An open treatment trial of duloxetine in elderly patients with dysthymic disorder

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Abstract

Objective: We evaluated the efficacy and side effects of the selective serotonin and norepinephrine reuptake inhibitor antidepressant duloxetine in older adults with dysthymic disorder.

Methods: Patients ≥ 60 years old with dysthymic disorder received flexible dose duloxetine 20–120 mg daily in an open-label 12-week trial. The main outcomes were change from baseline to 12 weeks in 24-item Hamilton Depression Rating Scale scores and Treatment Emergent Symptoms Scale scores. Response required ≥ 50% decline in Hamilton Depression Rating Scale scores with a Clinical Global Impression of much improved or better, and remission required final Hamilton Depression Rating Scale ≤ 6. Intent-to-treat analyses were conducted with the last observation carried forward.

Results: In 30 patients, the mean age was 70.7 (standard deviation (SD) = 7.6) years and 56.7% were female. In intent-to-treat analyses, there were 16 responders (53.3%) and 10 remitters (33.3%). Of these, 19 patients completed the trial. The mean maximum dose was 76.3 mg (SD = 38.5) in the total sample and 101 mg (SD = 17.9) in completers. In the total sample, the mean final dose was 51 mg (SD = 27.2) and correlated significantly with decline in Hamilton Depression Rating Scale ($p < .03$); decline in Hamilton Depression Rating Scale correlated significantly with decline in Treatment Emergent Symptoms Scale ($p < .001$). Daily doses above 60 mg were associated with greater improvement and well tolerated. This result was partly confounded by early dropouts having received low doses. Demographic and medical comorbidities, including cardiac disease and hypertension, were not related to response. Somatic side effects were common prior to duloxetine treatment and improved rather than worsened with duloxetine. There were no serious adverse events.

Conclusion: Duloxetine at relatively high doses showed moderate efficacy in elderly patients with dysthymic disorder and was well tolerated in successful completers. Reduced somatic symptoms were associated with improvement in depressive symptoms. A systematic placebo-controlled trial of duloxetine in older patients with dysthymic disorder may be warranted.

Keywords

Duloxetine, dysthymic disorder, elderly, serotonin-norepinephrine reuptake inhibitor (SNRI), antidepressant, depression

Introduction

By the year 2030, there will be 65 million Americans over the age of 65 years and the number of people 85 and older will more than double. Depression was ranked the fourth leading cause of disease burden in 2002; it is projected to be the second leading cause worldwide and the first in high-income countries (e.g. United States) by 2030. Late-life depression can cause significant morbidity and mortality and is a major public health problem. Dysthymia in Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) is defined as a chronic subtype of depressive disorder with fewer depressive symptoms than major depression. In Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), dysthymic disorder is considered a subtype of persistent depressive disorder with "pure dysthymic syndrome" (Code 300.4), in which full criteria for a major depressive episode have not been met in at least the preceding 2 years. The prevalence of dysthymic

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disorder is 1%–4% in the general population and it is higher in primary care.[1,2] Dysthymia is often undiagnosed and untreated; it is associated with increased use of medical services and often leads to disability with poor quality of life.[1,3–7] There are distinguishing features of dysthymic disorder between young adults and older adults. Young adults with dysthymic disorder often develop major depression and frequently have comorbid psychiatric disorders, such as anxiety disorder and personality disorder.[1,8,9] In contrast, late-life dysthymia typically has a late age at onset without an increased family history of depression and it often presents as a "pure dysthymic syndrome" without major depression or other psychiatric comorbidities.[10–14] Therefore, response to antidepressant treatment may differ between young and older adults with dysthymic disorder, and it raises the question of whether older adults will show a lower response rate.

A systematic review of 52 research studies in young adults with dysthymic disorder concluded that antidepressant medication was significantly more effective than psychotherapy (e.g. cognitive behavioral therapy (CBT), interpersonal therapy (IPT), problem-solving treatment (PST)).[15] Both tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs) have been shown to be superior to placebo in young adults with dysthymic disorder but the SSRI–placebo differences are not large.[16,17] In older patients with dysthymic disorder, the SSRIs fluoxetine and paroxetine have shown a small advantage over placebo in controlled trials.[18,19] A single-blind study compared the response rate between venlafaxine and nortriptyline in elderly patients with moderate to severe depression.[20] The study found both venlafaxine and nortriptyline were effective in treating late-life depression, while nortriptyline had a higher rate of dropout due to adverse effects compared to venlafaxine, mainly anticholinergic side effects. There are no double-blind studies comparing serotonin and norepinephrine reuptake inhibitors (SNRIs) like duloxetine and venlafaxine to TCA in depressive disorders.

Among SNRIs, an initial open-label trial of venlafaxine (Effexor) showed moderate improvement with acceptable tolerability.[21] Several studies have shown that the SNRI duloxetine (Cymbalta) is effective and well tolerated in older patients with major depression;[22–26] other studies suggested that duloxetine was effective in the treatment of resistant depression[27] and SSRI non-responders.[25] However, there is a lack of information on duloxetine treatment of dysthymic disorder in older adults. We evaluated duloxetine's efficacy and side effects in an open-label treatment trial in older adults with dysthymic disorder.

Methods

Subjects

Patients were recruited by clinician referral and by radio or newspaper advertisements that offered free evaluation by experienced clinicians for participation in clinical trials in the Late Life Depression Clinic at the New York State Psychiatric Institute. After a telephone screen to rule out exclusions for enrollment for depression trials in the clinic (e.g. unstable medical conditions), a psychiatrist conducted a detailed evaluation and completed the Cumulative Illness Rating Scale–Geriatric (CIRS-G). Patients with a provisional clinical diagnosis of dysthymic disorder were interviewed by a research rater (social worker or nurse) with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I disorders–Patient edition (SCID-P). Based on the psychiatrist's evaluation and the SCID-P interview, a consensus DSM-IV diagnosis was made at a staff conference. Physical examination, electrocardiogram, and blood work including complete blood count, electrolytes, and liver, renal, and thyroid function tests were completed prior to study entry.

Medical exclusion criteria were determined by the study physician based on information obtained from self-report, medical records, and laboratory test reports as well as screening blood tests done at evaluation. Patients with untreated hypertension (BP > 140/90 mm Hg on two consecutive measurements) were excluded from the study. Patients with clinical stroke, dementia, or other major neurological disorder were excluded, as were patients with unstable medical conditions as determined by the study physician.

Inclusion criteria were age ≥ 60 years, DSM-IV diagnosis of dysthymic disorder, 24-item Hamilton Rating Scale for Depression (HAM-D) score ≥ 12 and ≤ 25, and Folstein Mini-Mental State Score (MMSE) ≥ 24. Psychiatric exclusion criteria were a diagnosis of major depression at evaluation or earlier during the index episode (i.e. double depression was excluded), active suicidal ideation or plan, diagnosis of bipolar disorder, schizophrenia or other psychotic disorder, alcohol or substance abuse or dependence in the past year, non-response to a minimum 6-week trial of duloxetine ≥ 90 mg/day during the prior year, and history of allergy to duloxetine. The protocol was approved by the Institutional Review Board of the New York State Psychiatric Institute (IRB #5077). All patients provided written informed consent. The study is registered at clinicaltrials.gov (NCT01852383).

Duloxetine trial

A minimum 1-week psychotropic medication washout, and a washout of 3 weeks for fluoxetine and monoamine oxidase inhibitors (MAO) inhibitors, was required. Lorazepam (up to 1 mg/day equivalents), zolpidem (up to 10 mg at bedtime), and zaleplon (up to 10 mg at bedtime) were permitted. Duloxetine was prescribed at 20 mg daily for the first week, 30 mg daily for the second week, then 60 mg daily for another 4 weeks. Patients could subsequently be raised to 90 mg daily for another 2–4 weeks and then to a maximum dose of 120 mg daily. At all visits, the study psychiatrist had the option of adjusting the dose based on clinical response and

Table 1. Demographic and baseline clinical features of patients with dysthymic disorder treated with duloxetine.

Baseline feature	Total sample N = 30		Responders N = 16		Non-responders N = 14		Responder vs non-responder	
Continuous variables	Mean	SD	Mean	SD	Mean	SD	t-test	p
Age in years	70.7	7.6	69.6	6.0	71.9	9.2	0.80	0.44
Age first-ever depressed in years	46.8	22.8	46.3	19.1	47.4	27.1	0.13	0.90
Number of prior depressive episodes	2.1	1.9	1.9	1.0	2.3	2.6	0.57	0.56
Duration of current dysthymic episode, years	3.0	3.9	3.4	4.2	2.6	3.7	0.55	0.57
Hamilton Depression Rating Scale-24-item	18.0	2.8	18.2	3.3	17.9	2.2	0.29	0.78
CDRS	28.8	10.4	28.0	10.6	29.7	10.5	0.44	0.66
MMSE 30-item	28.7	1.6	29.0	1.6	28.4	1.7	0.10	0.33
CIRS-G	5.9	3.7	5.3	3.4	6.6	4.0	0.96	0.34
CGI	3.67	0.55	3.68	0.60	3.62	0.51	0.30	0.77
Categorical variables	No. (%)		No. (%)		No. (%)		χ^2	p
Sex, female	17 (56.7)		10 (62.5)		7 (50.0)		0.46	0.49
Prior antidepressant used in current episode	21 (70)		11 (69)		10 (71)		0.35	0.56
Family history of mood disorder	16 (53.3)		9 (53.3)		7 (46.7)		0.12	0.74
Comorbid DSM-IV Axis I disorder	2 (6.8)		1 (6.3)		1 (7.1)		0.01	0.93

CDRS: Cornell Dysthymia Rating Scale; MMSE: Folstein Mini-Mental State Exam; CIRS-G: Cumulative Illness Rating Scale-Geriatric; CGI: Clinical Global Impression; SD: standard deviation; DSM-IV: Diagnostic and Statistical Manual of Mental Disorder, 4th Edition.

side effects. Patients were evaluated weekly for the first 6 weeks and every two weeks for the next 6 weeks. At 0, 1, 4, 8, and 12 weeks, the study psychiatrist completed the Cornell Dysthymia Rating Scale (CDRS), Clinical Global Impression (CGI) scale, and side effect ratings using the Treatment Emergent Symptom Scale (TESS). The research rater completed a SCID-P and the 24-item HAM-D, and the patient completed the Beck Depression Inventory-II (BDI). The primary outcome measure was the change in HAM-D scores from week 0 to week 12. Responder status was defined as ≥ 50% decrease in 24-item HAM-D scores with a CGI score of much improved or better at the final assessment compared to the week 0 (baseline) visit. Remission was defined as a final 24-item HAM-D score ≤ 6.

Results

Clinical characteristics

The mean age was 70.7 (standard deviation (SD) = 7.6) years, 56.7% were female, and the ethnic distribution was 70% White, 10% African American, 13.3% Hispanic, and 6.7% Asian (Table 1). Most patients (86%) were self-referred and 14% of the patients were referred by physicians. The majority (63.3%) had cardiovascular disease, defined as a positive score on either the cardiac (40%) or vascular (56.7%) items on the CIRS-G. The first-ever depressive episode (major depression or dysthymia) occurred at 47 years of age as identified by the SCID-P, and a history of other Axis I disorders was uncommon (see Table 1).
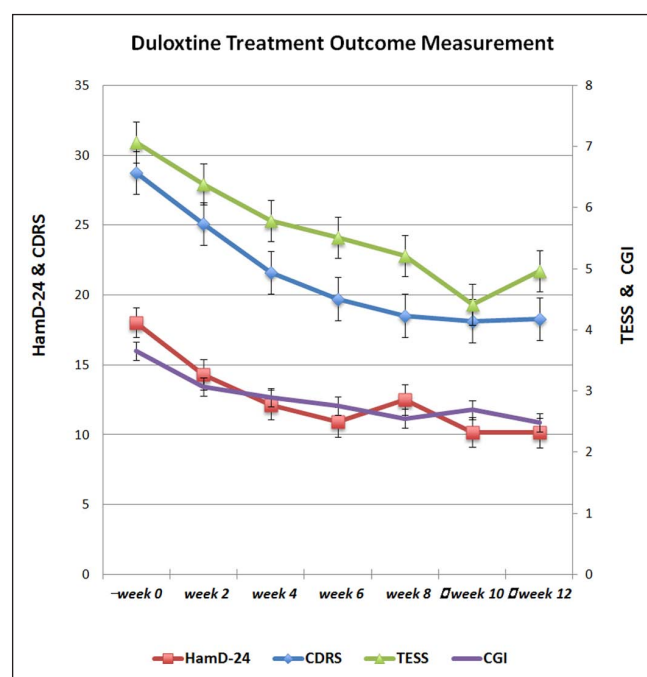
Efficacy

Of the 30 patients, 3 took benzodiazepines or hypnotics during the trial. Of these, 19 patients (63.3%) completed the trial, with dropout in 6.7% due to lack of response, 16.7% due to side effects, 3.3% due to inter-current medical illness, 3.3% due to relocation, and 6.7% for other reasons. Baseline 24-item HAM-D, CDRS, CIRS-G, and CGI scores did not differ significantly between responders and non-responders. Treatment response was not significantly related to baseline demographic and clinical variables (see Table 1) or benzodiazepine/hypnotic use (5% of the sample). Responders did not differ significantly in the rate of cardiovascular disease compared to non-responders (chisq = 0.201, p = 0.654). In intent-to-treat analyses with the last observation carried forward, there were 16 responders (53.3%) and 10 remitters (33.3%). Among 19 completers, 14 (73.7%) responded with duloxetine treatment (≥ 50% decrease in final 24-item HAM-D score) and 9 (47%) remitted with duloxetine. In the total sample, 24-item HAM-D scores declined by an average 7.9 (SD = 6.1) points with a mean percent change of 43.8% (SD = 33.8) from baseline to the last observed time-point (ps < .001). CGI scores improved significantly in completers (p < 0.0001) compared to

dropouts ($p = 0.78$). Changes over time in HAM-D, CDRS, and CGI scores are displayed in Figure 1.

The mean maximum duloxetine dose was 76.3 mg (SD = 38.5) daily and the mean final duloxetine dose was 51 mg (SD = 27.2) daily in the total sample. The mean maximum dose was 101 mg (SD = 17.9) daily and the mean final dose was 61.6 mg (SD = 27.3) in completers compared to the mean maximum dose of 36.4 mg (SD = 26.4) daily and the final dose of 39.3 mg (SD = 20.2) in dropouts. The maximum duloxetine doses in completers correlated significantly

with the decline in HAM-D ($r = 0.64$, $p < .001$) and decline in CDRS ($r = 0.63$, $p < .001$) scores. The final duloxetine doses in the total sample correlated significantly with the decline in HAM-D ($r = 0.41$, $p < .03$) but not with the decline in CDRS ($r = 0.25$, $p = 0.19$) scores. Of the 19 patients, 14 (73.7%) whose maximum duloxetine dose was greater than 60 mg daily were responders compared to 2 of 11 patients (18%) whose maximum dose was 60 mg daily or less (chisq = 8.6, $p = 0.003$). Of 6 patients, 5 (83.3%) whose final duloxetine dose was greater than 60 mg daily were responders compared to 11 of 24 patients (45.8%) whose final dose was 60 mg daily or less (chisq = 2.7, $p = 0.1$). Dropouts (n = 11) had a mean final duloxetine dose of 28 mg daily (see Table 2).

Somatic side effects

The most frequent side effects reported were dry mouth (n = 6, 20%), weakness (n = 4, 13.3%), sexual dysfunction (n = 4, 13.3%), constipation (n = 3, 10%), diarrhea (n = 2, 6.7%), insomnia (n = 2, 6.7%), and drowsiness (n = 2, 6.7%). Somatic side effects assessed by total TESS scores declined in responders by a mean 3.6 (SD = 2.5) points compared to a mean increase of 0.33 (SD = 2.5) points in non-responders ($t = 4.2$, $p < .001$). The maximum duloxetine dose in completers was positively correlated with decline in TESS scores ($r = 0.48$, $p = 0.01$) and the final duloxetine dose showed a trend correlation with decline in TESS scores ($r = 0.36$, $p = 0.06$). Decline in HAM-D correlated significantly with decline in TESS scores ($r = 0.60$, $p < .001$). TESS scores improved significantly in completers ($p < 0.0005$) compared to dropouts ($p = 0.80$). Blood pressure did not change from baseline to the final visit (systolic mean = 135, SD = 10 to systolic mean = 134, SD = 12; diastolic mean = 75, SD = 9.9 to diastolic mean = 73, SD = 9.8). There were no serious adverse events during the trial.

Discussion

In this trial, depressive symptoms improved with duloxetine on both the traditional HAM-D and the more specific

Figure 1. Change in efficacy and side effect measures during the 12-week duloxetine trial.
HAMD-24: 24-item Hamilton Rating Scale for Depression; CDRS: Cornell Dysthymia Rating Scale; TESS: Treatment Emergent Symptom Scale; CIRS-G: Cumulative Illness Rating Scale–Geriatric.
The y-axis on the left indicates the scores on the HAMD-24 and the CDRS, and the y-axis on the right indicates the scores on the TESS and CIRS-G.

Table 2. Comparison of the maximum and final duloxetine dose in all enrolled patients, responders, non-responders, completers, and dropouts.

	Intent-to-treat	Responders	Non-responders	Completers	Dropouts
No (%)	30 (100)	16 (53.3)	14 (46.7)	19 (63.3)	11 (36.7)
Maximal dose (mg/d)	76.3 ± 38.5	95.6 ± 25.0	56.3 ± 40.0	101 ± 17.9	33.3 ± 23.4
No. maximal dose > 60 mg/d	19	14	5	19	1
No. maximal dose ≤ 60 mg/d	11	2	9	0	10
Final dose (mg/d)	51.0 ± 27.2	60.0 ± 29.0	37.1 ± 22.7	61.6 ± 27.3	28.2 ± 14.0
No. final dose > 60 mg/d	6	5	1	6	0
No. final dose ≤ 60 mg/d	24	11	13	13	11

CDRS scale for dysthymia. The CDRS has been shown to have good convergent validity with the HAM-D, BDI, and CGI.[28] The inter-rater reliability of the CDRS has been shown to be as strong as that of the HAM-D.[29] Inter-rater reliability was not assessed systematically during the course of this study. The CDRS measures specific chronic depressive symptoms, such as pessimism, low self-esteem, and low productivity, while the HAM-D measures the severity of depressive symptoms in an episode, such as hopelessness, worthlessness, and work and activities.[30] In our study, patients showed a greater improvement in Ham-D scores and CDRS scores in completers but only improvement in Ham-D scores but not in CDRS scores in the total sample. This finding indicates that some key features of dysthymic disorder may need a longer period of treatment to achieve improvement.

Patients received flexible dose duloxetine 20–120 mg daily in this study. We used the "last observation carried forward" method to handle our data with informative dropout. The mean maximum duloxetine dose was 76.3 mg (SD = 38.5) daily and the mean final duloxetine dose was 51 mg (SD = 27.2) daily in the total sample and 60 mg (SD = 29.0) in responders.

The maximum daily dose above the recommended 60 mg daily led to better response though this finding was confounded by non-completers receiving low doses of duloxetine at the time of dropout.

In dysthymic disorder in older adults, prior trials with SSRIs have shown weak efficacy.[18,19] The response (53%) and remission (33.3%) rates in intent-to-treat analyses were comparable to those observed in an open trial of venlafaxine in older adults with dysthymic disorder (60.9% response and 47.8% remission),[21] and higher than the response rates of 45% to paroxetine and 27% to fluoxetine in placebo-controlled trials in similar patient samples. The higher response rate in open-label compared to placebo-controlled trials is a well-known phenomenon.[31] In older adults with dysthymic disorder, there have been no head-to-head comparisons of SNRIs like duloxetine with SSRIs, and no placebo-controlled trials of SNRIs. Therefore, although the results with duloxetine in this study and venlafaxine in an earlier study[21] are promising, their potential advantage as SNRIs over SSRIs or placebo remains to be established in older adults with dysthymic disorder. We previously showed that the majority of older adults with dysthymic disorder presenting clinically have a late age of onset with few comorbid Axis 1 disorders, unlike young adults with dysthymic disorder. The clinical features of the patients in this study are consistent with the literature on dysthymic disorder in older adults. Whether treatment response is superior in young adults compared to older adults is unclear because the advantage for antidepressant treatment over placebo in young adults with dysthymic disorder is not robust.[32,33]

TESS somatic symptom scores improved rather than worsened with duloxetine. This may seem counterintuitive, but the strong positive correlation between decline in HAM-D and TESS scores suggests that many of these somatic symptoms were features of depression in these patients, and therefore when depression improved, the somatic symptoms also improved. Cardiovascular illness, particularly hypertension, was common in this sample, but overall medical comorbidity and specifically cardiovascular illness was not related to duloxetine treatment response.[34] Blood pressure did not change during the course of the trial, supporting the safety of duloxetine in elderly patients.[34] The subjects enrolled in this study were relatively healthy, mainly because of the exclusion criteria, and the findings on the likelihood of side effects should therefore be interpreted with caution.

The small sample size and open-label treatment design with lack of placebo control were the main limitations to this study. The results with duloxetine were largely positive with acceptable side effects, and suggest that a more rigorous placebo-controlled trial of duloxetine in older adults with dysthymic disorder may be warranted.

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(7): 815–819.
2. Steiner M, Bell B, Browne G, et al. Prevalence of dysthymic disorder in primary care. *J Affect Disord* 1999; 54(3): 303–308.
3. Broadhead WE, Blazer DG, George LK, et al. Depression, disability days, and days lost from work in a prospective epidemiologic survey. *JAMA* 1990; 264(19): 2524–2528.
4. Friedman RA, Parides M, Baff R, et al. Predictors of response to desipramine in dysthymia. *J Clin Psychopharmacol* 1995; 15(4): 280–283.
5. Howland RH. General health, health care utilization, and medical comorbidity in dysthymia. *Int J Psychiatry Med* 1993; 23(3): 211–238.
6. Leader JB and Klein DN. Social adjustment in dysthymia, double depression and episodic major depression. *J Affect Disord* 1996; 37(2–3): 91–101.

7. Spitzer RL, Williams JB, Kroenke K, et al. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *JAMA* 1994; 272(22): 1749–1756.

8. Kocsis JH, Frances AJ, Voss C, et al. Imipramine treatment for chronic depression. *Arch Gen Psychiatry* 1988; 45(3): 253–257.

9. Klein DN and Shih JH. Depressive personality: associations with DSM-III-R mood and personality disorders and negative and positive affectivity, 30-month stability, and prediction of course of Axis I depressive disorders. *J Abnorm Psychol* 1998; 107(2): 319–327.

10. Abrams RC, Spielman LA, Alexopoulos GS, et al. Personality disorder symptoms and functioning in elderly depressed patients. *Am J Geriatr Psychiatry* 1998; 6(1): 24–30.

11. Devanand DP. Dysthymic disorder in the elderly population. *Int Psychogeriatr* 2014; 26(1): 39–48.

12. Devanand DP, Adorno E, Cheng J, et al. Late onset dysthymic disorder and major depression differ from early onset dysthymic disorder and major depression in elderly outpatients. *J Affect Disord* 2004; 78(3): 259–267.

13. Devanand DP. Comorbid psychiatric disorders in late life depression. *Biol Psychiatry* 2002; 52(3): 236–242.

14. Devanand DP, Nobler MS, Singer T, et al. Is dysthymia a different disorder in the elderly? *Am J Psychiatry* 1994; 151(11): 1592–1599.

15. Cuijpers P, Reynolds CF, 3rd, Donker T, et al. Personalized treatment of adult depression: medication, psychotherapy, or both? A systematic review. *Depress Anxiety* 2012; 29(10): 855–864.

16. Von Wolff A, Holzel LP, Westphal A, et al. Selective serotonin reuptake inhibitors and tricyclic antidepressants in the acute treatment of chronic depression and dysthymia: a systematic review and meta-analysis. *J Affect Disord* 2013; 144(1–2): 7–15.

17. Levkovitz Y, Tedeschini E and Papakostas GI. Efficacy of antidepressants for dysthymia: a meta-analysis of placebo-controlled randomized trials. *J Clin Psychiatry* 2011; 72(4): 509–514.

18. Williams JW, Jr., Barrett J, Oxman T, et al. Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults. *JAMA* 2000; 284(12): 1519–1526.

19. Devanand DP, Nobler MS, Cheng J, et al. Randomized, double-blind, placebo-controlled trial of fluoxetine treatment for elderly patients with dysthymic disorder. *Am J Geriatr Psychiatry* 2005; 13(1): 59–68.

20. Gasto C, Navarro V, Marcos T, et al. Single-blind comparison of venlafaxine and nortriptyline in elderly major depression. *J Clin Psychopharmacol* 2003; 23(1): 21–26.

21. Devanand DP, Juszczak N, Nobler MS, et al. An open treatment trial of venlafaxine for elderly patients with dysthymic disorder. *J Geriatr Psychiatry Neurol* 2004; 17(4): 219–224.

22. Nelson JC, Wohlreich MM, Mallinckrodt CH, et al. Duloxetine for the treatment of major depressive disorder in older patients. *Am J Geriatr Psychiatry* 2005; 13(3): 227–235.

23. Wohlreich MM, Mallinckrodt CH, Prakash A, et al. Duloxetine for the treatment of major depressive disorder: safety and tolerability associated with dose escalation. *Depress Anxiety* 2007; 24(1): 41–52.

24. Wohlreich MM, Sullivan MD, Mallinckrodt CH, et al. Duloxetine for the treatment of recurrent major depressive disorder in elderly patients: treatment outcomes in patients with comorbid arthritis. *Psychosomatics* 2009; 50(4): 402–412.

25. Karp JF, Whyte EM, Lenze EJ, et al. Rescue pharmacotherapy with duloxetine for selective serotonin reuptake inhibitor non-responders in late-life depression: outcome and tolerability. *J Clin Psychiatry* 2008; 69(3): 457–463.

26. Raskin J, Xu JY and Kajdasz DK. Time to response for duloxetine 60 mg once daily versus placebo in elderly patients with major depressive disorder. *Int Psychogeriatr* 2008; 20(2): 309–327.

27. Hellerstein DJ, Stewart JW, McGrath PJ, et al. A randomized controlled trial of duloxetine versus placebo in the treatment of nonmajor chronic depression. *J Clin Psychiatry* 2012; 73(7): 984–991.

28. Mason BJK, James H, Leon AC, et al. Measurement of severity and treatment response in dysthymia. *Psychiatr Ann* 1993; 23(11): 625–631.

29. Hellerstein DJ, Batchelder ST, Lee A, et al. Rating dysthymia: an assessment of the construct and content validity of the Cornell Dysthymia Rating Scale. *J Affect Disord* 2002; 71(1–3): 85–96.

30. Cohen J. Assessment and treatment of dysthymia. The development of the Cornell dysthymia rating scale. *Eur Psychiatry* 1997; 12(4): 190–193.

31. Rutherford BR and Roose SP. A model of placebo response in antidepressant clinical trials. *Am J Psychiatry* 2013; 170(7): 723–733.

32. Thase ME, Fava M, Halbreich U, et al. A placebo-controlled, randomized clinical trial comparing sertraline and imipramine for the treatment of dysthymia. *Arch Gen Psychiatry* 1996; 53(9): 777–784.

33. Thase ME, Gelenberg A, Kornstein SG, et al. Comparing venlafaxine extended release and fluoxetine for preventing the recurrence of major depression: results from the PREVENT study. *J Psychiatr Res* 2011; 45(3): 412–420.

34. Wise TN, Wiltse CG, Iosifescu DV, et al. The safety and tolerability of duloxetine in depressed elderly patients with and without medical comorbidity. *Int J Clin Pract* 2007; 61(8): 1283–1293.