Efficacy of Antidepressants for Dysthymia: A Meta-Analysis of Placebo-Controlled Randomized Trials

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Objective: The authors sought to determine the efficacy of antidepressants in dysthymic disorder and to compare antidepressant and placebo response rates between major depressive disorder (MDD) and dysthymic disorder.

Data Sources: PubMed/MEDLINE databases were searched for double-blind, randomized, placebo-controlled trials of antidepressants used as monotherapy for treatment of MDD or dysthymic disorder. We defined antidepressants as those with a letter of approval by the US, Canadian, or European Union drug regulatory agencies for treatment of MDD or dysthymic disorder, which included the following: *amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, trimipramine, protriptyline, dothiepin, doxepin, lofepramine, amoxapine, maprotiline, amineptine, nomifensine, bupropion, phenelzine, tranylcypromine, isocarboxazid, moclobemide, brofaromine, fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine, zimelidine, tianeptine, ritanserin, trazodone, nefazodone, agomelatine, venlafaxine, desvenlafaxine, duloxetine, milnacipran, reboxetine, mirtazapine,* and *mianserin.* Eligible studies were identified by cross-referencing the search term *placebo* with each of the above-mentioned agents. The search was limited to articles published between January 1, 1980, and November 20, 2009 (inclusive). To expand our database, we also reviewed the reference lists of the identified studies.

Study Selection: We selected randomized, double-blind, placebo-controlled trials of antidepressants for either MDD or dysthymic disorder according to preset criteria relating to comorbidities, patient age, drug formulation, study duration, diagnostic criteria, choice of assessment scales, and whether or not the study reported original data. Final selection of articles was determined by consensus among the authors.

Results: A total of 194 studies were found that were eligible for inclusion in our analysis. Of these, 177 focused on the treatment of MDD and 17 on the treatment of dysthymic disorder. We found that antidepressant therapy was significantly more effective than placebo in dysthymic disorder (risk ratio = 1.75; 95% CI, 1.49–2.04; $P < .0001$), while placebo response rates in dysthymic disorder trials were significantly lower compared to MDD trials (29.9% vs 37.9%, respectively; $P = .042$). Meta-regression suggested a statistically significant difference in the risk ratio of responding to antidepressants versus placebo when comparing studies either on dysthymic disorder or on MDD, suggesting a greater risk ratio for response in favor of antidepressant therapy versus placebo in patients with dysthymic disorder versus MDD (coefficient of –0.113; $P = .007$).

Conclusions: These results support the utility of antidepressants for dysthymic disorder. In fact, the margin of efficacy of antidepressants for dysthymic disorder was larger than for MDD. Future studies providing longer-term data on the treatment of dysthymic disorder with antidepressants are essential.

J Clin Psychiatry 2011;72(4):509–514

Submitted: *December 30, 2009; accepted March 16, 2010 (doi:10.4088/JCP.09m05949blu).*

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Depressive disorders have traditionally been perceived as acute, episodic conditions. Over the last 2 decades, however, it has been increasingly recognized that many patients experience a long-term, chronic course of depression. Dysthymic disorder is a depressive condition defined by a mild yet chronic course, persistent symptoms, and an insidious onset. Dysthymic disorder is relatively common, with a lifetime prevalence between 3% and 6%.[1,2] There is epidemiologic evidence of high comorbidity in patients with dysthymic disorder, with more than 75% of patients also meeting criteria for other Axis I disorders, particularly MDD, anxiety disorders, and alcohol or substance use disorder.[1,3] When dysthymic disorder is left untreated, its natural history is poor, with more than two-thirds of patients remaining symptomatic for a decade or more.[4] Dysthymic disorder can present with the full gamut of depressive symptoms, although cognitive, affective, and social motivational symptoms are more common than vegetative symptoms (eg, sleep or appetite disturbance). In fact, even though the *DSM-IV* currently requires at least 2 of 6 sets of symptoms in order to meet criteria for dysthymic disorder (including fatigue, sleep and/or appetite disturbance, low self-esteem, poor concentration, and helplessness), patients typically present with more than 2 depressive symptoms. Moreover, patients with the disorder experience considerable social dysfunction and disability and are more likely than the general population to use general medical services and to take nonspecific psychotropic drugs.[5–7] In fact, although patients with dysthymic disorder often present with lower overall severity of symptoms than patients with MDD, perhaps as a result of greater chronicity, the cumulative burden of persistent depressive symptoms and impaired functioning associated with this illness can sometimes be greater than that seen following most major depressive episodes.[4]

Considering these illness characteristics, it is clear that effective treatment for dysthymic disorder is needed. Antidepressant therapies are now commonly used as first-line treatment in dysthymic disorder. However, there has been much debate over the relative merits of pharmacotherapy as a reasonable primary treatment option for dysthymic disorder, perhaps due to its greater chronicity and presumed "nonbiological," "characterological" qualities that some clinicians, perhaps arbitrarily, ascribe to this illness as opposed to MDD.[8] Lending support to this view are results of several

For Clinical Use

- Dysthymia is a relatively common disorder (ie, lifetime prevalence of 3%–6%), with more than two-thirds of patients remaining symptomatic for a decade or more if not treated.
- Effective treatments for dysthymia are needed, and antidepressant therapies are now commonly used as first-line treatment.
- Our results have important practical consequences for both dysthymic patients and clinicians because they support the utilization of antidepressants for dysthymia.

randomized, double-blind, placebo-controlled trials that do not show a superiority of antidepressants versus placebo for dysthymic disorder. In parallel, there are relatively few systemic reviews about the use of antidepressants in dysthymic patients,[9–14] and there are none comparing the margin of efficacy of antidepressants versus placebo for dysthymic disorder versus MDD or comparing placebo response rates in dysthymic disorder and MDD. As a result, there is a paucity of evidence supporting the use of antidepressants in the treatment of dysthymic disorder, as well as a lack of evidence examining whether patients with dysthymic disorder are more or less likely to experience the benefits of antidepressant therapy versus MDD patients (as proponents ascribing "nonbiological" or "characterological" properties to dysthymic disorder vis-à-vis MDD would argue[8]). Therefore, the purpose of our meta-analysis is to answer 3 questions: (1) Are antidepressants effective in dysthymic disorder? (2) Are patients with dysthymic disorder more or less likely to exhibit a placebo response than those with MDD? and, most important, (3) Is the margin of efficacy of antidepressants versus placebo larger or smaller in dysthymic disorder patients than in MDD patients?

METHOD

Data Sources and Search Strategy

We sought to identify double-blind, randomized, placebo-controlled trials of antidepressants used as monotherapy for the treatment of either MDD or dysthymic disorder for possible inclusion in the meta-analysis. For antidepressants we defined pharmacologic agents that have received a letter of approval by the US, Canadian, or European Union drug regulatory agencies for treatment of either MDD or dysthymic disorder. According to this definition, the following pharmacologic agents met criteria to be considered as antidepressants: *amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, trimipramine, protriptyline, dothiepin, doxepin, lofepramine, amoxapine, maprotiline, amineptine, nomifensine, bupropion, phenelzine, tranylcypromine, isocarboxazid, moclobemide, brofaromine, fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine, zimelidine, tianeptine, ritanserin, trazodone, nefazodone, agomelatine, venlafaxine, desvenlafaxine, duloxetine, milnacipran, reboxetine, mirtazapine,* and *mianserin.*

Eligible studies were first identified using searches of PubMed/MEDLINE by cross-referencing the search term *placebo* with each of the above-mentioned agents. The PubMed/MEDLINE search was limited to articles published between January 1, 1980, and November 20, 2009 (inclusive). The year 1980 was used as a cutoff in our search to decrease diagnostic variability since the *DSM-III* was introduced in 1980. To expand our database, we then reviewed the reference lists of studies identified with PubMed/MEDLINE. Final inclusion of articles was determined by consensus among the authors.

Study Selection

We selected randomized, double-blind, placebo-controlled trials of antidepressants used as monotherapy either in the acute-phase treatment of MDD or in the treatment of dysthymic disorder. We then selected studies that also met all of the following criteria:

1. Defined MDD or dysthymic disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition[15]; *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised[16]; *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition[17]; Research Diagnostic Criteria[18]; or the Feighner diagnostic criteria.[19]
2. Were of at least 4 weeks' duration.
3. Focused on the use of antidepressants in their oral formulations.
4. Presented entirely original (not previously published) data.
5. Focused on the treatment of adult patients.
6. Did not focus exclusively on the treatment of patients with treatment-resistant depression, bipolar depressive disorder, depression with psychotic features, minor depression, or perinatal depression.
7. Did not focus exclusively on the treatment of MDD in patients with comorbid alcohol or substance use disorders or in patients with a specific comorbid medical illness.
8. Involved the use of the 17-item Hamilton Depression Rating Scale (HDRS-17),[20] the Montgomery-Asberg Depression Rating Scale (MADRS),[21] or the Clinical Global Impressions-Improvement (CGI-I)[22] scale as one of their outcome measures.

Definitions

Clinical response was defined as a 50% or greater reduction in HDRS-17 or MADRS scores, baseline to endpoint,

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or a CGI-I score < 3 at the final visit. For consistency, the HDRS-17 was chosen over the MADRS or CGI-I when response rates from multiple scales were reported. For studies that reported only CGI-I–based response rates, the HDRS-17–based response rates were either obtained from the sponsor or imputed using the method of Walsh et al.[23] Discontinuation rate was defined as per each protocol. For consistency, we used intent to treat (ITT)-based response rates in the present analysis. Whenever ITT-based response rates were not available in the publication, the sponsor was contacted to obtain ITT-based response rates. In cases in which the sponsor could not retrieve ITT-based response rates, we utilized response rates based on completers. The probability of receiving placebo was computed from the number of treatment arms and the randomization schedule (ie, 1:1:1) of each trial. For example, a 2-arm trial with a 2:1 randomization favoring antidepressant treatment yields a 1 in 3 chance of receiving placebo.

Quantitative Data Synthesis

Response rates between groups were compared with the use of analysis of variance. In addition to sample size, when antidepressant response rates were compared between trials involving patients with MDD versus dysthymic disorder, the probability of being randomized to placebo and the type of dosing (fixed vs flexible) were also entered as covariates because they were found to predict antidepressant response rates in a previous meta-analysis.[24] Similarly, in addition to sample size, when placebo response rates were compared between these 2 clinical trial groups (ie, MDD and dysthymic disorder), severity at baseline, year of publication, and the probability of being randomized to placebo were also entered as covariates for the same reason. Random-effects meta-analysis was utilized to estimate the pooled risk ratio (RR) of responding to antidepressants versus placebo in MDD versus dysthymic disorder trials. Finally, a meta-regression was used in order to compare RR of responding to antidepressants versus placebo between these 2 clinical trial groups (ie, MDD vs dysthymic disorder). For this meta-regression, year of publication, severity at baseline, and the probability of being randomized to placebo were also entered as covariates since they had also previously been found to influence the RR of clinical response following antidepressant versus placebo therapy. All tests conducted were 2-tailed, with α set at the .05 level.

RESULTS

Initially, 7,311 abstracts were identified in PubMed/MEDLINE. Of these, 6,889 were excluded for a number of reasons (eg, other topics, reviews). The remaining 422 abstracts described clinical trials of antidepressants for either MDD or dysthymic disorder. These 422 articles were obtained and reviewed thoroughly. Fifteen additional articles were identified after reviewing the reference lists of these 422 articles and 2 large meta-analyses. Ninety-eight articles were excluded because they presented data published elsewhere, 25 articles were excluded because they focused on children and/or adolescents with depression, and 24 articles were excluded because they focused on the treatment of depressive disorders other than MDD and dysthymic disorder (bipolar depressive disorder, minor depression, "neurotic depression"), because they focused on perinatal MDD, because the diagnosis of MDD was based on the *DSM-II*, or because they did not state which, if any, diagnostic criteria were used to define MDD. One article was excluded because it focused on patients with treatment-resistant depression, 27 articles were excluded because they focused on the treatment of patients with depression and comorbid alcohol and/or drug use disorders, and 60 articles were excluded because they focused on the treatment of patients with depression and comorbid Axis III disorders. Three were excluded because they did not involve the use of an oral form of an antidepressant (selegiline), 3 because they were less than 4 weeks in duration, and 2 because they did not involve the use of HDRS-17, MADRS, or CGI-I.

Thus, a total of 194 articles were found to be eligible for inclusion in our pooled analysis (list available upon request). Of these, 177 focused on the treatment of MDD and 17 on the treatment of dysthymic disorder. We were able to obtain antidepressant and placebo response rates for 174 (89.7%) of the 194 articles eligible for inclusion in the meta-analysis. Outcome in the remaining 20 trials was reported either as a continuous measure only (change in depression severity scores) or as pooled outcomes for dysthymic disorder and minor depression (response rates for dysthymic disorder, specifically, for these study results could not be obtained by contacting the study authors or sponsor). While 169 of these articles reported the results of a single trial, 5 reported results of several (a total of 12) trials. Nine of these trials focused on dysthymic disorder patients and involved treatment with amineptine (n = 1), fluoxetine (n = 3), imipramine (n = 3), moclobemide (n = 1), sertraline (n = 2), and ritanserin (n = 2) (some trials involved more than 1 antidepressant treatment arm) (Table 1). Thus, a total of 310 antidepressant versus placebo comparisons from 181 clinical trials were pooled (N = 45,694 patients randomized to an antidepressant [n = 28,807] versus placebo [n = 16,887]); of these, 12 comparisons were derived from clinical trials on the treatment of dysthymic disorder (N = 1,454 patients randomized to treatment with an antidepressant [n = 849] versus placebo [n = 605]).

Mean ± SD study duration (in weeks) was 7.1 ± 2.7 for MDD studies versus 9.7 ± 2.8 for dysthymic disorder studies ($P = .0031$). Mean ± SD sample size per treatment arm was 94.9 ± 58.7 for MDD studies versus 69.2 ± 51.8 for dysthymic disorder studies ($P = .0495$). There was no statistically significant difference in mean ± SD age (in years) per treatment arm (44.0 ± 8.9 vs 44.4 ± 9.2; $P = .861$) and in proportion of women in the randomized sample (61.6% vs 60.2%; $P = .558$), for MDD and dysthymic disorder trials, respectively. On the contrary, there was a statistically significant difference in mean baseline severity in terms of mean ± SD HDRS-17 score per treatment arm (21.4 ± 4.3 vs 17.3 ± 5.3 for MDD

Table 1. Dysthymia Trials

Study	Duration in Weeks	Treatment Arm (dose)
Bersani et al (1991)[25]	5	1. Ritanserin (10 mg/d) 2. Placebo
Bakish et al (1993)[26]	7	1. Ritanserin (5–20 mg/d) 2. Imipramine (50–200 mg/d) 3. Placebo
Hellerstein et al (1993)[27]	8	1. Fluoxetine (20–60 mg/d) 2. Placebo
Thase et al (1996)[28]	12	1. Sertraline (50–200 mg/d) 2. Imipramine (50–300 mg/d) 3. Placebo
Vanelle et al (1997)[29]	12	1. Fluoxetine (20 mg/d) 2. Placebo
Versiani et al (1997)[30]	8	1. Moclobemide (300–750 mg/d) 2. Imipramine (100–250 mg/d) 3. Placebo
Boyer et al (1999)[31]	12	1. Amisulpride (50 mg/d) 2. Amineptine (200 mg/d) 3. Placebo
Ravindran et al (2000)[32]	12	1. Sertraline (50–200 mg/d) 2. Placebo
Devanand et al (2005)[33]	12	1. Fluoxetine (20–60 mg/d) 2. Placebo

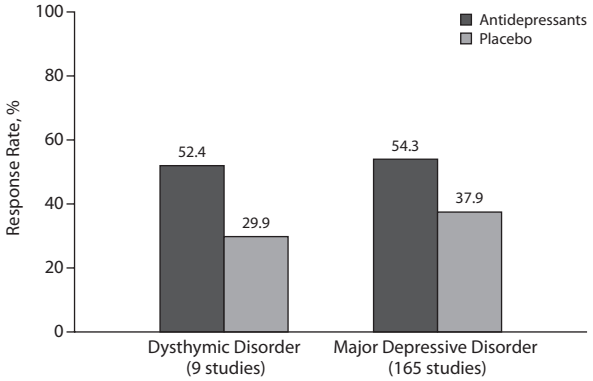
and dysthymic disorder, respectively; $P < .001$) as well as in the probability of receiving placebo (0.426 ± 0.088 vs 0.355 ± 0.092 for MDD and dysthymic disorder, respectively; $P = .0269$).

Meta-Analysis Results

Antidepressant therapy was found to result in statistically significantly higher response rates than placebo for the treatment of dysthymic disorder (RR = 1.75; 95% CI, 1.49–2.04; $P < .0001$). There was no statistical evidence for significant heterogeneity in the RR for response to antidepressants versus placebo in these trials ($Q_{11} = 5.526$; $P = .903$).

There was a statistically significant difference ($P = .042$) in placebo response rates when comparing studies focusing on dysthymic disorder (29.9% [181 of 605 subjects]) or MDD (37.9% [6,172 of 16,282 subjects]), respectively (Figure 1). On the other hand, the difference in antidepressant response rates when comparing studies on dysthymic disorder (52.4% [445 of 849]; number needed to treat [NNT] of approximately 1 in 4.4) or MDD (54.3% [15,177 of 27,958]; NNT of approximately 1 in 6.1) did not reach statistical significance ($P = .84$) (Figure 1). In fact, meta-regression analyses suggested a statistically significant difference in the RR of responding to antidepressants versus placebo when comparing studies either on dysthymic disorder or on MDD, suggesting a greater RR for response in favor of antidepressant therapy versus placebo in patients with dysthymic disorder versus MDD (coefficient of −0.113, $P = .007$).

Figure 1. Efficacy of Antidepressants Versus Placebo in Dysthymic Disorder and Major Depressive Disorder[a,b]



[a] $P < .001$ for antidepressants versus placebo in dysthymic disorder (n = 1,454) and in major depressive disorder (n = 44,240).
[b] $P = .007$ for comparison of the risk ratio of response with antidepressants versus placebo in dysthymic disorder versus major depressive disorder.

DISCUSSION

The present analysis, involving a total of 194 articles (177 on MDD and 17 on dysthymic disorder), makes a unique contribution to the literature on dysthymic disorder, even if 2 meta-analyses were recently published on the same subject,[34,35] because it is the first ever to compare antidepressant and placebo response rates between MDD and dysthymic disorder in randomized, double-blind, placebo-controlled clinical trials and, also, because it is the most comprehensive analysis published to date. In the present work, we found that antidepressant therapy was significantly more effective than placebo in the treatment of both MDD and dysthymic disorder, while placebo response rates in dysthymic disorder trials were significantly lower compared to MDD. The NNT in the dysthymic disorder population was approximately 1 in 4.4, suggesting that 4 and one-half patients have to be treated with antidepressants rather than placebo to obtain 1 additional responder. In fact, in the present analysis, we found the margin of efficacy of antidepressants versus placebo to be significantly larger in dysthymic disorder patients than in MDD patients. The results of this meta-analysis have important practical consequences for both dysthymic patients and clinicians because these results support the utilization of antidepressants for dysthymic disorder, an illness associated with disability, high rates of comorbidity, and increased use of general medical as well as specialty health services.

Our results are in consensus with previous meta-analyses by De Lima et al[13] and De Lima and Hotopf,[14] who found that antidepressants are effective in treating dysthymic disorder compared to placebo. However, our present analysis also yielded novel findings when specifically comparing antidepressant and placebo response rates between studies that enrolled patients with MDD and those that enrolled patients with dysthymic disorder. Surprisingly, we found lower placebo response rates in dysthymic disorder trials than in MDD trials. Previous findings[24] would suggest that greater depression severity at baseline would predict lower response rates for placebo. Therefore, in light of the fact that patients enrolled in MDD trials presented, on average, with greater symptom severity at baseline, one would expect placebo response rates to be lower in MDD than in dysthymic disorder trials, which is in contrast to our present finding.

There are several possible reasons that may explain why we obtained lower, rather than higher, placebo response rates in dysthymic disorder as opposed to MDD trials. First, patients with dysthymic disorder are, on average, more likely to experience a more chronic course of illness than patients with MDD, which, in turn, may confer lower placebo response rates (ie, via an adverse impact on the expectation of improvement, or some other indirect mechanism). Even though the results of the large, multicenter Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial[36] do not suggest that, controlling for other risk factors, the duration of the index depressive episode is related to the probability of symptom improvement, it should be pointed out that the STAR*D trial focused on MDD rather than dysthymic disorder and, most importantly, reported on the impact of duration on antidepressant, but not placebo, response (in accordance with this finding, our analysis shows no statistically significant difference in antidepressant response rates between MDD and dysthymic disorder).

Alternatively, it has previously been pointed out[24] that the year of publication is proportionately related to placebo response rates in MDD clinical trials (more recent publication is related to larger response rates). The reason for this phenomenon remains unclear, although several factors have been proposed, including changes in diagnostic tools used to define affective disorder, changes in the method of patient recruitment, and issues in reliability of primary efficacy measure assessments.[24] In fact, in our dataset, only 8% of dysthymic disorder trials were published after 2000, versus 29% of MDD trials, which may explain why placebo response rates in dysthymic disorder trials are lower than those in MDD trials. However, it should be pointed out that we compared placebo response rates between MDD and dysthymic disorder trials controlling for year of publication.

A discrepancy in the mean probability of being randomized to placebo between MDD and dysthymic disorder may also result in the apparent difference in placebo response rates between these 2 clinical trial groups (with a greater probability of being randomized to placebo being associated with lower placebo response rates). However, in the present dataset, we have found a *higher* rather than lower mean probability of being randomized to placebo in MDD than in dysthymic disorder trials. Finally, we also cannot exclude the possibility that differences in placebo response rates between patients in dysthymic disorder and MDD trials may be due to differences in other, yet unaccounted for, risk factors between these 2 populations (eg, comorbid Axis I or Axis III disorders) or due to differences in the underlying neurobiological basis of the 2 disorders.

A recent meta-analysis by Fournier et al[37] reported that the efficacy of antidepressants compared with placebo increases along with depression severity and may be minimal or nonexistent, on average, in patients with mild or moderate symptoms. Our meta-analysis has demonstrated that antidepressants are more efficacious than placebo for patients diagnosed with dysthymic disorder, which is characterized by less severe as well as more chronic symptoms than MDD. Chronicity is known to be associated with poor response to placebo,[38,39] which, thus, could explain the advantage of antidepressants over placebo in dysthymic disorder, although further studies are needed to examine whether chronicity moderates antidepressant/placebo differences in efficacy across various ranges of baseline severity.

There are several limitations to this analysis. One limitation specifically pertains to the identification of studies to be included in pooled analyses or meta-analyses. For example, it is quite possible that either publication bias or the file-drawer phenomenon, whereby unpublished studies are more likely to be equivocal than published trials, may have distorted our findings or inflated our results (since our study focused only on published clinical trials). Therefore, it would be interesting to examine whether the inclusion of unpublished studies strengthens or weakens our findings. However, it should also be pointed out that 16 or more studies (each having a sample size of 69 patients per treatment arm—the average treatment-arm size of dysthymic disorder studies in the literature) showing an identical antidepressant and placebo response rate for patients with dysthymic disorder as for patients with MDD would be required in order to change our findings, which demonstrate a greater RR of response for dysthymic patients than for MDD patients, from statistically significant to nonsignificant ($\alpha = .05$, 2-sided tests). Another limitation is that, while the total number of dysthymic disorder patients included in this trial ($N = 1,454$) is fairly large, the number of trials on which this trial-level data analysis is based is limited.

In addition, there are several limitations to the existing clinical literature regarding the use of antidepressants in dysthymic disorder. Dysthymic disorder is a not-as-well-defined entity as major depression. It may be hard to define a single "pure" dysthymia subtype, and it may be that patients who are entered into treatment trials have a worsening superimposed depressive illness and it is this, rather than the core syndrome of dysthymia, that is responding to treatment. For instance, many patients enrolled as having dysthymic disorder in clinical trials may be, in fact, presenting with an evolving major depressive episode superimposed on a chronic dysthymic disorder, and it is, in fact, the evolving major depressive episode that is responding to therapy rather than the underlying dysthymic disorder. Finally, all of the trials we reviewed were of relatively short duration. As dysthymic disorder is a chronic condition, longer-term data on the treatment of dysthymic disorder with antidepressants are essential.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), desvenlafaxine (Pristiq), doxepin (Zonalon, Silenor, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), isocarboxazid (Marplan), milnacipran (Savella), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), protriptyline (Vivactil and others), selegiline (Eldepryl and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), trazodone (Oleptro and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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Financial disclosure: **Dr Levkovitz** has been a consultant for Brainsway and NeuroDerm and has been a member of the speakers or advisory board for AstraZeneca. **Dr Papakostas** has served as a consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Evotec, GlaxoSmithKline, Inflabloc, Jazz, Otsuka, Pamlab, Pfizer, Pierre Fabre, Shire, and Wyeth; has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Evotec, GlaxoSmithKline, Inflabloc, Jazz, Lundbeck, Otsuka, Pamlab, Pfizer, Pierre Fabre, Shire, Titan, and Wyeth; has received research support from Bristol-Myers Squibb, Forest, the National Institute of Mental Health, Pamlab, Pfizer, and Ridge Diagnostics (formerly Precision Human Biolaboratories); and has been a member of the speakers bureaus for Bristol-Myers Squibb and Pfizer. **Dr Tedeschini** has no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Funding/support: None reported.

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. 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(1):8–19.
3. Howland RH. General health, health care utilization, and medical comorbidity in dysthymia. *Int J Psychiatry Med*. 1993;23(3):211–238.
4. Klein DN, Santiago NJ. Dysthymia and chronic depression: introduction, classification, risk factors, and course. *J Clin Psychol*. 2003;59(8):807–816.
5. Akiskal HS. Dysthymic disorder: psychopathology of proposed chronic depressive subtypes. *Am J Psychiatry*. 1983;140(1):11–20.
6. Akiskal H. Dysthymic disorder and its treatment. *Encephale*. 1993;19(spec no 2):375–378.
7. Marin DB, Kocsis JH, Frances AJ, et al. Desipramine for the treatment of "pure" dysthymia vs "double" depression. *Am J Psychiatry*. 1994;151(7): 1079–1080.
8. Howland RH, Thase ME. Biological studies of dysthymia. *Biol Psychiatry*. 1991;30(3):283–304.
9. Howland RH. Pharmacotherapy of dysthymia: a review. *J Clin Psychopharmacol*. 1991;11(2):83–92.
10. Lapierre YD. Pharmacological therapy of dysthymia. *Acta Psychiatr Scand suppl*. 1994;89(s383):42–48.
11. Invernizzi G, Mauri MC, Waintraub L. Antidepressant efficacy in the treatment of dysthymia. *Eur Neuropsychopharmacol*. 1997; 7(suppl 3):S329–S336.
12. Dunner DL. Treatment of dysthymic disorder. *Depress Anxiety*. 1998;8(suppl 1):54–58.
13. De Lima MS, Moncrieff J, Soares B. Drugs versus placebo for dysthymia. *Cochrane Database Syst Rev*. 2000;(4):CD001130.
14. De Lima MS, Hotopf M. Benefits and risks of pharmacotherapy for dysthymia: a systematic appraisal of the evidence. *Drug Saf*. 2003;26(1): 55–64.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition. Washington, DC: American Psychiatric Association; 1980.
16. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised. Washington, DC: American Psychiatric Association; 1987.
17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
18. Spitzer RL, Endicott J, Robins E. Research Diagnostic Criteria: rationale and reliability. *Arch Gen Psychiatry*. 1978;35(6):773–782.
19. Feighner JP, Robins E, Guze SB, et al. Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry*. 1972;26(1):57–63.
20. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
21. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
22. 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.
23. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*. 2002; 287(14):1840–1847.
24. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? a meta-regression of double-blind, randomized clinical trials in MDD. *Eur Neuropsychopharmacol*. 2009; 19(1):34–40.
25. Bersani G, Pozzi F, Marini S, et al. 5-HT_2 receptor antagonism in dysthymic disorder: a double-blind placebo-controlled study with ritanserin. *Acta Psychiatr Scand.* 1991;83(4):244–248.
26. Bakish D, Lapierre YD, Weinstein R, et al. Ritanserin, imipramine, and placebo in the treatment of dysthymic disorder. *J Clin Psychopharmacol.* 1993;13(6):409–414.
27. Hellerstein DJ, Yanowitch P, Rosenthal J, et al. A randomized double-blind study of fluoxetine versus placebo in the treatment of dysthymia. *Am J Psychiatry.* 1993;150(8):1169–1175.
28. 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.
29. Vanelle JM, Attar-Levy D, Poirier MF, et al. Controlled efficacy study of fluoxetine in dysthymia. *Br J Psychiatry.* 1997;170(4):345–350.
30. Versiani M, Amrein R, Stabl M; International Collaborative Study Group. Moclobemide and imipramine in chronic depression (dysthymia): an international double-blind, placebo-controlled trial. *Int Clin Psychopharmacol.* 1997;12(4):183–194.
31. Boyer P, Lecrubier Y, Stalla-Bourdillon A, et al. Amisulpride versus amineptine and placebo for the treatment of dysthymia. *Neuropsychobiology.* 1999;39(1):25–32.
32. 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(11):821–827.
33. 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.
34. Cuijpers P, van Straten A, van Oppen P, et al. Are psychological and pharmacologic interventions equally effective in the treatment of adult depressive disorders? a meta-analysis of comparative studies. *J Clin Psychiatry*. 2008;69(11):1675–1685, quiz 1839–1841.
35. Imel ZE, Malterer MB, McKay KM, et al. A meta-analysis of psychotherapy and medication in unipolar depression and dysthymia. *J Affect Disord*. 2008;110(3):197–206.
36. Gilmer WS, Gollan JK, Wisniewski SR, et al. Does the duration of index episode affect the treatment outcome of major depressive disorder? a STAR*D report. *J Clin Psychiatry*. 2008;69(8):1246–1256.
37. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA*. 2010; 303(1):47–53.
38. Dunner DL. Acute and maintenance treatment of chronic depression. *J Clin Psychiatry*. 2001;62(suppl 6):10–16.
39. Khan A, Dager SR, Cohen S, et al. Chronicity of depressive episode in relation to antidepressant-placebo response. *Neuropsychopharmacology*. 1991;4(2):125–130.

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