A Randomized Controlled Trial of Duloxetine Versus Placebo in the Treatment of Nonmajor Chronic Depression

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ABSTRACT

Objective: Numerous double-blind studies have assessed the efficacy of antidepressants in treating chronic depressive disorder, including dysthymic disorder, low-grade chronic depression. However, there are no double-blind, placebo-controlled studies of serotonin-norepinephrine reuptake inhibitors in chronic depressive disorder.

Method: Outpatients with chronic depressive disorder, but without concurrent major depressive disorder (MDD), were randomly assigned to prospective double-blind duloxetine (beginning at 30 mg/d, increased to a maximum dose of 120 mg/d) versus placebo for 10 weeks. Inclusion criteria were current *DSM-IV-TR* diagnosis of dysthymic disorder or depression not otherwise specified, age 18–75 years, and a Hamilton Depression Rating Scale (HDRS) score ≥ 12. Exclusion criteria included current major depression. The study was conducted between August 2006 and December 2011. HDRS, Cornell Dysthymia Rating Scale (CDRS), Clinical Global Impressions (CGI), Beck Depression Inventory (BDI), Global Assessment of Functioning (GAF), Social Adjustment Scale (SAS), and other assessments were administered at each visit. We hypothesized that duloxetine would be superior to placebo in (1) 24-item HDRS total score, (2) the percentage of subjects classified as responders and remitters, and (3) secondary measures (CDRS, BDI, CGI). Response was defined as > 50% decrease in 24-item HDRS and CGI-Improvement scale score of 1 or 2 ("very much improved" or "much improved"). Remission was defined as HDRS-17 item score ≤ 4 and 0 on item 1 of the HDRS (depressed mood).

Results: 65 subjects were enrolled, of whom 57 began medication. They ranged in age from 19 to 70 years (mean ± SD = 41.63 ± 11.22) and included 24 women and 33 men. Baseline 24-item HDRS score (mean ± SD) for both groups was 20.75 ± 4.92. After 10 weeks, duloxetine-treated subjects had significantly lower 24-item HDRS scores than placebo-treated subjects (time-by-drug group effect on analysis of variance: $F_{1,55} = 9.43$, $P = .003$). Responder and remitter analyses significantly favored duloxetine treatment. The response rate was 65.5% for duloxetine versus 25.0% for placebo ($\chi^2_1 = 9.43$, $P = .003$); and the remitter rate was 55.2% for duloxetine versus 14.3% for placebo ($\chi^2_1 = 10.46$, $P = .002$). After 10 weeks, duloxetine-treated subjects did not differ significantly better from placebo-treated subjects on the SAS (time-by-drug group effect on analysis of variance: $F_{1,46} = 0.35$, $P = .555$) or on the GAF (time-by-drug group effect on analysis of variance: $F_{1,51} = .01$, $P = .922$).

Conclusions: Results on the 24-item HDRS, CGI, and CDRS suggest that duloxetine is efficacious in acute treatment of chronic nonmajor depressive disorder. Response and remission rates also differed significantly, favoring duloxetine treatment, but BDI, GAF, and social functioning (Social Adjustment Scale) did not. Duloxetine appears to be effective in acute treatment of nonmajor chronic depression.

Trial Registration: ClinicalTrials.gov identifier: NCT00360724

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Chronic depression is a common condition affecting 1.5% to 5% of the population and is associated with functional impairment, negative health outcomes, and high social costs.[1–9] It is heterogeneous in presentation, with a cross-sectional severity ranging from mild (dysthymic disorder) to severe (chronic major depression), along with intermediate forms (residual major depression, dysthymic disorder with intermittent major depressive episodes, etc). Nevertheless, studies[4,6] have generally demonstrated that outcome of chronic depression in the community is usually poor, regardless of specific *DSM-IV* classification of the subtype—although chronicity may not be specifically associated with differential medication treatment outcome,[10] and antidepressant medication trials in dysthymic disorder nearly always separate from placebo.[11] Hence, the criteria in the current draft of the *DSM-5* propose to unify these various subtypes into a single classification of chronic depressive disorder, which will include dysthymic disorder, chronic and residual major depressive disorder (MDD), depression not otherwise specified (NOS), and even chronic bipolar depression.[12]

It is important to find effective treatments for chronic depressive disorder, in order to relieve symptoms and to improve psychosocial and health outcomes. Yet chronic depression remains understudied. For example, in dysthymic disorder (chronic low-grade depression), the world literature contains approximately only 20 double-blind, placebo-controlled medication studies, comprising a sample size of less than 2,200 individuals.[13] In reviewing treatment of dysthymic disorder with tricyclic antidepressants, serotonin reuptake inhibitors, monoamine oxidase inhibitors, and other drugs (sulpiride, amineptine, and ritanserin), Cochrane reviewers concluded that drugs are effective, with no differences between and within drug classes, though tolerability of tricyclic antidepressants (TCAs) appears to be worse than other medication classes. The literature on other forms of chronic depression, such as chronic major depression, is similarly limited.[14,15] At this time, there are no medications with indication from the US Food and Drug Administration for treating chronic

depression. Some data[16] (but not all[17]) suggest that serotonin-norepinephrine reuptake inhibitor (SNRI) medications may lead to a better outcome than single-mechanism medications. While there are numerous trials of selective serotonin reuptake inhibitor (SSRI), TCA, and monoamine oxidase inhibitor medications, as well as open-label studies of the SNRIs venlafaxine[18,19] and duloxetine,[20] to our knowledge there are no prior double-blind, placebo-controlled studies of SNRI medications in nonmajor chronic depression. (Of note, there are studies of the tricyclic imipramine in both dysthymic disorder and chronic major depression[12,21–23]; however, although imipramine does block reuptake of both serotonin and norepinephrine, it usually is not included under the SNRI category, perhaps because it is not selective for these neurotransmitters but also because it has significant effects on blockade of muscarinic, α adrenergic, and H_1 histaminic receptors.)

We conducted a 10-week, double-blind, placebo-controlled study of duloxetine, a marketed SNRI,[24] in treatment of nonmajor chronic depression (individuals meeting criteria for dysthymic disorder or depression NOS, but without current major depression) at the Depression Evaluation Service of the New York State Psychiatric Institute. The initial double-blind phase was followed by a 12-week open-label treatment phase with duloxetine. We report the acute double-blind phase results in this article.

Hypotheses

We expected that duloxetine would be superior to placebo over a 10-week period in the following primary outcomes: (1) improving depression, measured by the 24-item Hamilton Depression Rating Scale (HDRS-24) item total score; and (2) the percentage of subjects classified as responders and remitters.

We also hypothesized that duloxetine would be superior to placebo on the following exploratory measures: (1) improving secondary measures of depression (Beck Depression Inventory [BDI], Cornell Dysthymia Rating Scale) and overall severity of illness (Clinical Global Impressions-Severity of illness [CGI-S]) and (2) improving psychosocial functioning (measured by the Social Adjustment Scale), global outcome (Global Assessment of Functioning [GAF]), and temperament (measured by the Temperament and Character Inventory).

METHOD

Study Procedures

The study received approval by the New York State Institute/Columbia University Department of Psychiatry Institutional Review Board (IRB). Subjects were recruited by advertisements, Web site postings, and from the hospital's telephone referral service. The study was conducted between August 2006 and December 2011 and was registered at ClinicalTrials.gov (identifier: NCT00360724). Potential participants provided informed consent for study participation, and Depression Evaluation Service clinicians obtained psychiatric and medical history and standardized assessments, including the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Nonpatient Edition (SCID-I/NP)[25] and the Hamilton Depression Rating Scale (HDRS).[26] A physical examination was performed, and blood and urine samples were collected, including urine toxicology.

Inclusion criteria allowed enrollment of male and female subjects aged 18–75 years who scored ≥ 12 on the HDRS-24 at baseline, had a current *DSM-IV-TR* diagnosis of dysthymic disorder or depression NOS; and were deemed likely to be compliant with study procedures.

Exclusion criteria included *DSM-IV* diagnosis of MDD in the past 3 months, bipolar disorder, schizophrenia or other psychotic disorders, dementia or other cognitive impairment, drug or alcohol abuse or dependence within the past 6 months, current psychoactive medication use (washout of antidepressants was required), serious risk for suicide during the course of the study, unstable medical conditions, current or planned pregnancy, current eating disorder, and lack of capacity to consent to study participation.

For patients taking current ineffective psychotropic medication, washout was required, with ≥ 7 medication-free days (≥ 28 days for fluoxetine). Concurrent sleep medication (zolpidem) was allowed for a maximum of 5 days during the study. Baseline randomization visit occurred 1 week after intake, with assignment to double-blinded treatment group based on a random number table. Further assessments occurred at weeks 1, 2, 4, 6, 8, and 10, at which time physicians administered clinical rating scales and patients completed self-rating forms. Self-rating forms included BDI,[27] Cornell Dysthymia Rating Scale,[28,29] Temperament and Character Inventory,[30,31] Medical Outcomes Trust Cognitive Scale,[32,33] Aldenkamp-Baker Neuropsychological Assessment Schedule,[34] Arizona Sexual Experience Scale (ASEX),[35] Brief Pain Inventory,[36] and Social Adjustment Scale.[37] Measures assessed depressive symptoms (BDI, HDRS, Cornell Dysthymia Rating Scale), general functioning (Social Adjustment Scale, GAF, Clinical Global Impressions [clinician and patient rated][38]), pain (Brief Pain Inventory [subscales for overall severity and pain-related impairment]), sexual functioning (ASEX), cognitive functioning (Medical Outcomes Trust Cognitive Scale), patient-perceived drug-related

Clinical Points

- Dysthymic disorder, a form of chronic nonmajor depression, responds to a variety of antidepressant medications.
- In this study, duloxetine, a serotonin-norepinephrine reuptake inhibitor medication, was more effective than placebo in primary outcome measures.
- Clinicians should assess patients for chronic depression and offer treatment options including medication and psychotherapy.

cognitive impairment (Aldenkamp-Baker Neuropsychological Assessment Schedule), and adverse events. As required by the New York State Psychiatric Institute IRB, verbal reconsenting of each participant was obtained at week 6 to confirm willingness to continue in double-blind treatment.

Drug Administration

Subjects were randomly assigned to double-blind treatment with duloxetine 30-mg capsules or matching placebo. Dosing began at 1 capsule every morning at randomization visit; dose could be increased after 1 week to 2 capsules every morning, then by 1 capsule every morning every 2 weeks to a maximum of 4 capsules every morning (120 mg of duloxetine) in the absence of sufficient response (ie, CGI-Improvement of Illness scale [CGI-I] score > 2) or significant adverse events.

Statistical Analyses

Summary statistics are presented as means and standard deviations for continuous variables and percentages for discrete variables. Student *t* tests and χ^2 tests were used to compare baseline demographic features, outcome measures, and tolerability measures, as well as response and remission status. Because this is a longitudinal study, our primary and secondary outcome measures were examined at different time points, so we used repeated-measures analysis of variance (ANOVA). Because of the small sample size, we compared only our results between week 0 (baseline) and week 10 (end of acute phase) for most of our outcome measures. Drug group was included as a covariate to test the significance of the interaction between time and treatment. In addition, we ran an analysis of covariance (ANCOVA), taking the baseline factors CGI-S, BDI, and GAF as covariates, to determine whether any of these had a significant effect on the primary outcome. The primary outcome measure of this study was HDRS-24 total score. In order to test the time-by-treatment group differences on the primary outcome, we conducted the generalized linear model, using SPSS 18.0 (IBM Corp, Somers, New York), with week 10 HDRS-24 score as the dependent variable and weekly HDRS-24 scores and treatment as the independent variables. Subjects were categorized as responders using the following criteria: a ≥ 50% drop in HDRS-24 score compared to baseline and a clinician-rated CGI-I score of 1 ("very much improved") or 2 ("much improved") at last study visit. Patients were categorized as remitters using a version of Thase's[21] criteria: 17-item (HDRS-17) score ≤ 4 and HDRS item 1 (depressed mood) score = 0. We did not conduct diagnostic interviews at week 10 and thus cannot include Thase's third criterion of not meeting diagnostic criteria for chronic depression. Frequency of side effects is also reported. All reported statistical tests are 2-tailed.

RESULTS

Sample

Sixty-five subjects were enrolled, of whom 60 received medication. Postrandomization data were available for 57 subjects who provided data after baseline visit. (Of the remaining 8 subjects, 4 did not appear for randomization visit; 1 was removed before starting medication because of abnormal liver function tests. After receiving medication, 2 subjects withdrew consent and 1 was administratively discharged for enrolling in multiple studies.) The 57-subject sample was 42.1% female, and mean ± SD age was 41.63 ± 11.22 years (range, 19–70). Most subjects were white (70.2%, 40/57). Nearly one-tenth (7.1%; 4/57) had high school education or less, and most had college (61.4%; 35/57) and/or graduate (31.6%; 18/57) education. Almost half of the subjects (40.4%; 23/57) were unemployed, 26.3% (15/57) were employed part-time, and 31.6% (18/57) were employed full-time. Most had single marital status (71.9%; 41/57) or were separated or divorced (5.3%; 3/57); only 22.9% (13/57) were currently married or cohabiting. About two-thirds of subjects (63.2%; 36/57) had early-onset dysthymic disorder, with mean ± SD age at onset of 19.93 ± 15.0 years (n = 52; 5 missing) and duration of current episode of 95.2 ± 199.9 months (n = 45; 12 missing). Nearly half of the subjects (47.4%; 27/57) had a current Axis I anxiety disorder, including generalized anxiety disorder (22.8%; 13/57) (if SCID-I/NP requirement of no concurrent mood disorder is ignored), social phobia (17.5%; 10/57), agoraphobia without panic (n = 3), and obsessive-compulsive disorder (n = 1). Prior alcohol abuse was present in 15.8% (9/57) and prior drug abuse in 10.5% (6/57) of the sample (though all subjects had negative drug urinalyses at intake). Five subjects had a history of eating disorders (binge-eating disorder, n = 3; bulimia, n = 2). Half of the subjects (50.9%; 29/57) reported no previous major depressive episodes, 21.1% (12/57) reported 1 prior major depression, and 28.0% (16/57) reported 2 or more prior episodes of major depression.

The mean ± SD duloxetine or placebo dose at week 10 was 3.2 ± 1.0 capsules/d (94.7 mg if taking duloxetine). At last study visit, 4 subjects were taking 1 capsule/d, 9 were taking 2 capsules/d, 18 were taking 3 capsules/d, and 26 were taking 4 capsules/d. Broken down by treatment group, the active medication group had a mean final dose of 88.97 (SD = 28.33) mg/d of duloxetine, with 2 subjects taking 30 mg/d, 7 taking 60 mg/d, 10 taking 90 mg/d, and 10 taking 120 mg/d. In the placebo group, the average final dose equivalence (30 mg/capsule) was 100.71 mg/d (SD = 27.34) of placebo. There was no association between treatment group and dose (n = 57; $\chi^2_3 = 4.4$, $P = .224$).

Baseline scores for both the placebo and active medication groups are presented in Table 1, with results of *t* tests to ascertain the comparability of the groups. At baseline, the placebo sample had significantly lower scores on the GAF and higher CGI-S measures than the duloxetine sample. For the other measures, no significant differences were seen at baseline.

Efficacy Analyses

Change on rating scales over time. Repeated-measures ANOVA were conducted for each outcome measure (HDRS, Cornell Dysthymia Rating Scale, BDI, GAF, CGI-S, and

Social Adjustment Scale) with randomization group (active drug or placebo) as the between-subjects factor and time (baseline and week 10 or last-observation-carried-forward [LOCF] ratings) as the within-subjects factor. All subjects who provided data after baseline (week 0) visit were included in LOCF analyses. Results of these ANOVAs are presented in Table 2. An ANCOVA taking baseline scores on CGI-S, BDI, and GAF as covariates showed no significant effect: CGI ($F = 1.16$, $P = .28$); BDI ($F = 1.21$, $P = .277$); and GAF ($F = 1.936$, $P = .171$). All measures of depressive symptoms and psychiatric functioning showed a significant main effect of time, indicating that, on average, both groups showed improvement over time, regardless of treatment group. On the HDRS-17 and HDRS-24, Cornell Dysthymia Rating Scale, CGI-S, and patient-rated CGI-I, greater improvement was seen over time in the active drug group than in the placebo group. No significant time-by-group differences were found on patient-rated measures of depressive symptomatology (BDI) and social functioning (Social Adjustment Scale) or on the clinician-rated GAF. Duloxetine-treated subjects' HDRS-24 scores separated significantly from placebo-treated subjects at week 8 and week 10 (Figure 1).

Table 1. Differences Between Duloxetine and Placebo Groups on Outcome Measures at Baseline

	Placebo			Duloxetine					
Measure	n	Mean	SD	n	Mean	SD	*t*	*df*	*P*[a]
Outcome measures									
HDRS-17	28	14.89	3.47	29	14.14	3.76	−0.79	55	.434
HDRS-24	28	21.39	5.09	29	20.14	4.33	−1.00	55	.320
CDRS	28	37.36	7.97	29	36.90	8.02	−0.22	55	.829
BDI	27	15.48	5.49	29	12.66	5.83	1.86	54	.068
GAF	28	58.25	6.96	29	62.62	5.83	2.57	55	**.013**
CGI-S	28	4.11	0.57	29	3.76	0.51	−2.44	55	**.018**
SAS	27	2.61	0.48	28	2.46	0.40	1.22	53	.228
TCI-harm avoidance	25	23.96	7.32	28	22.14	7.48	−0.892	51	.377
TCI-reward dependence	25	14.32	4.24	28	14.32	4.55	0.001	51	.999
TCI-novelty seeking	25	18.04	4.50	28	17.86	6.21	−0.121	51	.904
TCI-persistence	25	4.20	1.91	28	4.75	2.08	0.996	51	.324
BPI-severity	22	1.89	1.76	21	2.37	2.35	0.133	39	.719
BPI-interference with life	18	1.67	1.27	20	2.26	2.63	0.477	36	.496
Tolerability measures									
MOTCS	27	14.48	4.77	29	16.00	3.96	−1.30	54	.199
ASEX	27	12.63	4.82	29	11.55	3.54	0.96	54	.342
ABNAS	27	30.56	14.70	29	26.10	13.54	1.18	54	.615

[a]Bold values represent significance.
Abbreviations: ABNAS = Aldenkamp-Baker Neuropsychological Assessment Schedule, ASEX = Arizona Sexual Experience Scale, BDI = Beck Depression Inventory, BPI = Brief Pain Inventory, CDRS = Cornell Dysthymia Rating Scale, CGI-S = Clinical Global Impressions-Severity of illness scale, GAF = Global Assessment of Functioning, HDRS-17 = 17-item Hamilton Depression Rating Scale, HDRS-24 = 24-item Hamilton Depression Rating Scale, MOTCS = Medical Outcomes Trust Cognitive Scale, SAS = Social Adjustment Scale, TCI = Temperament and Character Inventory.

Treatment response and remission. Of 57 subjects in the intention-to-treat sample, the response rate was 65.5% (19/29) for duloxetine versus 25.0% (7/28) for placebo (n = 57; $\chi^2_1 = 9.43$, $P = .003$); and the remitter rate was 55.2% (16/29) for duloxetine versus 14.3% (4/28) for placebo (n = 57; $\chi^2_1 = 10.46$, $P = .002$) (Figure 2). Of those who responded to the active drug (n = 19), 1 was taking 30 mg, 4 were taking 60 mg, 8 were taking 90 mg, and 6 were taking 120 mg. Of those who responded to placebo (n = 7), 0 were taking 30 mg, 1 was taking 60 mg, 1 was taking 90 mg, and 5 were taking 120 mg. Of the nonresponders to placebo (n = 21), 2 were taking 30 mg, 1 was taking 60 mg, 7 were taking 90 mg, and 11 were taking 120 mg. Of the nonresponders to the active drug (n = 10), 1 was taking 30 mg, 3 were taking 60 mg, 2 were taking 90 mg, and 4 were taking 120 mg.

Social adjustment and global functioning. Social Adjustment Scale global scores were analyzed for duloxetine- and placebo-treated subjects by using ANOVA. At LOCF, both treatment groups showed improvement in Social Adjustment Scale, but there was no drug-by-time effect, indicating there was not greater improvement in social functioning at week 10 with duloxetine than placebo. Similarly, there was a time effect with improvement of GAF but no difference between treatment groups at 10 weeks.

Temperament. The Temperament and Character Inventory includes 4 factors for temperament: harm avoidance, novelty seeking, reward dependence, and persistence. At baseline, harm avoidance mean ± SD scores (22.14 ± 7.48 for duloxetine subjects; 23.96 ± 7.32 for placebo subjects) were approximately 2 standard deviations above community norms of 10.6 ± 6.0 for men and 12.9 ± 6.1 for women,[39] similar to our prior findings.[40] After 10 weeks of treatment, there were no significant changes by time or group-by-time in harm avoidance, novelty seeking, reward dependence, or persistence (see Table 2).

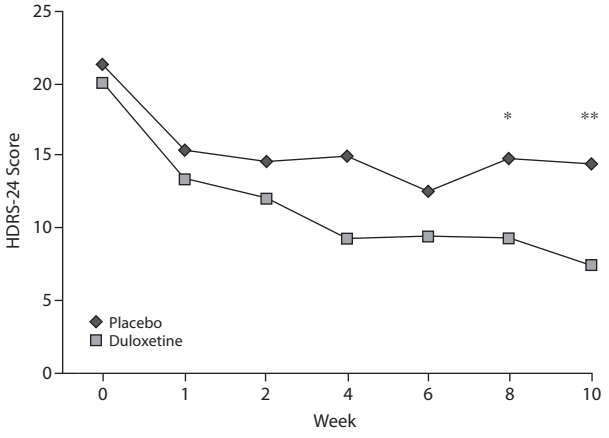
Tolerability. Tolerability was assessed by patient-rated scales (Medical Outcomes Trust Cognitive Scale, ASEX, Aldenkamp-Baker Neuropsychological Assessment Schedule) and by clinician-rated adverse events. There were no significant differences between placebo- and duloxetine-treated subjects on measures of cognitive functioning (Medical Outcomes Trust Cognitive Scale), sexual functioning (ASEX), or patient-perceived drug-related cognitive impairment (Aldenkamp-Baker Neuropsychological Assessment Schedule). Both placebo- and medication-treated subjects showed worsening in sexual functioning (ASEX) (Table 2), although there were no significant treatment-by-time effects. Clinician assessment of adverse events was collected using open-ended questions at each visit; each reported adverse event was assessed for duration and severity. Adverse events were reported by 86.0% of subjects (49/57). Twenty-two of 28 subjects (78.6%) on placebo reported adverse events, and 27 of 29 subjects (93.1%) on duloxetine reported adverse events. The mean number of adverse events for duloxetine subjects was 4.0 (SD = 2.3) and for placebo subjects was 2.7 (SD = 2.0), which are statistically different ($t_{53} = 2.214$, $P = .031$). The frequency of specific adverse events reported by subjects in the 2 groups is displayed in Table 3. The most common side effects in placebo-treated subjects were gastrointestinal upset (32.1%), fatigue (28.6%), and nausea

Table 2. Primary and Secondary Outcome Measures for Subjects With Dysthymic Disorder Receiving Duloxetine (n = 29) Versus Those Receiving Placebo (n = 28): Results of Repeated-Measures ANOVA Comparing Week 0 to Week 10/LOCF

	Week 0				Week 10/LOCF				ANOVA					
	Placebo		Duloxetine		Placebo		Duloxetine		Time			Time × Drug Group		
Measures	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	*F*	*df*	*P*[b]	*F*	*df*	*P*[b]
Outcome measures														
HDRS-17	14.89	3.47	14.14	3.76	10.00	5.52	5.00	3.58	23.09	1,55	< .001	8.85	1,55	**.004**
HDRS-24	21.39	5.09	20.14	4.33	14.82	7.92	7.83	5.17	24.30	1,55	< .001	9.43	1,55	**.003**
CDRS	37.36	7.97	36.90	8.02	28.50	14.57	19.07	9.45	17.50	1,51	< .001	8.72	1,51	**.005**
BDI	15.48	5.49	12.66	5.83	10.07	6.17	8.50	6.99	39.33	1,50	**<.001**	0.26	1,50	.616
GAF	58.25	6.96	62.62	5.83	65.74	13.99	69.85	20.93	5.33	1,51	**.025**	0.01	1,51	.922
CGI-S	4.11	0.57	3.76	0.51	3.21	0.83	2.31	0.93	27.10	1,55	< .001	5.51	1,55	**.023**
SAS	2.61	0.48	2.46	0.40	2.42	0.51	2.22	0.46	5.14	1,46	**.028**	0.35	1,46	.555
TCI-harm avoidance	23.96	7.32	22.14	7.48	22.83	6.31	18.88	7.54	2.79	1,42	.102	16.48	1,42	.190
TCI-reward dependence	14.32	4.24	14.32	4.55	15.58	4.18	13.88	4.25	2.47	1,42	.123	2.0	1,42	.326
TCI-novelty seeking	18.04	4.50	17.86	6.21	18.50	5.70	16.83	5.74	0.26	1,42	.611	0.15	1,42	.874
TCI-persistence	4.20	1.91	4.75	2.08	4.04	2.05	4.75	2.11	2.38	1,42	.128	0.84	1,42	.364
BPI-severity	1.89	1.76	2.37	2.35	2.24	1.79	1.42	2.42	0.13	1,26	.719	2.46	1,26	.131
BPI-interference with life	1.67	1.27	2.26	2.63	2.17	1.98	.95	1.85	0.48	1,25	.496	3.61	1,25	.069
CGI-I-PT	…	…	…	…	2.96	1.06	2.41	.80	…	…	…	2.183[a]	52	**.034**
Tolerability measures														
MOTCS	14.48	4.77	16.00	3.96	16.63	4.43	18.48	7.01	4.31	1,51	**.005**	.001	1,51	.973
ASEX	12.63	4.82	11.55	3.54	16.66	5.36	17.25	5.18	12.78	1,50	**.001**	.369	1,50	.546
ABNAS	30.56	14.70	26.10	13.54	23.74	14.27	17.35	15.04	11.07	1,50	**.002**	.049	1,50	.826

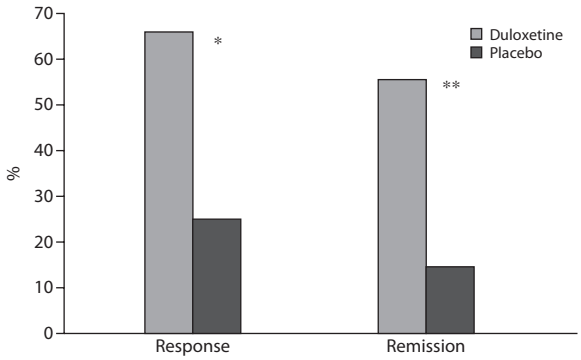
[a]Value is derived from *t* test.
[b]Bold values represent significance.
Abbreviations: ABNAS = Aldenkamp-Baker Neuropsychological Assessment Schedule; ANOVA = analysis of variance; ASEX = Arizona Sexual Experience Scale; BDI = Beck Depression Inventory; BPI = Brief Pain Inventory; CDRS = Cornell Dysthymia Rating Scale; CGI-S = Clinical Global Impressions-Severity of illness scale; CGI-I-PT = CGI-Improvement scale, patient rated; GAF = Global Assessment of Functioning; HDRS-17 = 17-item Hamilton Depression Rating Scale; HDRS-24=24-item Hamilton Depression Rating Scale; LOCF = last observation carried forward; MOTCS = Medical Outcomes Trust Cognitive Scale; SAS = Social Adjustment Scale; TCI = Temperament and Character Inventory.

Figure 1. Weekly HDRS-24 Scores for Duloxetine-Treated Versus Placebo-Treated Subjects



*P = .026; 95% CI, −7.160 to −0.492.
**P = .005; 95% CI, −7.82 to −1.540.
Abbreviation: HDRS-24 = 24-item Hamilton Depression Rating Scale.

Figure 2. Response and Remission Rates for Duloxetine-Treated Versus Placebo-Treated Subjects



*Duloxetine versus placebo (n = 57): $\chi^2_1 = 9.43$, $P = .003$.
**Duloxetine versus placebo (n = 57): $\chi^2_1 = 10.46$, $P = .002$.

(17.9%). The most common side effects in duloxetine-treated subjects were agitation and fatigue (each 31%); decreased appetite (27.6%); and vivid dreams, gastrointestinal upset, and headache (each 24.1%). Side effects were generally mild to moderate in severity.

DISCUSSION

Results of this double-blind study demonstrate significant differences between duloxetine and placebo after acute treatment of nonmajor chronic depression, with superiority of active medication on predefined major outcomes including HDRS-24 score (hypothesis 1) and on response and remission rates (hypothesis 2). Duloxetine-treated subjects showed better outcome on core depression symptoms (HDRS-17), with significant improvement over placebo appearing by week 8, and on severity of illness (CGI-S) and patient-rated improvement CGI-I. One secondary measure of depression (the clinician-rated Cornell Dysthymia Rating Scale) showed a significant difference from placebo, while another (the patient-rated BDI) did not. Contrary to expectations, secondary measures of social functioning (Social Adjustment Scale) and global outcome (GAF) did

Table 3. Adverse Events Observed in Duloxetine (n = 29) or Placebo (n = 28) Treatment

Adverse event	Duloxetine, n (%)	Placebo, n (%)
Agitation*	9 (31.0)	2 (7.1)
Fatigue	9 (31.0)	8 (28.6)
Decreased appetite	8 (27.6)	4 (14.3)
Gastrointestinal upset	7 (24.1)	9 (32.1)
Headache	7 (24.1)	3 (10.7)
Vivid dreams**	7 (24.1)	1 (3.6)
Decreased sleep	6 (20.7)	4 (14.3)
Nausea	6 (20.7)	5 (17.9)
Constipation	5 (17.2)	2 (7.1)
Dry mouth	5 (17.2)	1 (3.6)
Anxiety	3 (10.3)	2 (7.1)
Delayed orgasm	3 (10.3)	1 (3.6)
Rash	3 (10.3)	1 (3.6)
Dizziness	2 (6.9)	4 (14.3)
Sexual side effect (unspecified)	2 (6.9)	2 (7.1)
Decreased concentration	1 (3.4)	3 (10.7)
Decreased libido	1 (3.4)	3 (10.7)
Palpitations	1 (3.4)	3 (10.7)

*Duloxetine > placebo, $P = .041$.
**Duloxetine > placebo (trend), $P = .052$.

not show significant differences at week 10, and temperamental abnormalities (harm avoidance, reward dependence, and novelty seeking on the Temperament and Character Inventory) did not improve significantly. In contrast, other studies have shown improvement on the Social Adjustment Scale[7,41,42] and, in larger samples, on the harm avoidance factor of the Temperament and Character Inventory.[40] The BDI has historically less commonly been used as an outcome measure for pharmacotherapy studies, possibly because of a belief that it is less sensitive to change with medication treatment.

Duloxetine appears to be well tolerated and to have significant acute efficacy at week 10 by a variety of measures compared to placebo. Side effects were generally mild to moderate when reported on an open basis and rarely resulted in discontinuation. Rating scales (Medical Outcomes Trust Cognitive Scale, Aldenkamp-Baker Neuropsychological Assessment Schedule, ASEX) confirmed the tolerability of duloxetine in this patient population. Notably, sexual side effects on the ASEX were not significantly higher with duloxetine treatment compared to placebo. Worsening sexual complaints were found among placebo as well as duloxetine-treated subjects. Nelson et al,[43] studying MDD, found treatment-emergent sexual dysfunction among 28.8% of placebo-treated subjects compared to 46.4% of duloxetine-treated subjects. Baseline sexual dysfunction may result from depression or comorbid medical or psychiatric disorders, which may worsen over the course of placebo treatment; alternatively, placebo-treated patients may believe they are on active medication and may report sexual side effects known to be associated with antidepressants.

While duloxetine was significantly better than placebo in prospectively defined primary outcomes, the results of this study are somewhat mixed since some measures (social adjustment) and patient-rated depression (BDI) did not differ at 10 weeks, supporting the need for further studies including follow-up with continuation treatment. To our knowledge, this is the first reported double-blind trial for an SNRI medication in treatment of chronic nonmajor depressive disorder, which is in contrast to the numerous studies of other classes of medications such as SSRIs and TCAs. By the nosology proposed for *DSM-5*, participants of this study would be characterized as having chronic depressive disorder, unipolar, dysthymic type, without current MDD. While our study subjects did not meet criteria for current MDD (based on the number of current symptoms), many did have HDRS scores in the range seen in MDD (score > 20). The proposed *DSM-5* chronic depressive disorder diagnosis, by consolidating various forms of chronic depression, would potentially eliminate a number of somewhat arbitrary distinctions (for instance, the difficulty in determining whether a chronically depressed individual has 5 current *DSM-IV-TR* criterion A depressive symptoms and therefore meets criteria for "double depression" or whether the individual has only 4 current symptoms and meets criteria for "pure" dysthymic disorder). As noted above, the umbrella category of chronic depressive disorder (defined by chronicity rather than severity) is associated with significant psychosocial morbidity and costs, regardless of subtype or cross-sectional severity, as has been demonstrated both in clinical and epidemiologic samples.

Individuals presenting with sub-MDD severity often do not receive optimal pharmacologic management because, on a cross-sectional view, their disorder may appear to be deceptively mild. Klein et al[9] have described this as paradoxical since, by longitudinal evaluation, dysthymic disorder is a severe disorder. This is confirmed by the current sample, with average onset of illness at 19.3 years and current depressive episode averaging 10 years. Although 92% of study participants had college or graduate degrees, 66.7% were unemployed or working part-time. Similar to other chronic depression studies, most subjects (over 70%) had single marital status, suggesting impaired interpersonal relationships. Baseline scores on Social Adjustment Scale averaged 2.53 ± 0.44, nearly 3 standard deviations above the mean value found in Weissman and colleagues' community sample[44] (1.59 ± 0.33), with higher scores indicating greater impairment. Following medication (2.22 ± 0.46) or placebo (2.42 ± 0.51) treatment, scores remain elevated by approximately 2 standard deviations.

From a public health point of view, it is important to find effective and easily tolerated medication treatments that will alleviate depressive symptoms and improve psychosocial functioning. It is possible that social functioning might demonstrate improvement after a greater duration of treatment than just 10 weeks (as we can assess in our 22-week continuation data from the current study). If medication alone does not lead to significant improvement in psychosocial functioning, alternative approaches might include combined medication-psychotherapy strategies, which could include augmenting medication with psychotherapies such as forms of cognitive-behavioral therapy targeted for chronic depression,[45] interpersonal psychotherapy,[46] or behavioral activation therapy.[47]

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Study Limitations and Future Directions

Limitations of the current study include a relatively small sample size, which may have prevented finding significant differences in some outcome measures (factors of the Temperament and Character Inventory or on the Brief Pain Inventory). This limitation also prevented analyses for subgroups such as pure dysthymic disorder versus history of prior MDD, and early- versus late-onset depression. (Contrary to the above, it is worth noting that studies with larger sample sizes often find smaller effects than studies with smaller samples.) Our study's definition of remission[21] did not include a time component (eg, > 2 months), which would be required for a meaningful remission from the chronic symptoms of chronic depressive disorder. In our statistical analyses, we did not correct for multiple comparisons (eg, perform a Bonferroni correction) in this small study, which may increase the chance of type I errors for our exploratory analyses. The exclusion of patients deemed to be at acute suicide risk, as well as those with various medical and psychiatric comorbidities, might limit generalizability of these findings. Unlike most depression studies, the majority of our patients were male; the reasons for the higher proportion in this group are not clear, but the results may be limited in their applicability to women. Patient self-ratings did not always agree with doctor assessments (though patient-rated CGI did show significant improvement). It is possible that clinicians were biased by adverse events into thinking that subjects having adverse events were on active medication and therefore must be improved; alternatively, the patient-rated BDI may be less sensitive to real change with acute treatment than clinician ratings.

It is increasingly realized that chronicity of depression is a major factor in poor outcome, which is underlined by the *DSM-5* draft criteria for chronic depressive disorder.[10] Chronic depression, regardless of severity, presents significant risk factors for poor outcome over time. Therefore it is important to continue doing studies of both short-term and long-term treatment of chronic depressive disorder, in particular to find treatments that can induce long-term remission. Future directions in chronic depressive disorder psychopharmacology should include comparative and long-term studies, perhaps following the Sequenced Treatment Alternative to Relieve Depression design,[48] in which a large cohort of chronically depressed patients could be followed for an extended time and offered various treatments. These include the commonly used medication classes, such as SSRIs, SNRIs, bupropion, and other antidepressant agents, as well as psychotherapy, including medication switches, augmentation, and other strategies, to enhance response and remission and, particularly, to improve social functioning.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), imipramine (Tofranil and others), venlafaxine (Effexor and others), zolpidem (Ambien, Edluar, and others).

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