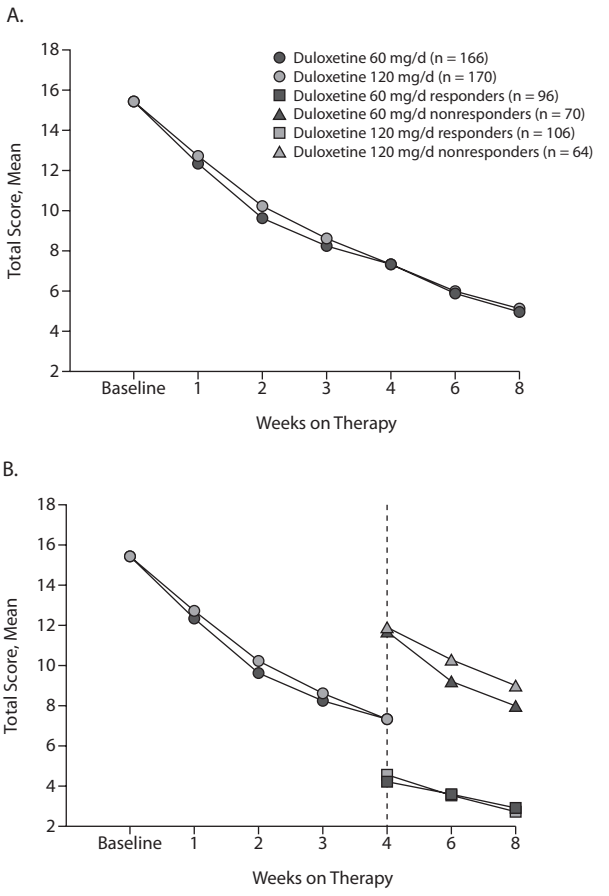


Figure 4. (A) 6-Item Hamilton Depression Rating Scale Total Score Over Time From Baseline to Endpoint in Duloxetine 60-mg/d and 120-mg/d Treatment Groups and (B) 6-Item Hamilton Depression Rating Scale Total Score From Baseline to Week 4 and in Responders and Nonresponders From Week 4 to Endpoint in 60-mg/d and 120-mg/d Treatment Groups (last observation carried forward, full-analysis set population)



(week 8) ($P \leq .0001$) for both treatment groups. However, the difference between the 2 treatment groups was not significant ($P = .88$).

Patients identified as responders and nonresponders per protocol at week 4 were uptitrated as described in the Method section. The results of this uptitration (rescue option) for MADRS total scores in both treatment groups are presented in Figure 3B. The data showed that the difference between the 2 treatment groups either from baseline to week 4 or in responders and nonresponders from week 4 to endpoint were comparable. However, the within-group changes from baseline to week 4 in both the 60-mg and 120-mg groups were significant ($P \leq .0001$), and the changes from week 4 to endpoint in both responders and nonresponders were also significant ($P \leq .0001$).

HDRS-6 scores. Changes in mean total scores of HDRS-6 from baseline to all visits up to week 8 (endpoint) in both the duloxetine 60-mg and 120-mg groups are presented in Figure 4A. A significant reduction in HDRS-6 score was observed from baseline to endpoint (week 8) ($P < .0001$). However, the difference between the 2 treatment groups was comparable at any time point.

The results of dose escalation (rescue option) on HDRS-6 total scores in both treatment groups are presented in Figure 4B. The data showed that the difference between the 2 treatment groups from baseline to week 4 and in responders and nonresponders from week 4 to endpoint were comparable. However, the within-group changes were significant ($P \leq .0001$) from baseline to week 4 in both the 60-mg and 120-mg groups as well as from week 4 to endpoint in both responders and nonresponders.

Responders. The percentage of responders in both responder and nonresponder groups classified by MADRS and HDRS-6 scale scores at week 8 are shown in Table 2. In both scales, the responder status at all time points was comparable between the 2 treatment groups. However, within both treatment groups, the percentage of responders increased with time.

Table 2. Overview of the Responders Defined as at Least 50% Reduction From Baseline (visit 2, week 0, LOCF, FAS population) and Remission[a]

	Duloxetine 60 mg/d (randomization: weeks 1–4), n = 166		Duloxetine 120 mg/d (randomization: weeks 1–4), n = 170	
Treatment Group, as Defined by the Investigator at Week 4	Responders[b] (n = 96)	Nonresponders[b] (n = 70)	Responders[b] (n = 106)	Nonresponders[b] (n = 64)
Patients who had ≥ 50% reduction in MADRS score at week 8 for each group, n (%)	90 (93.8)	46 (65.7)	104 (98.1)	35 (54.7)
Patients who had ≥ 50% reduction in HDRS-6 score at week 8 for each group, n (%)	89 (92.7)	42 (60.0)	101 (95.3)	30 (46.9)
Patients with remission,[c] MADRS, n (%)	85 (88.5)	29 (41.4)	94 (88.7)	18 (28.1)

[a]Logistic regression baseline versus week 4 (MADRS): treatment effect, $P = .32$; country effect, $P = .34$; pretreatment effect, $P = .06$; MADRS baseline effect, $P \leq .001$. Logistic regression baseline versus week 4 (HDRS-6): treatment effect, $P = .57$; country effect, $P = .66$; pretreatment effect, $P = .21$; MADRS baseline effect, $P = .06$. [b]Patients were assigned their responder status at week 4. [c]Major depressive disorder remission defined as a total MADRS score of ≤ 12 at endpoint (week 8).
Abbreviations: FAS = full-analysis set, HDRS-6 = 6-item Hamilton Depression Rating Scale, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 3. Secondary Efficacy Measures (LOCF, FAS population)

Measure	Duloxetine 60 mg/d (n = 166), Mean (SD)	Duloxetine 120 mg/d (n = 170), Mean (SD)
CGI-S score		
Week 0	5.0 (0.7)	5.1 (0.7)
Week 4	3.0 (1.4)	3.1 (1.3)
Week 8	2.3 (1.4)	2.4 (1.5)
CGI-I score		
Week 1	3.1 (0.8)	3.2 (0.8)
Week 4	2.3 (1.1)	2.1 (1.0)
Week 8	1.9 (1.2)	1.9 (1.1)
PGI-I score		
Week 1	3.0 (1.0)	3.1 (0.9)
Week 4	2.3 (1.2)	2.2 (1.2)
Week 8	2.0 (1.3)	1.9 (1.2)
HARS score		
Week 0	26.0 (6.4)	27.0 (7.0)
Week 4	13.0 (8.8)	13.4 (8.9)
Week 8	9.6 (8.8)	9.8 (9.2)

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, FAS = full-analysis set, HARS = Hamilton Anxiety Rating Scale, LOCF = last observation carried forward, PGI-I = Patient Global Impression-Improvement scale.

Remission. The MDD remission rates of patients in regard to responder status are shown in Table 2. At endpoint, the remission rates were comparable in both treatment groups.

Other secondary efficacy measures. All other efficacy measures are shown in Table 3, including CGI-S, CGI-I, PGI-I, and HARS scores at baseline, week 4, and week 8. In both treatment groups, the mean scores within each group decreased from baseline to endpoint, but the differences between the 2 treatment groups were comparable at any time point.

Reasons For Living (RFL) long- and short-version total scores. The RFL long-version and short-version total scores are presented in Table 4. The total scores of the long-version RFL increased from baseline to endpoint in both treatment groups regardless of responder status. The increases were statistically significant in the duloxetine 60-mg group from baseline to endpoint in responders ($P \leq .0001$) and nonresponders ($P = .001$) and also in 120-mg group responders ($P \leq .0001$) but not in 120-mg group nonresponders ($P = .28$).

Table 4. Mean Total Score of Long and Short Versions of RFL, FAS, and LOCF

	Duloxetine 60 mg/d (randomization: weeks 1–4), n = 166		Duloxetine 120 mg/d (randomization: weeks 1–4), n = 170	
Time Point	Responders[a] (n = 96)	Nonresponders[a] (n = 70)	Responders[a] (n = 106)	Nonresponders[a] (n = 64)
Long-version score, mean (SD)				
Week 0	4.0 (1.1)	3.6 (1.0)	3.7 (1.0)	3.7 (1.0)
Week 8	4.6 (0.9)	4.0 (1.2)	4.6 (0.9)	3.8 (1.1)
Short-version score, mean (SD)				
Week 0	3.9 (1.3)	3.6 (1.3)	3.7 (1.3)	3.5 (1.3)
Week 8	4.9 (1.1)	4.0 (1.3)	4.8 (1.1)	4.0 (1.3)

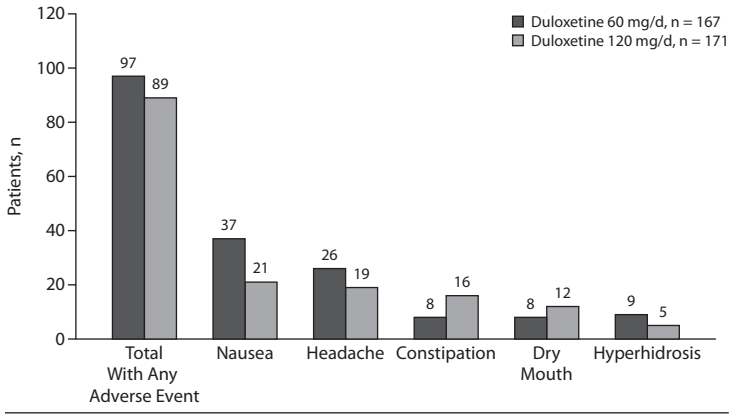
[a]Patients were assigned their responder statuses at week 4.
Abbreviations: FAS = full-analysis set, LOCF = last observation carried forward, RFL = Reasons For Living inventory.

However, the differences between the 2 treatment groups were not significant regardless of responder status. The total scores of short-version RFL increased from baseline to endpoint in both treatment groups regardless of responder status. The increases were significant in the duloxetine 60-mg group from baseline to endpoint in responders ($P \leq .0001$) and nonresponders ($P = .004$) and also in 120-mg group responders ($P \leq .0001$) and nonresponders ($P = .002$). However, the differences between the 2 treatment groups were not significant at any time point during the study regardless of responder status.

Safety Measures

Serious adverse events. No deaths occurred during the study. During the treatment period, 7 patients (4.2%) in the duloxetine 60-mg group and 6 patients (3.5%) in the duloxetine 120-mg group experienced SAEs. The SAEs included suicide attempt (n = 4; 2.4%), suicidal ideation (n = 3; 1.8%), self-injurious behavior (n = 1; 0.6%), irritability (n = 1; 0.6%), and back pain (n = 1; 0.6%) in the duloxetine 60-mg group. Serious adverse events occurring in the duloxetine 120-mg group included anxiety (n = 2; 1.2%), depression (n = 2; 1.2%), brain neoplasm (n = 1; 0.6%), and serotonin syndrome (n = 1; 0.6%). The SAEs considered study-drug–related were suicidal ideation and irritability in the 60-mg

Figure 5. Patients With Treatment-Related Adverse Events at ≥ 5% Incidence in Any Treatment Group in Treated Set Population



group, suicide attempt in the 120-mg group (following dose escalation in a patient originally randomly assigned to receive duloxetine 60 mg daily), and serotonin syndrome in the 120-mg group.

Discontinuations due to adverse events. Nine (5.5%) patients in the duloxetine 60-mg group and 8 (4.7%) patients in the duloxetine 120-mg group discontinued the study medication because of adverse events. Most common adverse events in the duloxetine 60-mg group that led to the discontinuation were suicide attempt (n = 3); suicidal ideation (n = 2); and hypothyroidism, depression, major depression, psychotic disorder, schizoaffective disorder, self-injurious behavior, headache, nausea, and irritability (n = 1 for each). Adverse events that led to treatment discontinuation in the duloxetine 120-mg dose group were depression (n = 2) and brain neoplasm, suicidal ideation, dizziness, sedation, serotonin syndrome, upper abdominal pain, drug eruption, renal failure, and urinary retention (n = 1 for each).

Treatment-emergent adverse events (TEAEs). During the treatment period, 97 (58.1%) patients in the duloxetine 60-mg group and 89 (52.0%) patients in the duloxetine 120-mg group experienced at least 1 TEAE (Figure 5). The most common TEAEs were nausea, headache, constipation, dry mouth, hyperhidrosis, and nasopharyngitis. Nausea occurred more often in the duloxetine 60-mg group (22.2% compared with 12.3% in the 120-mg group) for unknown reasons. The adverse event profile and frequency were no different between responders and nonresponders regardless of treatment doses. In 60-mg group nonresponders, the uptitration to 120 mg did not reintroduce the occurrence of TEAEs.

Vital signs. Systolic blood pressure increased from baseline to endpoint in 23 (13.8%) patients in the duloxetine 60-mg group and in 25 (14.6%) patients in the duloxetine 120-mg group. The diastolic blood pressure was increased in 28 (16.8%) patients in the duloxetine 60-mg group and in 37 (21.6%) patients in the duloxetine 120-mg group. A total of 24 (7.1%) patients experienced high pulse rate: 10 (6.0%) patients in the duloxetine 60-mg group and 14 (8.2%) patients in the duloxetine 120-mg group. None of the changes in vital signs were different between the 2 treatment groups.

Laboratory analytes. The incidence of potentially clinically important abnormalities was comparable for the 2 duloxetine treatment groups. A very small number of patients in both treatment groups showed an increase or decrease in their laboratory analytes, and the changes were not clinically meaningful.

DISCUSSION

This study demonstrated for the first time duloxetine's efficacy, safety, and tolerability in hospitalized patients diagnosed with *DSM-IV* severe depression with or without suicidal behavior. Although the primary endpoint was not met, duloxetine at doses 60 mg/d and 120 mg/d was effective in the improvement of overall depression symptoms in this patient population. However, the improvement was similar in both treatment groups in primary and secondary endpoints.

A large number of patients completed the study, including 86.2% in the duloxetine 60-mg group and 81.9% of patients in the 120-mg group, suggesting that high completion rates may be the result of controlled clinical care in the hospital setting for at least 2 weeks or the lack of a placebo treatment group. Similar or slightly lower completion rates were observed in hospitalized patients with severe depression treated with other SNRIs.[17,18]

Severe depression is not considered a different disease entity, rather it is a continuum of moderate depression. Patients respond often to most antidepressants, including duloxetine. However, evaluating antidepressant response at different levels of severity requires a clear definition of the severity of the disease. Severe depression has been defined in patients with an HDRS score of 25 or greater and a MADRS score of 30 or greater.[8] The patients in this study fit into this classification because their baseline scores were more than 30 on MADRS and more than 12 on HDRS-6; they responded similarly at all time points to both doses of duloxetine, 60 mg once daily and 120 mg once daily. These data support earlier observation, in a pooled analysis, demonstrating that duloxetine at a 60-mg once daily dose significantly improved core MDD symptoms, regardless of disease severity at baseline.[11] However, earlier studies reported that there were differences in efficacy between classes of antidepressants. For example, the Danish University Antidepressant Group[41] reported that TCAs were superior to SSRIs in the improvement of symptoms in severe depression. The design flaws in that study[41] included a relatively low baseline severity score of HDRS ≥ 18 as compared with HDRS ≥ 25 required for the definition of severe depression.[8] The SNRIs are superior to SSRIs in the treatment of severe depression,[17,22] although in meta-analysis studies in patients with higher baseline HDRS scores, TCAs were not demonstrated to be more efficacious than SSRIs.[42] These reports suggest that the improvement of symptoms

in severe depression is independent of the class of antidepressant. These inconsistent findings justify a study design comparing 2 dosages of the same antidepressant in patients with severe depression needing urgent treatment.

The increase in dose of an antidepressant is often associated with symptom improvement,[43] and for individual antidepressants, trends of dose-response have been suggested with few studies showing per-protocol superiority between 2 active doses of the same antidepressant.[44,45] The purpose of the current study was to test the hypothesis that duloxetine 120 mg/d would provide better and earlier symptom improvement in severe depression than the 60 mg/d dosage. The data did not support the hypothesis, but both dosages of duloxetine (60 mg/d or 120 mg/d) showed profound efficacy on many depression endpoints as early as 4 weeks into treatment. These findings are in line with other studies showing improvement in depression symptoms, regardless of disease severity. Robust dose-response profile was not evident for a number of antidepressants, including TCAs,[46] SSRIs,[31,47] and SNRIs.[48] Effect sizes of previous duloxetine studies suggest that HDRS-6 may be more sensitive than HDRS-17 in detecting treatment differences; therefore, we used the HDRS-6 scale in the present study to observe a possible increase in treatment effect with the 120-mg duloxetine dosage.[43] Because of the expected difficulty of showing the efficacy differences of 2 doses of the same antidepressant, MADRS and HDRS-6 were used as 2 sensitive assessment scales for severe depression in the current study.

To investigate the relation between suicidal ideation and mental well-being in patients with severe depression, the RFL inventory was included in this study. In general, patients with severe depression were able to fill out a 48-item questionnaire about suicide-related questions. As did the PGI-I scores, the RFL scores improved during the course of the study. The RFL scores showed better improvement in responders, but also improved somewhat in nonresponders. Secondly, the improvement in the RFL short-form score was larger compared with the RFL long-form score, suggesting that the "coping beliefs" domain might be more dynamic in the short form than in the long form, which includes all RFL domains. The association of baseline suicidal thinking, depression response, anxiety in depression, and patient-rated improvement by the PGI-I and RFL warrants additional analyses. To our knowledge, this is the first time that the RFL inventory has been used to describe mental well-being in a severe depression treatment study.

The safety profile of duloxetine at both doses in this patient population with severe depression and hospitalization is not different from the safety profiles demonstrated in other duloxetine studies. No deaths were reported in this study, and 7 patients in the duloxetine 60-mg group and 6 patients in 120-mg group experienced SAEs. Among these SAEs, 3 of the 7 suicidal events that occurred in the 60-mg group were considered by the investigator to be drug-related; no suicidal events occurred in the 120-mg group. In previous clinical trials, drug-related suicidal events were uncommon during acute therapy (8 weeks) with duloxetine; however, patients at suicidal risk were not excluded per protocol. In this study, some suicide-related SAEs were observed, and it may be because the included patients were severely depressed and had suicidal thoughts at baseline (n = 32, 19.3% of patients in the 60-mg group and n = 29, 17.0% of patients in the 120-mg group had ≥ 4 score on MADRS item 10, suicidal thoughts). In a long-term study of 52-week treatment with duloxetine, 7 patients reported suicidal events but none committed suicide.[49]

The most common (≥ 5% incidence) TEAEs were nausea, headache, dry mouth, constipation, and hyperhidrosis, and these events are in agreement with other duloxetine studies. Similarly, the discontinuation rates, vital signs, and laboratory values reported in this study are consistent with previous findings. The adverse event profile and frequency of adverse events were very similar in responders and nonresponders. In addition, dose-uptitration to 120 mg/d in patients who did not respond to 60 mg/d at week 4 did not result in re-emerging TEAEs, emphasizing that the 120 mg/d dose is effective and safe as per the European Summary of Product Characteristics.[29,31,50]

Although this study had a major strength in the inclusion of a unique population with severe depression with or without suicidal thoughts, the study lacks a placebo or active comparator arm, thus limiting our comparisons of efficacy of duloxetine. However, use of placebo in these seriously ill patients is not ethical, and use of a comparator is not the question we wanted to answer. Overall, the data provide much-needed information on whether duloxetine is effective in the treatment of patients with severe depression. The study also provides evidence that duloxetine at the therapeutic dose (60 mg/d) is as effective as a 120 mg/d dose in the treatment of patients with severe depression.

In conclusion, duloxetine at both 60 mg/d and 120 mg/d doses was shown to be effective in the treatment of patients with severe MDD with safety and tolerability comparable with the profile observed in previous duloxetine trials.

Drug names: duloxetine (Cymbalta), fluoxetine (Prozac and others).
Author affiliations: Boehringer Ingelheim GmbH, Ingelheim, Germany (Dr Brecht); Eli Lilly, Indianapolis, Indiana (Dr Desaiah); Boehringer Ingelheim France, Paris (Ms Marechal); Boehringer Ingelheim Italy, Milan (Ms Santini); Boehringer Ingelheim GmbH, Biberach, Germany (Dr Podhorna); and Paris Descartes University, Sainte-Anne Hospital, Paris, France (Dr Guelfi).
Potential conflicts of interest: **Dr Guelfi** was the principal investigator on this study and received funding from Boehringer Ingelheim GmbH and Eli Lilly; is a consultant for Janssen-Cilag; has received honoraria from Janssen-Cilag and Boehringer Ingelheim; is a member of the speakers/advisory board for Janssen-Cilag; and has received other financial or material support from Elsevier Masson. **Drs Brecht** and **Podhorna** are employees of Boehringer Ingelheim GmbH, Germany. **Ms Marechal** is an employee of Boehringer Ingelheim, France. **Ms Santini** is an employee of Boehringer Ingelheim, Italy. **Dr Desaiah** is an employee of Eli Lilly and holds company stock.
Funding/support: This study was sponsored by Eli Lilly, Indianapolis, Indiana, and Boehringer Ingelheim GmbH, Ingelheim, Germany.
Previous presentation: The results of this study were presented as a poster at the Annual Conference of the European College of Neuropsychopharmacology; Istanbul, Turkey; September 12–16, 2009.
Acknowledgment: The authors wish to thank all the patients and investigators who participated in the study.

 © Copyright 2010 Physicians Postgraduate Press, Inc.

REFERENCES

1. Kessler RC, Berglund P, Demler O, et al; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003; 289(23):3095–3105.
2. Murray CJL, Lopez AD. *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020*. Cambridge, MA: Harvard University Press; 1996.
3. Beekman AT, Penninx BW, Deeg DJ, et al. The impact of depression on the well-being, disability and use of services in older adults: a longitudinal perspective. *Acta Psychiatr Scand*. 2002;105(1):20–27.
4. Herrman H, Patrick DL, Diehr P, et al. Longitudinal investigation of depression outcomes in primary care in six countries: the LIDO study. functional status, health service use and treatment of people with depressive symptoms. *Psychol Med*. 2002;32(5):889–902.
5. Blair-West GW, Cantor CH, Mellsop GW, et al. Lifetime suicide risk in major depression: sex and age determinants. *J Affect Disord*. 1999; 55(2–3):171–178.
6. Blair-West GW, Mellsop GW. Major depression: does a gender-based down-rating of suicide risk challenge its diagnostic validity? *Aust N Z J Psychiatry*. 2001;35(3):322–328.
7. Nierenberg AA. The treatment of severe depression: is there an efficacy gap between SSRI and TCA antidepressant generations? *J Clin Psychiatry*. 1994;55(suppl A):55–59, discussion 60–61, 98–100.
8. Montgomery SA, Kasper S. Severe depression and antidepressants: focus on a pooled analysis of placebo-controlled studies on agomelatine. *Int Clin Psychopharmacol*. 2007;22(5):283–291.
9. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
10. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
11. Montgomery SA, Lecrubier Y; European College of Neuropsychopharmacology. Is severe depression a separate indication? ECNP Consensus Meeting September 20, 1996, Amsterdam. *Eur Neuropsychopharmacol*. 1999;9(3):259–264.
12. Bremner JD. A double-blind comparison of Org 3770, amitriptyline, and placebo in major depression. *J Clin Psychiatry*. 1995;56(11):519–525.
13. Zivkov M, de Jongh GD. Org 3770 vs amitriptyline: a 6-week, randomized, double-blind multicentre trial in hospitalized depressed patients. *Hum Psychopharmacol*. 1995;10(3):173–180.
14. Mullin J, Lodge A, Bennie E, et al. A multicentre, double-blind, amitriptyline-controlled study of mirtazapine in patients with major depression. *J Psychopharmacol*. 1996;10(3):235–240.
15. Kasper S. Efficacy of antidepressants in the treatment of severe depression: the place of mirtazapine. *J Clin Psychopharmacol*. 1997; 17(suppl 1):19S–28S.
16. Kasper S, Zivkov M, Roes KC, et al. Pharmacological treatment of severely depressed patients: a meta-analysis comparing efficacy of mirtazapine and amitriptyline. *Eur Neuropsychopharmacol*. 1997;7(2):115–124.
17. Guelfi JD, White C, Hackett D, et al. Effectiveness of venlafaxine in patients hospitalized for major depression and melancholia. *J Clin Psychiatry*. 1995;56(10):450–458.
18. Guelfi JD, Ansseau M, Timmerman L, et al; Mirtazapine-Venlafaxine Study Group. Mirtazapine versus venlafaxine in hospitalized severely depressed patients with melancholic features. *J Clin Psychopharmacol*. 2001;21(4):425–431.
19. Shelton RC, Prakash A, Mallinckrodt CH, et al. Patterns of depressive symptom response in duloxetine-treated outpatients with mild, moderate or more severe depression. *Int J Clin Pract*. 2007;61(8):1337–1348.
20. Pande AC, Sayler ME. Adverse events and treatment discontinuations in fluoxetine clinical trials. *Int Clin Psychopharmacol*. 1993;8(4):267–269.
21. Hirschfeld RM. Efficacy of SSRIs and newer antidepressants in severe depression: comparison with TCAs. *J Clin Psychiatry*. 1999;60(5):326–335.
22. Clerc GE, Ruimy P, Verdeau-Pallès J; The Venlafaxine French Inpatient Study Group. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. *Int Clin Psychopharmacol*. 1994;9(3):139–143.
23. Sonawalla SB, Fava M. Severe depression: is there a best approach? *CNS Drugs*. 2001;15(10):765–776.
24. Sokero TP, Melartin TK, Rytsälä HJ, et al. Prospective study of risk factors for attempted suicide among patients with DSM-IV major depressive disorder. *Br J Psychiatry*. 2005;186(4):314–318.
25. Thase ME. Treatment of severe depression. *J Clin Psychiatry*. 2000; 61(suppl 1):17–25.
26. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. *J Clin Psychiatry*. 2002;63(4):308–315.
27. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. *J Psychiatr Res*. 2002;36(6):383–390.
28. Goldstein DJ, Mallinckrodt C, Lu Y, et al. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *J Clin Psychiatry*. 2002;63(3):225–231.
29. Nemeroff CB, Schatzberg AF, Goldstein DJ, et al. Duloxetine for the treatment of major depressive disorder. *Psychopharmacol Bull*. 2002; 36(4):106–132.
30. Hirschfeld RM, Vornik LA. Newer antidepressants: review of efficacy and safety of escitalopram and duloxetine. *J Clin Psychiatry*. 2004; 65(suppl 4):46–52.
31. Hunziker ME, Suehs BT, Bettinger TL, et al. Duloxetine hydrochloride: a new dual-acting medication for the treatment of major depressive disorder. *Clin Ther*. 2005;27(8):1126–1143.
32. Girardi P, Pompili M, Innamorati M, et al. Duloxetine in acute major depression: review of comparisons to placebo and standard antidepressants using dissimilar methods. *Hum Psychopharmacol*. 2009;24(3):177–190.
33. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
34. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
35. Bech P, Allerup P, Gram LF, et al. The Hamilton depression scale. Evaluation of objectivity using logistic models. *Acta Psychiatr Scand*. 1981;63(3):290–299.
36. Guy W. *ECDEU Assessment Manual for Psychopharmacology, Revised*. Rockville, MD: National Institute of Mental Health; 1976.
37. Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the Montgomery-Asberg Depression Rating Scale corresponding to the definition of remission on the Hamilton Rating Scale for Depression. *J Psychiatr Res*. 2004;38(6):577–582.
38. Faries D, Herrera J, Rayamajhi J, et al. The responsiveness of the Hamilton Depression Rating Scale. *J Psychiatr Res*. 2000;34(1):3–10.
39. Bech P, Gram LF, Dein E, et al. Quantitative rating of depressive states. *Acta Psychiatr Scand*. 1975;51(3):161–170.
40. Bagby RM, Ryder AG, Schuller DR, et al. The Hamilton Depression Rating Scale: has the gold standard become a lead weight? *Am J Psychiatry*. 2004;161(12):2163–2177.
41. Danish University Antidepressant Group. Citalopram: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. *Psychopharmacology (Berl)*. 1986;90(1):131–138.
42. Anderson IM, Tomenson BM. The efficacy of selective serotonin re-uptake inhibitors in depression: a meta-analysis of studies against tricyclic antidepressants. *J Psychopharmacol*. 1994;8(4):238–249.
43. Bech P, Tanghøj P, Andersen HF, et al. Citalopram dose-response revisited using an alternative psychometric approach to evaluate clinical effects of four fixed citalopram doses compared to placebo in patients with major depression. *Psychopharmacology (Berl)*. 2002;163(1):20–25.
44. Mendels J, Johnston R, Mattes J, et al. Efficacy and safety of bid doses of venlafaxine in a dose-response study. *Psychopharmacol Bull*. 1993; 29(2):169–174.
45. Rudolph RL, Fabre LF, Feighner JP, et al. A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. *J Clin Psychiatry*. 1998;59(3):116–122.
46. Danish University Antidepressant Group (DUAG). Clomipramine dose-effect study in patients with depression: clinical end points and pharmacokinetics. *Clin Pharmacol Ther*. 1999;66(2):152–165.
47. Wernicke JF, Dunlop SR, Dornseif BE, et al. Fixed-dose fluoxetine therapy for depression. *Psychopharmacol Bull*. 1987;23(1):164–168.
48. Fabre LF, Abuzzahab FS, Amin M, et al. Sertraline safety and efficacy in major depression: a double-blind fixed-dose comparison with placebo. *Biol Psychiatry*. 1995;38(9):592–602.
49. Raskin J, Goldstein DJ, Mallinckrodt CH, et al. Duloxetine in the long-term treatment of major depressive disorder. *J Clin Psychiatry*. 2003; 64(10):1237–1244.
50. Brecht S, Courtecuisse C, Debieuvre C, et al. Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. *J Clin Psychiatry*. 2007;68(11):1707–1716.