Duloxetine Treatment of Dysthymia and Double Depression: An Open-Label Trial

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Background: Although not as common as major depressive disorder, dysthymia is not rare and is associated with substantial impairment. Antidepressants and some psychotherapies are often effective. We explored the efficacy of the antidepressant duloxetine, a serotonin and norepinephrine reuptake inhibitor.

Method: Between February 2005 and April 2006, we recruited 24 adults with DSM-IV dysthymia or dysthymia and concurrent major depression ("double depression") who had an entry score of ≥ 17 on the clinician-rated Inventory for Depressive Symptomatology (IDS-C). We excluded subjects with significant medical illnesses and those requiring other psychotropic agents or undergoing psychotherapy. Subjects received duloxetine 60 mg/day for 6 weeks, increased as tolerated to 120 mg/day for the remainder of the 12-week trial for those with an inadequate treatment response.

Results: The subjects' mean ± SD IDS-C scores decreased significantly from baseline (27.3 ± 6.3) to endpoint (7.8 ± 7.4, Student $t = 12.38$, $df = 23$, $p \leq .001$). The IDS-C response rate (intent-to-treat [ITT]) was 83% (20/24); the remission rate (ITT) was 79% (19/24). Among study completers, these rates were 89% (17/19) and 84% (16/19). Five subjects (21%) discontinued for side effects.

Conclusion: Duloxetine appears to be an effective and well-tolerated treatment for dysthymia and double depression. A double-blind, placebo-controlled study is under way. If duloxetine is found to be effective, studies powered to detect potential, clinically important differences between duloxetine and other antidepressants will be needed.

Clinical Trials Registration: ClinicalTrials.gov identifier NCT00185575.

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Although not as common as major depression, dysthymia is not rare. In the Epidemiologic Catchment Area study, lifetime prevalence ranged from 1.3% to 2.3% in men and from 2.3% to 4.8% in women.[1] The subsequent National Comorbidity Study reported a higher lifetime prevalence of 6%.[2] Dysthymia is associated with lengthy periods of substantial psychosocial impairment.[3] A 10-year naturalistic follow-up study of 97 adults with early-onset dysthymia revealed that the median time to recovery was more than 4 years, and that 71.4% of those who recovered relapsed into another chronic depression.[4]

Despite its relatively high prevalence and associated psychosocial morbidity, dysthymia remains both underdiagnosed and undertreated.[5] This lack of attention is all the more regrettable in that many psychotherapeutic and pharmacotherapeutic treatments that are effective for major depression are also effective for dysthymia.[6]

Duloxetine is a dual serotonin-norepinephrine reuptake inhibitor approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depressive disorder.[7] In light of this, we conducted an open trial to explore the duloxetine's efficacy and tolerability in subjects with either dysthymia alone or dysthymia with concurrent major depressive disorder ("double depression").

METHOD

We conducted a 12-week open-label study of duloxetine in adult patients with DSM-IV dysthymia, as established by the Mini International Neuropsychiatric Interview (MINI),[8] or double depression (concurrent DSM-IV dysthymia and major depressive disorder). Subjects were

recruited between February 2005 and April 2006 by means of advertising and referrals from colleagues.

Eligible subjects were ≥ 18 years of age and had an entry score of ≥ 17 on the clinician-rated Inventory for Depressive Symptomatology (IDS-C).[9] After receiving an explanation of the study, all subjects signed an informed consent approved by our institutional review board. We excluded potential subjects with organic mental conditions; psychotic, factitious, somatoform, or dissociative disorders; obsessive-compulsive disorder; depressive disorders with current suicidal risk; substance or alcohol abuse within the past 3 months; or personality disorders sufficiently severe to interfere with cooperation with the study. We also excluded potential subjects with a history of bipolar disorder, significant current medical conditions, a history of treatment with duloxetine or of dysthymia unresponsive to an adequate antidepressant trial (≥ 8 weeks of bupropion ≥ 150 mg/day, citalopram ≥ 20 mg/day, escitalopram ≥ 15 mg/day, fluoxetine ≥ 40 mg/day, fluvoxamine ≥ 200 mg/day, mirtazapine ≥ 30 mg/day, paroxetine ≥ 40 mg/day, sertraline ≥ 100 mg/day, venlafaxine ≥ 75 mg/day), a history of major depression unresponsive to 2 or more adequate antidepressant trials (≥ 6 weeks at the doses given above), and those who were pregnant or breast-feeding. In subjects with comorbid conditions other than major depression, dysthymia had to be the primary focus, causing greater interference with functioning, greater distress, or the most motivation for seeking treatment.

Because duloxetine is a moderate inhibitor and a substrate of hepatic P450 enzyme 2D6,[10] we excluded individuals taking medications that may interact with duloxetine, as well as those who required any other psychotropic medication. We also excluded individuals engaged in psychotherapy aimed at their dysthymia and those who wished to begin psychotherapy within the study's 12-week duration.

Duloxetine was started at 60 mg/day, the minimum dose approved by the FDA for the treatment of major depressive disorder. The dose could be reduced temporarily to 30 mg/day for several days if necessitated by side effects, but it had to be increased subsequently to 60 mg/day by the end of week 1. Subjects unable to tolerate at least 60 mg/day were to be withdrawn from the study. Depending on response and tolerability, duloxetine could be increased to 120 mg/day at the end of week 6. Subjects continued on their maximum-tolerated dose.

The primary measure of drug effect was the change from baseline in the IDS-C score. The IDS-C is a reliable and valid measure of major depressive disorder and dysthymia that correlates highly with the 17-item Hamilton Rating Scale for Depression (HAM-D-17) and the Beck Depression Inventory.[9] Unlike these scales, the IDS-C gives each symptom equal weight.[9] In a psychometric study, the upper boundary of normal was an IDS-C score of 9, and depressed patients had a mean ± SD score of 36.5 ± 9.7.[9] In a second psychometric study, 14 dysthymia patients had a mean ± SD score of 21.6 ± 6.4.[11] Secondary outcome measures were scores on the Clinical Global Impressions-Improvement scale (CGI-I)[12] and the Patient Global Impressions-Improvement scale (PGI-I).[12] We defined response as a decrease in IDS-C score of ≥ 50% at final study visit (early withdrawal or end of week 12), and remission as a score ≤ 9 (analogous to a HAM-D score < 6).[13] We also report as secondary outcome measures responder and remitter rates recommended by a National Institute of Mental Health (NIMH) conference on the assessment of dysthymia[13]: *responders* defined as subjects with ≥ 2 consecutive weeks (endpoint rating) with a CGI-I score of 1 ("very much improved") or 2 ("much improved") and *remitters* defined as subjects with ≥ 3 consecutive weeks (end of weeks 10 and 12) with a CGI-I score of 1.

The IDS-C was administered at screening, baseline, and the end of weeks 1, 2, 3, 4, 6, 8, 10, and 12, or early termination. The CGI-I and PGI-I were administered at the end of week 1 and at each visit thereafter. Safety and tolerability measures recorded at each visit included the UKU Side Effects Scale,[14] spontaneously reported adverse events, and vital signs.

Statistical Methods

Data were analyzed with the last observation carried forward (LOCF), intent-to-treat (ITT) (all subjects given medication at baseline); completer analyses are reported where these seemed of interest. We tested the change in IDS-C from baseline to endpoint for statistical significance utilizing Student t test, 1-tailed, $p \leq .05$. We also compared the mean decrease in IDS-C from baseline to endpoint between subjects with dysthymia alone and those with double depression utilizing the Wilcoxon signed rank test, 2-tailed, with $p \leq .05$.

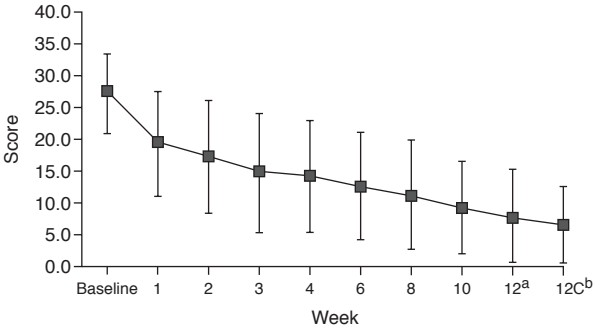
RESULTS

Of the 82 individuals who inquired about study participation, 25 (30%) did not return our calls, 8 (10%) did not have dysthymia, 3 (4%) did not wish to take medications, and 22 (24%) were ineligible (6 [7%] already responding to medication, 5 [6%] because of medical problems, 3 [4%] because of failed medication trials, 2 [2%] receiving psychotherapy, and 6 [7%] for miscellaneous reasons). We enrolled 24 subjects, 13 women (54%) and 11 men (46%), with a mean ± SD age of 47.3 ± 11.4 years (Table 1). In many cases, subjects had had only brief treatment trials or did not recall whether or to what degree treatment had been helpful. Thirteen subjects (54%) had a comorbid condition (Table 1), of whom 8 subjects had 1 comorbid condition and 3 had 2, 1 had 3, and 1 had 4 comorbid conditions.

Table 1. Baseline Characteristics of 24 Subjects With Dysthymia or Double Depression

Characteristic	Subjects, N (%)
Ethnicity	
White	17 (71)
African American	1 (4)
Hispanic	1 (4)
Asian/Pacific Islander	5 (21)
Marital status	
Single	9 (38)
Married	10 (42)
Divorced	4 (17)
Separated	1 (4)
Occupational status	
Employed, full-time	14 (58)
Employed, part-time	4 (17)
Student, full-time	2 (8)
Unemployed, seeking work	4 (17)
Prior treatment trials	
Medication for dysthymia	7 (29)
Medication for major depression	11 (46)
Psychotherapy for either disorder	15 (63)
Comorbid conditions	
Major depression	8 (33)
Generalized anxiety disorder	4 (17)
Social anxiety disorder	4 (17)
Agoraphobia	1 (4)
Panic disorder	1 (4)
Posttraumatic stress disorder	1 (4)
Bulimia	1 (4)
Trichotillomania	1 (4)

Figure 1. Mean IDS-C Scores by End of Study Week (LOCF) for 24 Subjects With Dysthymia or Double Depression



[a]Significance for the baseline to endpoint change in the ITT group is $p \leq .01$.
[b]12C = study completers (N = 19).
Abbreviations: IDS-C = clinician-rated Inventory for Depressive Symptomatology, ITT = intent to treat, LOCF = last observation carried forward.

Table 2. Duloxetine Side Effects Affecting at Least 10% of Subjects (N = 24)

Side Effect	Subjects Complaining, N (%)
Decreased appetite	10 (41.7)
Fatigue, lassitude	10 (41.7)
Insomnia	8 (33.3)
Nausea	8 (33.3)
Sexual side effects	8 (33.3)
Constipation	7 (29.2)
Increased sweating	7 (29.2)
Somnolence, drowsiness	7 (29.2)
Dizziness, light-headedness	5 (20.8)
Dry mouth	5 (20.8)
Headache	4 (16.7)
Diarrhea	3 (12.5)
Yawning	3 (12.5)

The subjects' mean ± SD IDS-C scores decreased significantly from baseline (27.3 ± 6.3) to endpoint (7.8 ± 7.4, Student t = 12.38, df = 23, $p \leq .001$) (Figure 1). The IDS-C response rate (ITT) was 83% (20/24); the remission rate (ITT) was 79% (19/24). Among study completers, the response rate was 89% (17/19) and the remission rate was 84% (16/19). When the NIMH panel's 3-week duration criterion[13] was added in defining IDS-C response and remission rates among study completers, these rates decreased to 79% (15/19) and 68% (13/19).

Of the subjects who took duloxetine 60 mg/day, 88% (14/16, ITT) were IDS-C responders and 81% (13/16) were remitters. Of the subjects who took 120 mg/day, the same 75% (6/8, ITT) were responders and remitters.

Percent decrease in IDS-C scores at endpoint (ITT) and week 12 (completers) did not differ significantly between subjects with dysthymia alone and those with double depression, although the double depression completer subjects experienced a smaller mean percent change (week 12 decrease = 76.1% ± 21.6% versus 59.8% ± 36.9%, Wilcoxon 2-sample test statistic = 84.00, Z = –0.95, p = .34). Consistent with this trend, among subjects completing at least 6 weeks of treatment, 93% (13/14) of those with dysthymia alone received an endpoint CGI-I rating of "very much improved" versus only 67% (4/6) of those with double depression.

The ITT (2-week) CGI-I response rate was 88% (21/24); the rate among study completers was 95% (18/19). The ITT (3-week) CGI-I remission rate was 79% (19/24); the rate among study completers was 63% (12/19). No patient rated as in CGI-I remission met criteria for dysthymia during the 3-week period included in the rating.

Subjects rated themselves as less improved than did clinicians. On PGI-I ratings, only 9 subjects (38%) rated themselves at endpoint as very much improved and only 8 (33%) as much improved.

Nineteen subjects (79%) completed the study and 5 (21%) discontinued: 1 for vomiting (week 1); 1 for panic symptoms, with a prior history of panic disorder (week 2); 1 for an unrelated rash (week 2); and 2 for sexual side effects (weeks 3 and 8). Otherwise, side effects were usually mild and occasionally moderate (Table 2). Nine subjects (38%) had side effects that persisted to week 12, but only fatigue (N = 3) and sexual side effects (N = 4) affected more than 2 subjects at this point. No subject experienced a clinically significant increase in resting heart rate or blood pressure.

DISCUSSION

This study is limited by its open-label design, the small sample size, the exclusion criteria, the lack of an active comparator, and the lack of a second scale (other than the PGI) to confirm the findings. The results, however, suggest the potential effectiveness of duloxetine in treating dysthymia and double depression. Our ITT endpoint responder rate (83%) appears to at least equal those observed in 12-week, double-blind, placebo-controlled trials of sertraline, fluoxetine, and either sertraline or imipramine: 52%–60%,[15] 58%,[16] and 59%–64%.[17] However, comparing response rates across trials utilizing different methods, including methods of recruitment and inclusion/exclusion criteria, has limited validity. Moreover, response rates are usually higher in open-label trials such as ours than in double-blind trials. Our observation of high response and remission rates among completers when a ≥ 3-week duration criterion is imposed suggests that our results are not merely due to natural fluctuations in dysthymia symptoms. A study of 22 dysthymia patients found that their mean duration of euthymia was only 8 days, and only 1 patient described euthymic periods of longer than 2 weeks.[18]

Although our sample size is small, this study, like a larger, open-label study utilizing desipramine,[19] found no statistically significant difference in the degree of improvement between subjects with dysthymia alone and those with double depression. In our study, the latter group did, however, exhibit a somewhat less robust treatment response. Since individuals with dysthymia may delay seeking treatment until they suffer a concurrent major depression,[6] this finding of no significant difference is somewhat reassuring. In the longer term, however, subjects with double depression experience serious morbidity and impairment,[20] and their treatment requires considerable skill.[21]

As in other studies,[11,22] our subjects rated themselves (PGI-I) less improved at endpoint than did the treating clinicians (CGI-I). In part, it seemed that in making their ratings, subjects included unpleasant work or home situations and distress related to immediately preceding events.

Duloxetine was generally well tolerated, and the discontinuation rate for side effects was similar to rates observed in a large, double-blind sertraline trial[15] and 2 small, open-label venlafaxine trials.[23,24] In clinical practice, the sexual side effects that led 2 subjects to discontinue duloxetine could be managed with either a "drug holiday" approach or an antidote strategy.[25]

CONCLUSION

The study's results suggest the potential efficacy and tolerability of duloxetine treatment for dysthymia and double depression. For patients who tolerate 6 weeks of treatment, the response appears to be robust. At the time of writing, a study combining a 6- to 10-week, double-blind, placebo-controlled phase is under way to test the efficacy of duloxetine in subjects with dysthymia alone; this study also includes an open-label 12-week extension phase for responders (ClinicalTrials.gov identifier NCT00360724). If duloxetine is found to be effective, studies powered to detect potential, clinically important differences between duloxetine and other antidepressants will be needed.

Drug names: bupropion (Wellbutrin and others), citalopram (Celexa and others), desipramine (Norpramin and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

REFERENCES

1. Weissman MM, Leaf PJ, Bruce ML, et al. The epidemiology of dysthymia in five communities: rates, risks, comorbidity, and treatment. Am J Psychiatry 1988;145:815–819
2. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
3. Friedman RA, Markowitz JC, Parides M, et al. Six months of desipramine for dysthymia: can dysthymic patients achieve normal social functioning? J Affect Disord 1999;54:283–286
4. Klein DN, Shankman SA, Rose S. Ten-year prospective follow-up study of the naturalistic course of dysthymic disorder and double depression. Am J Psychiatry 2006;163:872–880
5. Shelton RC, Davidson J, Yonkers KA, et al. The undertreatment of dysthymia. J Clin Psychiatry 1997;58:59–65
6. Dunner DL. Current therapeutic approaches for dysthymic disorder. Expert Rev Neurother 2003;3:119–125
7. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine 60 mg once daily versus placebo in the acute treatment of major depression. J Psychiatr Res 2002;36:383–390
8. 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
9. Rush JA, Giles DE, Schlesser MA, et al. The Inventory for Depressive Symptomatology (IDS): preliminary findings. Psychiatry Res 1986;18:65–87
10. Skinner MH, Kuan HY, Pan A, et al. Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. Clin Pharmacol Ther 2003;73:170–177
11. Rush AJ, Hiser W, Biles DE. A comparison of self-reported versus clinician-rated symptoms in depression. J Clin Psychiatry 1987;48:246–248
12. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76–338. Rockville, Md: National Institute of Mental Health; 1976:218–222
13. Gwirtsman HE, Blehar MC, McCullough JP Jr, et al. Standardized assessment of dysthymia: report of a National Institute of Mental Health Conference. Psychopharmacol Bull 1997;33:3–11
14. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU side effects rating scale: a new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 1987;334:1–100
15. Ravindran AV, Guelfi JD, Lane RM, et al. Treatment of dysthymia with sertraline: a double-blind, placebo-controlled trial in dysthymic patients without major depression. J Clin Psychiatry 2000;61:821–827
16. Vanelle JM, Attar-Levy D, Poirier MF, et al. Controlled efficacy study of fluoxetine in dysthymia. Br J Psychiatry 1997;170:345–350
17. Thase ME, Halbreich U, Kocsis J, et al. A placebo controlled trial comparing sertraline and imipramine for the treatment of dysthymia.

Arch Gen Psychiatry 1996;53:777–784
18. Dunner DL. Duration of euthymia in dysthymic patients. Am J Psychiatry 1999;156:1992–1993
19. Marin DB, Kocsis JH, Frances AJ, et al. Desipramine for the treatment of "pure" dysthymia versus "double" depression. Am J Psychiatry 1994; 151:1079–1080
20. Klein DN, Taylor EB, Harding K, et al. Double depression and episodic major depression: demographic, clinical, familial, personality, and socioenvironmental characteristics and short-term outcome. Am J Psychiatry 1988;145:1226–1231
21. Haykal RF, Akiskal HS. The long-term outcome of dysthymia in private practice: clinical features, temperament, and the art of management. J Clin Psychiatry 1999;60:508–518
22. Rush AJ, Gullion CM, Basco RM, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996;26:477–486
23. Dunner DL, Hendrickson HE, Bea C, et al. Venlafaxine in dysthymic disorder. J Clin Psychiatry 1997;58:528–531
24. Hellerstein DJ, Batchelder ST, Little SAS, et al. Venlafaxine in the treatment of dysthymia: an open-label study. J Clin Psychiatry 1999; 60:845–849
25. Clayton AH, Montejo AL. Major depressive disorder, antidepressants, and sexual dysfunction. J Clin Psychiatry 2006; 67(suppl 6):33–37