Antidepressant Effectiveness in Severe Depression and Melancholia

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While outcome has improved in patients with depressive disorders since the introduction of the newer antidepressants, some physicians still treat severely depressed patients with the older tricyclic antidepressants because of conflicting reports about the efficacy of the newer agents, particularly the selective serotonin reuptake inhibitors, in severe depression. However, a standardized operational definition of severe depression is lacking, and treatment studies are difficult to evaluate due to variation in methodology. Remission rates are relatively low in many of the short-term clinical trials of the newer antidepressants in severe depression, but may improve if the research design were to include a longer trial and aggressive dosing. There is some evidence that venlafaxine, a serotonin-norepinephrine antidepressant, may offer some advantage for severely depressed patients.

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The advent of the newer antidepressants—e.g., selective serotonin reuptake inhibitors (SSRIs), venlafaxine—has improved outcome in patients with depressive disorders, since these agents are as effective as but better tolerated than the older tricyclic antidepressants (TCAs). Patients are more likely to continue taking the newer antidepressants than the TCAs because of the milder side effect profile. In a meta-analysis of 42 controlled treatment studies, Montgomery et al.[1] found that the incidence of premature discontinuation attributed to side effects was 14.9% for the SSRIs and 19.0% for the TCAs ($p < .01$).

Although the efficacy of the newer antidepressants has been well established for the treatment of mild-to-moderate depression, several investigators have suggested that the SSRIs, in particular, are less effective than the TCAs for severe depression and melancholia,[2–4] and some clinicians continue to use TCAs for severely ill depressed patients. However, the body of literature on the treatment of severe depression is limited due to lack of a standardized operational definition of severe depression, variation in methodology among studies, and, not surprisingly, equivocal results from acute treatment studies. This article will discuss issues in the definition of severe depression and the evaluation of treatment studies before reviewing evidence for the efficacy of the newer antidepressants for severe depression and melancholia.

DEFINING SEVERE DEPRESSION

In treatment studies, the severity of depression is generally determined by scores on a rating instrument such as the Hamilton Rating Scale for Depression (HAM-D), the Global Assessment of Functioning (GAF), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impressions (CGI) scale. A fixed endpoint cutoff score is often used to distinguish mild-to-moderate depression from severe depression. For example, a score equal to or greater than 25 on the 17-item HAM-D is widely used as a cutoff point. However, there are also 21-item, 24-item, and 28-item versions of the HAM-D, and the cutoff scores used for specific studies often vary, depending on the number of HAM-D items. As the number of items increases, Axis II psychopathology is sometimes factored into the degree of severity.[5]

The subtype of depression can also help to differentiate between mild-to-moderate and severe depression. Traditionally, diagnostic criteria for melancholia and psychotic depression with delusions or hallucinations have been used to classify severity.[6,7] According to the DSM-IV,[8] a diagnosis of a major depressive episode with melancholic features requires the loss of pleasure or reactivity to usually pleasurable stimuli. Additional criteria include 3 of the following: (1) distinct quality of depressed mood that is different from bereavement, (2) depression that is worse in the morning, (3) awakening at least 2 hours before the usual time, (4) marked psychomotor retardation or agita-

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tion, (5) significant anorexia or weight loss, and (6) excessive or inappropriate guilt. Under current diagnostic criteria, depression with melancholic features is not synonymous with severe depression[9]; lack of reactivity, anhedonia, and diurnal mood variation may distinguish the patients with the melancholic subtype from those with severe depression. Psychotic depression with delusions and/or hallucinations is also generally associated with more severe depressive symptoms and greater dysfunction than nonpsychotic depression.

Hospitalization status is another traditional delimiter for the presence of severe depression. However, in the United States as opposed to Europe, patients are unlikely to be hospitalized unless they are suicidal or exhibit severe functional impairment. Thus, using hospitalization to define severity may skew between-study comparisons. Depression that is complicated by comorbid psychiatric or medical problems also tends to be more severe than a single episode of major depression. The depressed patient with heart or kidney disease, alcoholism, or panic disorder tends to have greater distress, as assessed by the number and severity of symptoms, than patients with depression only.

Rather than gauging severity by rating scale scores, subtype, hospitalization status, or comorbidity, clinicians generally make a judgment on the basis of a combination of the overall symptomatology and the degree of functional impairment at home, at work, and in relationships. The number of symptoms and amount of dysfunction tend to be markers for the severity of the depression. While some patients who have mild symptoms may be unable to function at work and others with severe symptoms may force themselves to work every day, for the most part, the greater the number of and severity of symptoms, the worse the dysfunction. Severely ill patients also tend to be more anxious and agitated than those who are mildly depressed.[10]

EVALUATING TREATMENT STUDIES

Issues that arise from the literature on the treatment of severe depression involve the study population and methodology, e.g., definition of response, duration of treatment, and drug regimen. Historically, patients were classified as having severe depression, a melancholic subtype, or endogenous depression, but some studies enroll a heterogeneous population of inpatients and outpatients who have diagnoses ranging from mild to severe depression. Depression in the elderly may differ in symptomatology and biological mechanisms from depression in younger patients.

Definition of response and duration of treatment are other factors that are relevant to evaluating the literature on treating severe depression. Most studies submitted to the Food and Drug Administration (FDA) as part of the new drug approval process define a clinical response as a 50% reduction from baseline in the HAM-D total score at the end of a 6- to 8-week study. But baseline HAM-D scores, which generally decline at a similar rate in most patients irrespective of severity, are likely to be higher at baseline in severely depressed than in mildly or moderately depressed patients. If the HAM-D score in a patient with a baseline score of 30 is reduced by 50% during 6 to 8 weeks of treatment, the endpoint score of 15 may still represent the presence of substantial symptomatology. A more realistic definition of clinical response may be a 60% drop in HAM-D scores from baseline to endpoint or an endpoint HAM-D score equal to or less than 10 or 8 at the end of a 6- to 8-week clinical trial, but only about half the clinical trials link outcome to a predetermined rating scale score. Prien et al.[11] reviewed the definition of clinical response in 84 acute-treatment studies and found that 41 (49%) used a specific cutoff score on a rating scale as an outcome measure. The majority of those that used a specific score chose a HAM-D score of between 5 and 15, which may be problematic for evaluating severely depressed patients whose scores are unlikely to decrease by 20 to 25 points in a few weeks. Severely depressed patients may need a longer trial to achieve euthymia,[7] and thus, the criterion of a 50% reduction in baseline HAM-D score after 6 to 8 weeks of treatment may not be appropriate.

While patients who are severely depressed may also require aggressive dose titration and combination therapy, few protocols call for the dose to be increased with the goal of lowering the score further after the outcome criterion is met. Severe depression warrants aggressive dose titration but, particularly when a TCA is used as a comparator, there is concern about exposing patients to potential side effects when the dose is at the high end of the recommended range. This failure to aim for a complete remission, i.e., single-digit HAM-D scores, is a major limitation in many studies of severe depression, and results from studies that use lower antidepressant doses may not be generalizable to severely depressed patients. In clinical practice, low doses of a single antidepressant are frequently ineffective in severe depression, which is often treated with combination therapy.

NEWER ANTIDEPRESSANTS IN SEVERE DEPRESSION

Selective Serotonin Reuptake Inhibitors

The debate over the efficacy of SSRIs versus TCAs in severe depression started in Europe with 2 studies by the Danish University Antidepressant Group (Table 1).[2,3] In both studies, complete response was defined as an endpoint score on the 17-item HAM-D as equal to or less than 7; partial response as a HAM-D score between 8 and 15; and no response as a HAM-D score of 16 or above. In

Table 1. Tricyclic Antidepressants Versus Serotonin Selective Reuptake Inhibitors in Severe Depression*

	Study 1[a] (5-wk outcome)						Study 2[b] (4-wk outcome)					
	Citalopram (%) (N = 50)			Clomipramine (%) (N = 52)			Paroxetine (%) (N = 56)			Clomipramine (%) (N = 46)		
Patients	CR	PR	NR	CR	PR	NR	CR	PR	NR	CR	PR	NR
Endogenous depression	34	32	34	62	8	30	15	40	45	28	58	14
Nonendogenous depression	8	75	17	54	33	13	25	31	44	30	60	10
Total	28	42	30	60	15	25	18	37	45	28	59	13

*Complete response (CR) = 17-item Hamilton Rating Scale for Depression (HAM-D) score ≤ 7 score; partial response (PR) = HAM-D score 8–15; no response (NR) = HAM-D score ≥ 16.
[a]Data from reference 2.
[b]Data from reference 3.

study 1,[2] the authors compared the SSRI citalopram with the TCA clomipramine in 102 inpatients whose HAM-D scores were equal to or greater than 18 after 1 week of placebo treatment. The patients, who were classified as having endogenous (N = 75) or nonendogenous (N = 27) depression, were randomly assigned to receive either 40 mg/day of citalopram (N = 50) or 150 mg/day of clomipramine (N = 52) for 5 weeks. Patients who completed more than 2 weeks of treatment were included in the statistical analyses of therapeutic effect. A complete response was achieved in 60% of the clomipramine-treated patients and 28% of the citalopram-treated patients, a partial response in 15% of the clomipramine-treated patients and 42% of the citalopram-treated patients, and no response in 25% of the clomipramine-treated patients as opposed to 30% of the citalopram-treated patients. The clomipramine remission rate in study 1 was high; the incidence of remission, as defined by a HAM-D score equal to or less than 7, is usually around 30% in severe depression.[12]

The trend toward greater efficacy for the TCA was similar, but the difference in response was not as large in study 2, a comparison of the SSRI paroxetine versus clomipramine.[3] The inpatients (N = 102) were treated with 30 mg/day of paroxetine (N = 56) or 150 mg/day of clomipramine (N = 46) for 6 weeks except that nonresponders were terminated after 4 weeks. Of the patients, 76 were classified as having endogenous depression and 26 as having nonendogenous depression. At week 4, a complete response was achieved in 28% of the clomipramine-treated patients and 18% of the paroxetine-treated patients, a partial response in 59% of the clomipramine-treated patients and 37% of the paroxetine-treated patients, and no response in 13% of the clomipramine-treated patients as opposed to 45% of the paroxetine-treated patients. In study 2, the nonresponse rate for paroxetine was unusually high, which may be attributed to either the relative low daily dose or the brief duration of the study. In addition, the remission rates seen with clomipramine were similar to those in other studies (< 30%) and were lower than in the previous Danish University Antidepressant Group study on clomipramine versus citalopram.[2]

In the United States, support for the use of TCAs over SSRIs in severe depression came from a study of elderly inpatients with depression and cardiovascular illness. In a retrospective analysis of pooled data, Roose et al.[4] found an SSRI to be significantly less effective than a TCA for treating severe depression. The sample consisted of 64 hospitalized elderly patients with unipolar depression and heart disease, most of whom met DSM-III criteria for the melancholic subtype, who were treated with either fluoxetine (N = 22) for 6 weeks or nortriptyline (N = 42) for 4 weeks. The mean baseline HAM-D scores were high: 28 for the nortriptyline-treated group and 26 for the fluoxetine-treated group. The maximum dosage of fluoxetine was 60 mg/day and of nortriptyline, 1 mg/kg/day (plasma nortriptyline level was 50–150 ng/mL), and patients who received medication for 4 weeks were considered to be completers. Response criteria were (1) patient self-assessment of return to baseline function, (2) discharge for 2 weeks without a dosage adjustment or medication change, and (3) final HAM-D score less than 8. Of the 34 patients who completed nortriptyline treatment, 28 (82%) met the response criteria. The response rate for the melancholic completers was 83% (20 of 24). Of the 18 patients who completed the fluoxetine trial, 5 (28%) of the total group and 1 (10%) of 10 with melancholia met the response criteria. The dropout rates were similar—19% (8 of 42) for the nortriptyline group and 18% (4 of 22) for the fluoxetine group, and the statistical difference between the groups was significant for both completers ($p < .01$) and those with melancholia ($p < .001$).

The nature of this study population makes it difficult to generalize the results.[4] The sample comprised elderly patients with cardiovascular disease and substantial melancholia who were hospitalized on a depression research unit for at least 2 months. The mean age was 70 years for the nortriptyline group and 73 years for the fluoxetine group. A major methodological limitation of the study was that the comparison group was created through a retrospective chart review rather than by random assignment. The nortriptyline data came from patients who participated in studies of nortriptyline versus imipramine, doxepin, and bupropion. At baseline, the mean ± SD HAM-D score was higher for

the nonresponders (30 ± 9 for nortriptyline, 30 ± 7 for fluoxetine) than the responders (25 ± 6 for nortriptyline, 23 ± 4 for fluoxetine), which provides additional support for the suggestion that patients, and particularly the elderly, who are severely ill are less likely to meet criteria for response or remission than those who are mildly or moderately depressed. Nelson et al.[13] also reported a low response in a group of severely depressed hospitalized patients (N = 41) who were treated with desipramine. Only 6 (46%) of 13 patients who achieved a therapeutic blood desipramine level (≤ 115 ng/mL) met the criteria of a decrease of 50% and a HAM-D score less than 10 after 4 weeks of treatment.

Recently, however, in a double-blind study, Roose et al.[14] found similar efficacy between a TCA and a SSRI but significantly fewer adverse cardiac events with the SSRI in a group of depressed outpatients with ischemic heart disease. The patients (N = 81) were treated for 6 weeks with either 20 to 30 mg/day of paroxetine or nortriptyline targeted to a blood drug level of 50 to 150 mg/mL. Improvement in depression was assessed by a 50% decrease in the HAM-D score. According to this criterion, 25 (61%) of 41 paroxetine-treated patients and 22 (55%) of 40 nortriptyline-treated patients improved. Paroxetine had no sustained effects on heart rate or rhythm or indexes of heart rate variability, while nortriptyline treatment produced a sustained 11% increase in heart rate and a reduction in heart rate variability. Adverse cardiac events occurred in 1 paroxetine-treated and 7 nortriptyline-treated patients. The differences in response between fluoxetine and paroxetine in the 2 studies[4,14] may be attributed to recent findings[15] that paroxetine possesses moderately high affinity for the norepinephrine transporters.

The response rate is likely to be lower when more stringent outcome criteria are used. Tignol et al.[16] measured response in a meta-analysis of the worldwide database of hospitalized patients with severe depression who were treated with paroxetine (N = 178). Thirty-two percent of the patients were classified as responders when the criterion was a HAM-D score equal to or less than 10, whereas about 45% were responders when the measure was at least a 50% or greater decrease in HAM-D score.

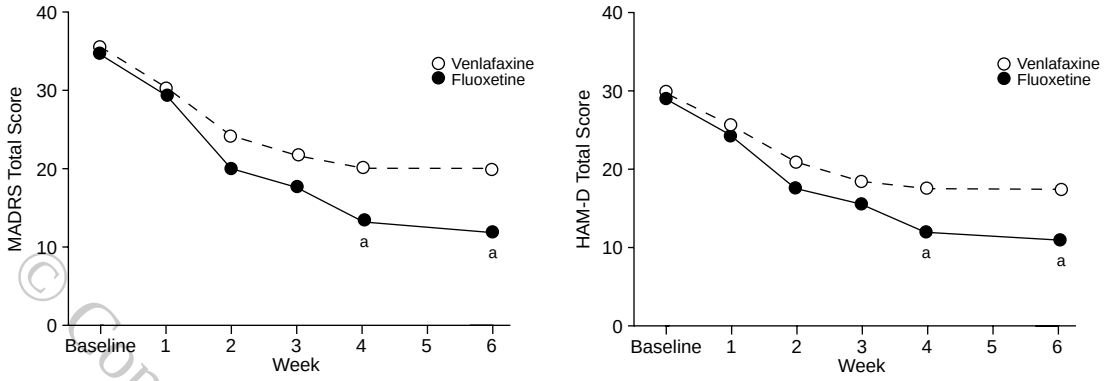
In contrast, several researchers have found little difference in effectiveness between SSRIs and TCAs. In a comparison of paroxetine and amitriptyline,[17] efficacy between the drugs was similar, but the dropout rate was high for both agents. The double-blind, 6-week multicenter European trial enrolled 153 hospitalized patients. The mean dose of paroxetine was 33.3 mg/day and of amitriptyline, 166 mg/day, while the maximum allowed dose of paroxetine was 50 mg/day and of amitriptyline, 250 mg/day. Response was defined as at least a 50% reduction in total HAM-D score and/or a score equal to or less than 14, which is generally considered to be representative of response but not remission. Between 80% and 89% of completers in both groups met these criteria, but 32 patients in the paroxetine group and 29 in the amitriptyline group dropped out of the study. The percentage of patients with HAM-D scores equal to or less than 14 increased from 51% at week 4 to 89% at week 6 in the paroxetine group and from 60% at week 4 to 80% at week 6 in the amitriptyline group.

Wheadon[18] also found similar efficacy for both paroxetine and imipramine in a 6-week trial. Both drugs were significantly ($p < .05$) more efficacious than placebo. The mean reduction from baseline HAM-D score was 13.7 in the paroxetine group and 9.87 in the imipramine group, and paroxetine also was significantly ($p < .05$) better than imipramine in the HAM-D anxiety/somatization and cognition subfactors.

There were no significant differences between the SSRI fluvoxamine and the TCA imipramine for severe depression, as classified by a HAM-D score equal to or more than 26, in a double-blind, placebo-controlled, randomized trial.[19] The 103 patients who participated in the multicenter, 4-week trial were divided into 3 groups: fluvoxamine (N = 33), imipramine (N = 40), and placebo (N = 30). Fifty-five percent of the fluvoxamine-treated patients and 35% of the imipramine-treated patients were responders on the basis of at least a 50% decrease in HAM-D score. However, even in responders, the mean final HAM-D scores remained high: 15.2 for fluvoxamine and 18.4 for imipramine. Results were also similar in a comparison of the SSRI sertraline and the TCA amitriptyline in late-life depression.[20] A total of 241 patients enrolled in the 8-week, double-blind study; 161 were randomly assigned to receive 50 to 200 mg/day of sertraline and 80 to receive 50 to 150 mg/day of amitriptyline (plasma amitriptyline levels were not measured). As defined by a 50% decrease in the HAM-D score, 66.9% of the sertraline-treated patients and 62.9% of the amitriptyline-treated patients were responders.

While Bowden et al.[21] found that both desipramine and fluoxetine were efficacious in a 6-week, double-blind, parallel group study of severely depressed patients, further analysis of the data (A.F.S., unpublished data, 1996) suggested that desipramine was more likely than fluoxetine to produce remission, as defined by at least a 60% reduction in HAM-D score and a final HAM-D score less than or equal to 8. The 58 patients were randomly assigned to treatment with up to 60 mg/day of fluoxetine or 300 mg/day of desipramine; the mean final daily dose of fluoxetine was 27 mg/day and of desipramine 145 mg/day. At baseline, the mean HAM-D score in both groups was slightly over 25, which is indicative of severe depression. Overall, 64% of the fluoxetine-treated patients and 68% of the desipramine-treated patients had at least a 50% reduction in HAM-D score after at least 3 weeks of treatment, and, in general, fluoxetine produced fewer and less severe side effects than desipramine. The mean standing heart rate increased from 80 to 95 beats per minute only in the patients treated with desipramine.

Figure 1. Venlafaxine Versus Fluoxetine in Severe Depression*



*From reference 24, with permission. Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Rating Scale for Depression (HAM-D) total scores for intent-to-treat population as a function of time. All on-therapy values for MADRS and HAM-D are significantly different ($p \leq .05$) from baseline values.
[a]$p \leq .05$.

When the 45 patients who completed the study were analyzed separately by change in HAM-D score (A.F.S., unpublished data, 1996), 15 of the fluoxetine-treated patients and 16 of the desipramine-treated patients met the initial response criteria of a 50% reduction in HAM-D score; 10 of the fluoxetine-treated patients and 14 of the desipramine-treated patients met the more stringent criteria of a 60% reduction in HAM-D score; and 8 of the fluoxetine-treated patients, and 13 of the desipramine-treated patients met criteria for remission (a 60% reduction in HAM-D score and a final HAM-D score ≤ 8. Thus, 35% of the fluoxetine-treated patients and 59% of the desipramine-treated patients met criteria for remission. When the patients were classified according to baseline HAM-D score, only 2 of the 11 fluoxetine-treated patients, but 7 of the 12 desipramine-treated patients whose baseline HAM-D score was equal to or greater than 25 met the criteria for remission. Limitations of this study include a small sample size, a relatively low fluoxetine dosage, and the 6-week duration. More aggressive titration and a longer duration might have produced greater efficacy for the SSRI in the severely depressed patients.

Levels of urinary 3-methoxy-4-hydroxyphenylglycol (MHPG), a catecholamine metabolite that is a marker for catecholamine, have been used to predict response to antidepressants. Pretreatment lower MHPG levels were reported to predict response to norepinephrine drugs such as maprotiline and imipramine,[22,23] and, in the further analysis of the Bowden et al.[21] study (A.F.S., unpublished data, 1996), a better response to both fluoxetine and desipramine was found in the patients who were low, as opposed to high, MHPG excreters. Using logistic regression, MHPG levels, but not baseline severity, were significant predictors of remission.

Even if rating scale scores are slightly higher in TCA-treated than SSRI-treated patients in clinical studies of severe depression, the risk/benefit ratio still favors the SSRIs because they are associated with less morbidity and mortality, especially with overdoses, than are the TCAs.

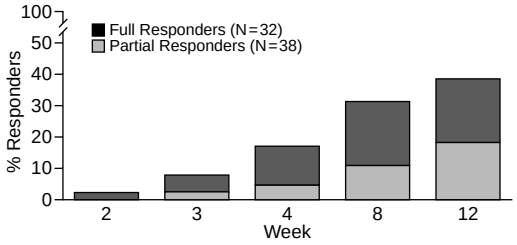
Venlafaxine and Venlafaxine XR

There is some evidence that venlafaxine, a serotonin-norepinephrine uptake inhibitor, may be more efficacious than fluoxetine in treating patients with severe depression. In a head-to-head study of the 2 agents in 68 inpatients with major depression and melancholia, as defined by the DSM-III-R, Clerc et al.[24] found that 200 mg/day of venlafaxine was superior in efficacy to 40 mg/day of fluoxetine. Decreases in scores on both the MADRS and the HAM-D were significantly ($p < .05$) different between fluoxetine and venlafaxine at week 4 and week 6 (Figure 1).

Remission rates, as defined by a final total HAM-D score equal to or less than 7, were significantly higher for venlafaxine extended release (XR) than fluoxetine at the end of an 8 week double-blind, placebo-controlled study of 301 outpatients with major depressive disorder.[25] Full remission occurred in 37% of the venlafaxine XR–treated patients, 22% of the fluoxetine-treated patients, and 18% of the placebo-treated patients. In another placebo-controlled study, Guelfi et al.[26] also reported on the efficacy of up to 375 mg/day of venlafaxine in 93 patients who were hospitalized for major depression and melancholia. Venlafaxine provided significantly greater improvement than placebo in the MADRS scores after 4 days ($p < .026$) and HAM-D scores after 1 week ($p < .043$), and the response rate, as defined by a 50% decrease in MADRS score after 4 weeks of treatment, was 65% (30 of 46 patients) for venlafaxine versus 28% (13 of 47 patients) for placebo.

More support for the usefulness of venlafaxine in patients with severe depression comes from an open study

Figure 2. Venlafaxine in Treatment-Resistant Depression*



*Data from reference 27. Full response = 21-item Hamilton Rating Scale for Depression (HAM-D) score < 8 and Clinical Global Impressions (CGI) score of 1; partial response = 50% decrease in HAM-D score and a CGI score of 2.

of 70 treatment-refractory patients with unipolar depression.[27] The patients, who had failed to respond to adequate trials of at least 3 antidepressants from at least 2 different antidepressant classes or electroconvulsive therapy (ECT) plus at least 1 augmentation attempt, had 21-item HAM-D scores equal to or greater than 21 at baseline after a 4-day antidepressant washout period. They received up to 450 mg/day of venlafaxine (mean ± SD dose = 245.2 ± 99.3). Full response was defined as a HAM-D score of 8 or lower, a MADRS score of 12 or lower, and a CGI score of 1, and partial response was defined as a 50% decrease in the HAM-D and MADRS (final HAM-D score > 8, final MADRS score >12) and CGI score of 2. About one third of patients were considered to be either full or partial responders after 12 weeks of venlafaxine treatment (Figure 2), and 46% continued to sustain this response for at least 3 months. This response rate is not unusual when a new class of antidepressant is tried in refractory patients, who are the most difficult to treat.[28]

Remission occurred significantly more often in a group of patients (N = 359) treated with venlafaxine XR versus fluoxetine in a 12-week, double-blind, placebo-controlled, randomized study of outpatients with depression and concomitant anxiety.[29] At week 12, the HAM-D remission rate was significantly higher ($p < .05$) for venlafaxine than for fluoxetine. Venlafaxine was also found to be as effective as clomipramine and more effective than trazodone in a randomized, double-blind, 42-day study of elderly inpatients and outpatients with depression.[30]

Reboxetine

Reboxetine, a pure norepinephrine uptake blocker that is not available in the United States, has been reported to be superior to fluoxetine in severe depression.[31] A total of 549 inpatients and outpatients with major depression received 8 to 10 mg/day of reboxetine or 20 to 40 mg/day of fluoxetine for 8 weeks. The overall efficacy of reboxetine and fluoxetine was similar, as assessed by the mean reduction in HAM-D total score, but reboxetine demonstrated superior efficacy compared with fluoxetine in severely ill patients. This study provides further evidence that norepinephrine blockade may play a role in treating severe depression.

NEWER ANTIDEPRESSANTS IN PSYCHOTIC DEPRESSION

The presence of major depression with psychotic features (psychotic depression, delusional depression) is also used as a yardstick for severity. Historically, patients with psychotic depression tended to respond poorly to placebo, to TCAs alone, and to antipsychotics, but they often improved after treatment with a combination of a TCA plus an antipsychotic, amoxapine, or ECT. ECT remains an effective treatment, particularly for psychotically depressed patients, but maintenance treatment is necessary and may lead to ECT-related confusion and/or memory impairment. Recently, support has grown for the use of the newer antidepressants alone and in combination for patients with psychotic depression.

When fluoxetine was combined with perphenazine for the treatment of 30 patients who had major depression with psychotic features, 22 patients (73%) had a 50% or greater reduction in total HAM-D score by week 5.[32] The mean ± SD HAM-D score decreased significantly ($p < .001$) from 30 ± 6 at baseline to 12 ± 7 at week 5, and the Brief Psychiatric Rating Scale score decreased from 53 ± 8 at baseline to 30 ± 9 at week 5. These results are similar to the response that has been reported for the combination of TCAs and an antipsychotic.[33]

Fluvoxamine alone has also been reported to be useful in the treatment of delusional depression.[34] Inpatients (N = 59) who met DSM-III-R criteria for major depression with psychotic features were openly treated for 6 weeks with up to 300 mg/day of fluvoxamine in a study conducted by an Italian research group. Patients who were taking lithium at the beginning of the study were allowed to continue the drug. Depressive symptoms were assessed with the 21-item HAM-D, and delusional symptoms with the Dimensions of Delusional Experience rating scale. Of the 57 patients who completed the trial, 48 (84.2%) were classified as responders (HAM-D score < 8 and Dimensions of Delusional Experience Rating Scale score = 0). The mean HAM-D score decreased substantially from 33 to 4. These results are extremely robust, although one may wonder whether there are possible cultural differences between the United States and Europe in the diagnosis of delusional depression, particularly in regard to how obsessive ruminations are characterized. Moreover, in this study and in the one below, some patients were also receiving lithium carbonate.

When the same criteria for response were used, the same research group[35] also found sertraline to be superior to paroxetine for the treatment of DSM-III-R-defined major depression with psychotic features. Under double-blind con-

ditions, 46 inpatients who met DSM-III-R criteria for major depression with psychotic features were treated with up to 150 mg/day of sertraline (N = 24) or up to 50 mg/day of paroxetine (N = 22). All 24 patients in the sertraline group completed the study and 18 (75%) met the response criteria as opposed to 6 (46%) of the 13 patients who completed the paroxetine trial. The mean ± SD total HAM-D score in responders who received sertraline declined from 32 ± 4 to 5 ± 1 and in those who received paroxetine from 36 ± 10 to 6 ± 2. The authors attributed the large difference in the number of dropouts between the 2 groups to the rapid titration and/or the 50 mg/day dose of paroxetine.

CONCLUSION

Remission rates are relatively low in many of the short-term clinical trials of antidepressants in severe depression, but are likely to improve with longer trials and aggressive dosing. However, aggressive dosing with the TCAs can be problematic in terms of side effects that often lead to noncompliance and of safety issues. Results from studies of the efficacy of the SSRIs in severe depression are conflicting, but, even if they are slightly less efficacious than the TCAs, their favorable side effect profile and fewer consequences of overdose make them a useful alternative to the SSRIs. Venlafaxine/venlafaxine XR, which has both serotonin and norepinephrine properties, particularly at high doses, and no anticholinergic effects may offer a greater advantage than either the TCAs or the SSRIs in severely depressed patients. Reboxetine may also have advantages in this group.

Drug names: amitriptyline (Elavil and others), amoxapine (Ascendin), bupropion (Wellbutrin), citalopram (Celexa), clomipramine (Anafranil), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), maprotiline (Ludiomil), nortriptyline (Pamelor and others), paroxetine (Paxil), perphenazine (Trilafon), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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DISCLOSURE OF OFF-LABEL USAGE

The following agents mentioned in this article are *not* indicated for these specified uses: fluvoxamine for treatment of major depression and reboxetine for any use in the United States.