Efficacy of SSRIs and Newer Antidepressants in Severe Depression: Comparison With TCAs

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Background: The significant morbidity and mortality associated with severe depression and its psychotic or melancholic subtypes necessitate effective and well-tolerated therapy. This review evaluates antidepressant treatments for patients with severe depression.

Data Sources: Comparative clinical trials conducted on patients with severe depression were found by an English-language MEDLINE search (1985 to present). Additional studies were identified in article bibliographies. Search terms included *depressive disorders*, *depression* and *severe*, *hospitalized*, *melancholic* or *melancholia*, *psychotic*, and *endogenous*.

Study Findings: Evidence for efficacy of SSRIs in severe or melancholic depression comes from a small but growing number of controlled studies with adequate samples, as well as meta-analyses and retrospective subgroup analysis of premarketing trials. In studies that defined response as a 50% or greater reduction in Hamilton Rating Scale for Depression (HAM-D) scores, response rates ranged from 53% to 64% for SSRIs and 43% to 70% for TCAs. In separate trials on severe depression, venlafaxine and mirtazapine were both more effective than placebo and an active comparator. Nefazodone and bupropion were each found to be more effective than placebo in studies of severe depression. Venlafaxine and mirtazapine have been found to be more effective than fluoxetine.

Conclusion: SSRIs and TCAs are comparably effective for the treatment of severe or melancholic depression. SSRIs and other newer agents appear to be better tolerated than TCAs, specifically lacking adverse anticholinergic and cardiovascular effects that may limit the use of TCAs. Emerging data with venlafaxine and mirtazapine in severely depressed patients with or without melancholia support the efficacy of these treatments. Nefazodone and bupropion were found to be effective in hospitalized depressed patients. Electroconvulsive therapy (ECT) or combined antidepressant therapy may be useful in some patients with severe depression. Patients with severe psychotic depression may respond better to an antipsychotic-antidepressant combination.

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Depression is not only underrecognized and undertreated but is associated with significant morbidity and mortality.[1] The prognosis and course of severe depression are even worse. Studies examining the response of severely depressed patients to tricyclic antidepressant (TCA) therapy generally have found that severe depression predicts a poor response to TCAs.[2,3] Moreover, TCAs are often not well tolerated. Melancholic depression, a subtype of severe depression, responds poorly to nonsomatic therapy.[4,5] Although melancholia is commonly considered a predictor of response to TCAs, this relationship has not been demonstrated consistently.[6,7] Increasing data support the use of selective serotonin reuptake inhibitors (SSRIs) and other newer agents (bupropion, nefazodone, venlafaxine, and mirtazapine) in patients with severe depression. Combination antidepressant therapy or electroconvulsive therapy (ECT) may be useful for severely depressed patients who do not respond to other measures.

An issue generating considerable controversy is whether the SSRIs are as effective as TCAs in severe depression. This controversy may, in part, have been fueled by the fact that most phase 3 and phase 4 studies of these newer agents have excluded the most severely ill patients and by reports of reduced efficacy as compared with TCAs.[8–10] On the other hand, there are many reports supporting the efficacy of the SSRIs in severe depression. In this article, newer treatments for patients with severe depression are reviewed, with the primary focus on the comparative efficacy of the SSRIs and TCAs. Reasons for difficulties in comparing results across studies of severe depression also are discussed.

METHODOLOGICAL ISSUES IN STUDIES OF SEVERE DEPRESSION

Data Sources

Comparative clinical trials conducted on patients with severe depression were found by an English-language MEDLINE search (1985 to present). Additional studies were identified in article bibliographies. Search terms included *depressive disorders*, *depression* and *severe*, *hospitalized*, *melancholic* or *melancholia*, *psychotic*, and *endogenous*.

Defining Severe Depression

In clinical studies, a variety of methods and markers have been used to define severe depression.[11] Commonly used criteria include hospitalization, symptom severity, symptomatic and functional impairment, and depressive subtype. However, there is no consensus on the definition of severe depression.

Hospitalization. In the past, a commonly used marker for severe depression was hospitalization. However, substantial changes in practice patterns in the United States in recent years have led to treatment of most severely ill depressed patients on an ambulatory basis, reserving hospitalization for a group of atypical patients.

Symptom severity. In the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV),[12] severe depression is defined as depressive symptoms in excess of those required to meet the diagnosis of major depression in conjunction with impaired social or occupational functioning. The Hamilton Rating Scale for Depression (HAM-D) is the most commonly used clinician-rated measure of depressive symptoms. On the 17-item HAM-D, a score of 25 or higher is often considered to indicate severe depression.

Symptomatic and functional impairment. As mentioned above, the DSM-IV includes impaired social or occupational function in its definition of severe depression. The Global Assessment Scale (GAS) considers both symptoms and degree of functional impairment. A score of 50 or less (range, 0–90) has been used to signify severe depression.[13]

Depressive subtypes/features. Another way to define severe depression is by depressive subtype, particularly psychotic or melancholic depression.[12] Choosing study subjects on the basis of HAM-D scores can create a bias toward including melancholic patients because they often score high on severity scales.[7] In fact, melancholic patients may be more severely ill than their HAM-D scores suggest because of substantial anhedonia and psychomotor retardation. In contrast, nonmelancholic patients with severe depression may suffer from a distinct, nonmelancholic symptom profile, with high scores for anxiety, hypochondriasis, and suicidal ideation.[7] Although there appears to be considerable overlap between severe depression and melancholia, severe depression cannot categorically be substituted for melancholic depression because not all patients with melancholia are severely depressed.[6]

Defining Treatment Response

A variety of endpoints have been used to define the response to antidepressant therapy. Typically, antidepressant response is defined as a 50% or greater reduction in HAM-D score. The drawback to this method in studies of severe depression is that it does not differentiate between complete or partial responders when baseline HAM-D scores are high. For example, a severely depressed individual with a baseline HAM-D score of 30 would still be symptomatic even with a 50% reduction at the conclusion of the study (i.e., endpoint HAM-D score of 15).

An approach used to differentiate between partial and complete responders is to establish an absolute HAM-D score required for partial and complete response (rather than a percent drop in score from baseline). This absolute score approach to response is commonly used, but there is little agreement on what scores should be used. In a review examining the attributes of 123 research reports, the cutoff HAM-D score ranged from 5 to 15.[11]

The length of a particular trial can affect endpoint HAM-D levels.[14] For example, studies of 12 weeks' duration demonstrate continued decline of HAM-D scores throughout. So, 6- or 8-week studies may underestimate the response rate in patients with severe depression. This is particularly a problem when a low HAM-D cutoff score is used to define response.

Power and Sample Size

The inability to demonstrate differences in response rates between TCAs and SSRIs for the treatment of depression may also be a function of sample size. In many severe depression clinical trials, fewer than 70 patients were enrolled per group, making it difficult to detect significant differences in response rates between treatment groups.[15–18] To detect an absolute difference in efficacy as small as 20% requires 70 patients in each group, whereas to detect an absolute difference as small as 10% (alpha = .05; power = 80%), a parallel-group trial must include more than 350 patients in each group.[13,19]

Criteria for Inclusion in This Review

We selected studies of the treatment of severe depression using one of the above definitions that included random assignment, double-blind evaluations, and objective and independent measures of outcome variables (which were defined prior to study inception). We originally intended to implement restrictions regarding duration of treatment, dosing, etc., but elected not to do so after encountering the wide variety of designs employed in studies around the world.

Table 1. Comparative Clinical Trials of SSRIs and Other Newer Agents and TCAs for Severe Depression[a]

Study	N	Duration (wk)	Drug, mg/d (mean)	Baseline Mean HAM-D Score	Outcome
Inpatient population					
Ottevanger[15]	20	4	Fluvoxamine100–300 (204)	25.7–26.4	HAM-D reduction: fluvoxamine = clomipramine
	20	4	Clomipramine 50–150 (106)		
Arminen et al[16]	25	12	Paroxetine 20–40	≥ 24	HAM-D ≤ 7: paroxetine = imipramine
	32	12	Imipramine 100–200		
Beasley et al[17]	56	6	Fluoxetine 20–80 (median 80)	27–28	HAM-D ≤ 7: fluoxetine = imipramine; 50% reduction HAM-D: fluoxetine = imipramine
	62	6	Imipramine 75–300 (median 200)		
Tignol et al[20]	109	≤ 6	Paroxetine 10–40	29.2–29.8	≥ 50% reduction HAM-D: paroxetine = TCA; HAM-D < 10: paroxetine = TCA
	107	≤ 6	TCA[b]		
Danish University Antidepressant Group[8]	56	6	Paroxetine 30	~23	HAM-D ≤ 7: clomipramine[c] > paroxetine
	46	6	Clomipramine 150	~23	
Ginestet[21]	28	≤ 8	Fluoxetine 20–80 (60)	33.1–33.7	HAM-D reduction: fluoxetine = clomipramine
	26	≤ 8	Clomipramine 50–200 (150)		
Danish University Antidepressant Group[9]	50	5	Citalopram 40	20–23	HAM-D ≤ 7: clomipramine[c] > citalopram
	52	5	Clomipramine 150	20–23	
Fabre et al[22]	48	4	Bupropion 300–600	~29	CGI 1–2: bupropion (61%) > placebo (28%)
	27	4	Placebo	~28.5	
Merideth and Feighner[23]	44	4	Bupropion 300–600	~32	CGI 1–2: bupropion (79%) > placebo (13%)
	22	4	Placebo	~29	
Feighner et al[24]	61	6	Nefazodone 100–600 (366)	27.9	CGI 1–2: nefazodone (50%) > placebo (29%); HAM-D ≤ 10: nefazodone (36%) > placebo (14%)
	59	6	Placebo	27.5	
Clerc et al[25]	33	6	Venlafaxine (200)	29.1	≥ 50% reduction in MADRS:
	34	6	Fluoxetine (40)	29.7	venlafaxine (76%) > fluoxetine (47%)
Wheatley and Kremer[26]	66	6	Mirtazapine 15–60 (39.8)	26	Reduction in HAM-D:
	67	6	Fluoxetine 20–40 (23.8)	26.1	mirtazapine (14.2) > fluoxetine (10.3)
Bremner[27]	50	6	Mirtazapine (5–35)	28.3	≥ 50% reduction in HAM-D: mirtazapine (70%),
	50	6	Amitriptyline (40–280)	27.3	amitriptyline (58%) > placebo (33%)
	50	6	Placebo	26.6	
Mixed population					
Bowden et al[18]	28	6	Fluoxetine 20–60	25.4–25.7	≥ 50% reduction HAM-D: fluoxetine = desipramine
	30	6	Desipramine 150–250		
Kasper et al[28]	34	4	Fluvoxamine 50–300 (58.5)	28.6–29.4	HAM-D reduction: fluvoxamine[d]
	40	4	Imipramine 50–300 (151.0)		> imipramine, placebo; CGI 1–2:
	31	4	Placebo		fluvoxamine[c] > imipramine, placebo
Pande and Sayler[29]	781	≥ 4	Fluoxetine (dose NR)	≥ 25	50% reduction HAM-D: fluoxetine = TCA;
	788	≥ 4	TCA[e] (dose NR)		HAM-D ≤ 7: fluoxetine = TCA
Outpatient population					
Feighner et al[30]	240	6	Paroxetine 10–50 (30)	≥ 28	HAM-D reduction: paroxetine[c] > imipramine, placebo
	237	6	Imipramine 65–275 (140)		HAM-D < 10: paroxetine = imipramine, placebo
	240	6	Placebo		
Reimherr et al[31]	26	8	Sertraline 50–200 (132)	24.2–25.5	HAM-D reduction: sertraline = amitriptyline > placebo
	25	8	Amitriptyline 50–150 (78)		
	26	8	Placebo		

[a]Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, NR = not reported, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.
[b]Amitriptyline, clomipramine, maprotiline, mianserin.
[c]$p < .05$.
[d]$p = .055$ fluvoxamine > imipramine; $p = .004$ fluvoxamine versus placebo.
[e]Amitriptyline, desipramine, doxepin, imipramine, nortriptyline.

COMPARATIVE EFFICACY OF SSRIs AND TCAs IN SEVERE AND MELANCHOLIC DEPRESSION

We present studies in Table 1 according to whether the population was exclusively inpatient, mixed inpatient and outpatient, or exclusively outpatient.

Studies in Inpatients

Highlights of all identified comparative studies of SSRIs versus TCAs in severely depressed hospitalized inpatients are described below and in Table 1. Six were clinical trials of between 4 and 12 weeks' duration and 1 was a meta-analysis of data from European clinical trials. In 5 trials, the reduction in HAM-D score was comparable and not significantly different between patients receiving an SSRI and those receiving a TCA. In 2 trials, the TCA was more effective.

Fluvoxamine (100–300 mg/day) was compared with clomipramine (50–150 mg/day) in a 4-week trial in severely depressed inpatients.[15] The reduction in HAM-D score was not different between the 2 groups, but fluvoxamine was significantly better tolerated. More patients re-

ceiving clomipramine developed undesirable orthostasis or anticholinergic effects. The small sample size (40 patients) may have made it difficult to detect efficacy differences.

Arminen and associates[16] conducted a 12-week, randomized, inpatient trial comparing paroxetine (20–40 mg/day) with imipramine (100–200 mg/day) in 57 depressed inpatients. Baseline HAM-D scores were not reported numerically; inclusion criteria required a score of at least 18. However, descriptive data provided in the published report illustrated that mean HAM-D scores were actually 24 or higher. HAM-D scores after the first 2 weeks of therapy were nearly identical but after that time, favored paroxetine (not significantly). Anticholinergic side effects were more common in imipramine-treated patients, whereas headache, diarrhea, and weight loss were more common in paroxetine-treated patients.

Beasley and associates[17] compared fluoxetine (20–80 mg/day) with imipramine (75–300 mg/day) in a multicenter trial of hospitalized patients with major depression. After 6 weeks of therapy, the mean decrease in HAM-D scores was 8.5 for fluoxetine (N = 56) and 11.9 for imipramine (N = 62). Both values were significantly lower than baseline ($p < .001$), but did not differ statistically from each other. The study had 98% power to detect a 6-point difference in mean HAM-D scores. Response rate, defined as a 50% decline in HAM-D score, was similar for fluoxetine and imipramine (54.5% versus 60%; $p = .649$). Even using the more rigorous criterion of a HAM-D score of 7 or less after 4 or more weeks of therapy, response was not significantly different between treatment groups (21.2% for fluoxetine versus 34.3% for imipramine; $p = .230$).

Despite similar response rates, the duration of inpatient treatment was shorter with fluoxetine. By the third week, 54.5% of fluoxetine-treated patients had been discharged compared with 43.2% of patients receiving imipramine. Among patients who completed the study, the median length of stay was 15 days for fluoxetine and 21 days for imipramine.

Discontinuation rates in both groups, although comparable (fluoxetine, 58.9%; imipramine, 61.3%), were much higher than typically observed,[21] which may be related to the high doses of fluoxetine used (up to 80 mg/day). These high discontinuation rates may affect the generalizability of the study results.

In another trial,[21] fluoxetine (mean dose = 60 mg/day) was as effective as clomipramine (mean dose = 150 mg/day) in 54 inpatients with severe endogenous depression and melancholia. After 2 months of therapy, baseline HAM-D scores were reduced in both groups from approximately 33 to 10, approximately a 68% improvement from baseline. Overall adverse events were comparable between the 2 treatment groups, although anticholinergic effects were more frequent in clomipramine recipients and nausea and tremor more common in fluoxetine recipients.

Paroxetine (N = 109) was compared with active pharmacotherapy controls (N = 107; amitriptyline, clomipramine, mianserin, or maprotiline) in a meta-analysis of European clinical trial data in severely depressed hospitalized patients.[20] Approximately 53% of paroxetine-treated patients and 56% of active controls achieved a 50% reduction in HAM-D score; 33% and 41%, respectively, achieved a HAM-D score below 10.

The Danish University Antidepressant Group[8,9] conducted 2 separate comparative trials in which the SSRIs citalopram and paroxetine were compared with clomipramine in hospitalized depressed patients. Approximately 50% to 75% of patients in both studies had endogenous depression. Despite hospitalization, mean HAM-D scores were relatively low (endogenous depression mean score = 23; nonendogenous depression mean score = 20). In both studies, complete response rates (i.e., HAM-D ≤ 7) with clomipramine were 57%[8] and 60%[9] ($p \leq .002$), and these were significantly better than rates with either paroxetine (22%) or citalopram (28%). Clomipramine was associated with a mean decline in total HAM-D scores of approximately 15 points as compared with a 10-point decline for the 2 SSRIs.[32] These results are discordant with most other studies. Of the 13 patients who dropped out because of side effects, 12 were receiving clomipramine.

Studies in Mixed Populations (Inpatients and Outpatients)

Bowden and coworkers[18] compared fluoxetine (20–60 mg/day) with desipramine (50–250 mg/day) in 58 inpatients and outpatients with initial mean HAM-D scores greater than 25 (Table 1). After 6 weeks, both medications were associated with a significant decrease in HAM-D scores as compared with baseline ($p < .001$), but the treatments were not different from each other. An earlier and significant improvement in sleep disturbance was noted in the fluoxetine group ($p < .001$ at week 1). Response rates did not differ when patients with baseline HAM-D scores higher than 24 (severely ill) were compared with patients with lower scores (moderately ill). Desipramine blood levels were not measured in this trial.

Data from a multicenter, placebo-controlled comparison between fluvoxamine and imipramine were stratified according to depression severity.[28] An initial HAM-D score of 26 or higher was used to define severe depression; 86% of the patients also carried a diagnosis of melancholia. After 4 weeks, patients treated with fluvoxamine but not imipramine had significantly greater response rates than those treated with placebo on both HAM-D and Clinical Global Impressions (CGI) scales. In severely depressed patients treated with fluvoxamine, the mean HAM-D score declined from a baseline of 29.2 to

Table 2. Clinical Trials Evaluating SSRIs and Other Newer Agents for Melancholic Depression[a]

Study	N	Duration (wk)	Drug, mg/d (mean)	Baseline Mean HAM-D Score	Outcome
Heiligenstein et al[35]	24[b]	8	Fluoxetine 20	21.6–22.6	≥ 50% reduction HAM-D: fluoxetine > placebo[c]
	28[b]	8	Placebo		
	22[d]	8	Fluoxetine 20	19.7–20.3	≥ 50% reduction HAM-D: fluoxetine = placebo
	15[d]	8	Placebo		
Stuppaeck et al[36]	68	6	Paroxetine 30–50 (33.3)	28.6–28.9	≥ 50% reduction HAM-D: paroxetine = amitriptyline;
	66	6	Amitriptyline 150–250 (166)		HAM-D ≤ 14: paroxetine = amitriptyline
Tignol et al[20]	178	≤ 6	Paroxetine 10–40	26.7–27.7	≥ 50% reduction HAM-D: paroxetine > placebo[e];
	66	≤ 6	Placebo		HAM-D < 10: paroxetine > placebo[e]
Dunner and Dunbar[37]	46	4	Venlafaxine (150–375)	28	≥ 50% reduction MADRS:
	47	4	Placebo	29	venlafaxine (65%) > placebo (28%)
Feighner et al[38]	21	6	Fluvoxamine 85–280 (median 145)	25–27	Mean percentage improvement
	27	6	Imipramine 50–280 (median 159)		of HAM-D, CGI, and BPRS:
	12	6	Placebo		fluvoxamine > placebo, imipramine[f]

[a]Abbreviation: BPRS = Brief Psychiatric Rating Scale.
[b]Melancholic subset.
[c]$p = .002$.
[d]Nonmelancholic subset.
[e]$p < .05$ paroxetine versus placebo.
[f]$p < .02$.

15.3 ($p \leq .01$ versus placebo). In the imipramine group, the mean HAM-D score declined from 28.6 to 18.8 (not significant). Although the difference between fluvoxamine and imipramine did not reach statistical significance ($p = .055$), it suggests a trend toward a better response with fluvoxamine. Response rate based on the CGI improvement score was significantly better with fluvoxamine than with placebo.

Meta-analysis has been used to investigate treatment effects in subgroups of patients not large enough to analyze in original clinical trial reports. Pande and Sayler[29] pooled data from 19 double-blind, placebo-controlled, randomized clinical trials and identified patients who had HAM-D scores of 25 or higher and who were treated with fluoxetine (N = 781) or a TCA (N = 788). Response was defined as a 50% decline in HAM-D score; remission was defined as a HAM-D score of 7 or less. Consistent with the results from other mixed population studies, fluoxetine and TCAs had identical response rates (59%) and similar remission rates (29% versus 26%).

Additional information about response rates with SSRIs in patients with severe depression also has come from a subgroup analysis of a large placebo-controlled trial comparing fluoxetine with paroxetine.[33] Severe depression was defined as a baseline HAM-D score of 28 or higher. No differences in efficacy were detected between the 2 active agents, although patients treated with an SSRI achieved a significantly greater response rate than did those treated with placebo. A 50% or greater reduction in HAM-D scores was achieved by 50% of patients receiving fluoxetine or paroxetine compared with 18% of patients receiving placebo ($p = .034$). There was no significant difference between groups in the percentage of patients achieving a HAM-D score of 10 or less, although both active treatment groups had higher percentages (30% paroxetine, 25% fluoxetine, 14% placebo).

Studies in Outpatients

The outcomes of severe depression trials conducted in general psychiatric practice are becoming more pertinent as an increasing number of severely depressed patients are being treated in outpatient settings. Two multicenter, placebo-controlled trials are available for analysis[31,34] (Table 1), but one[34] was not included because the HAM-D was not used as the outcome variable.

Similar results were achieved in a comparison between paroxetine and imipramine; data were pooled from 6 study centers.[30] A subset of 250 of 717 depressed outpatients had HAM-D scores of 28 or higher. As early as week 2 and continuing through week 6, severely depressed patients treated with paroxetine demonstrated a significantly greater decrease in total HAM-D scores than did patients treated with placebo ($p \leq .05$). The change with imipramine was significantly different from the change with placebo from weeks 3 through 6. At week 2, patients receiving paroxetine had significantly greater improvement in anxiety scores than did imipramine-treated patients, with mean scores declining by 3.2 and 2.1, respectively ($p \leq .05$).

Another double-blind, outpatient trial of 8 weeks' duration demonstrated that sertraline (50–200 mg/day) and amitriptyline (50–150 mg/day) were equally effective in improving the condition of patients with a baseline HAM-D of 24.7.[31] At endpoint, the observed decline in mean HAM-D was 11.5 for sertraline and 14.3 for amitriptyline (not significantly different). Both active treatments were statistically superior to placebo ($p < .05$). The mean dose of amitriptyline taken by patients in this trial (78 mg/day) was quite low and was attributed to poor tolerability encountered during attempts to increase the dose.

Studies in Melancholic Patients

Heiligenstein and workers[35] compared the response of 89 DSM-III-R melancholic and nonmelancholic de-

pressed outpatients to 8 weeks of therapy with fluoxetine (20 mg/day) or placebo (Table 2). In melancholic patients, a 50% decrease in HAM-D score was achieved significantly more often with fluoxetine than with placebo (71.4% versus 29.6%; p = .002). In nonmelancholic patients, response rates were not significantly different (50% versus 60%, respectively). The authors attributed the lack of difference in the nonmelancholic patients to the high placebo response rate or to a lesser response to fluoxetine, and suggest that melancholia may prove a clinically useful predictor of treatment response.

In 3 studies, SSRIs were evaluated specifically for the treatment of melancholic depression (see Table 2). Stuppaeck and coworkers[36] reported a 6-week, prospective, multicenter study comparing paroxetine (N = 68) with amitriptyline (N = 66) in hospitalized patients with severe melancholic depression (DSM-III; mean baseline HAM-D > 28). At week 6, there was no difference in response rates (≥ 50% reduction in HAM-D score from baseline) between patients taking paroxetine (63%) and those taking amitriptyline (70%). Likewise, there was no difference in the number of patients whose HAM-D scores were 14 or less (66% and 64%, respectively). Overall therapeutic benefit, a measure that reflects tolerance and efficacy on a scale from –2 to +2, was also similar for the 2 agents, with a nonsignificant trend toward greater improvement with paroxetine (1.58) than with amitriptyline (1.32). Potential flaws in this study were the unusually high dropout rate in both groups for insufficient therapeutic effect or adverse effects (50% paroxetine, 48% amitriptyline) and the use of a high HAM-D cutoff score (14), which implies that patients were still significantly symptomatic at the end of the trial.

Tignol and colleagues[20] conducted a meta-analysis of European, placebo-controlled, clinical trials with paroxetine in patients with a diagnosis of DSM-III melancholia. Patients receiving paroxetine had a response rate twice that of placebo for all efficacy criteria (p < .05). With a mean baseline HAM-D of 27.5, approximately 46% of paroxetine-treated patients achieved a HAM-D score reduction of 50% or greater, and 31% achieved a score of less than 10. Patients receiving paroxetine exhibited an increasing dose-response relationship with doses ranging from 10 to 40 mg/day. More than 50% of patients receiving paroxetine 40 mg/day achieved a reduction in HAM-D of at least 50%, which may imply that higher doses are needed in this subtype of depressed patients.

Feighner and associates[38] compared fluvoxamine with imipramine in a placebo-controlled trial of hospitalized melancholic patients. Scores on 3 rating scales (HAM-D, CGI, and Brief Psychiatric Rating Scale [BPRS]) were subjected to analysis of covariance and then to pairwise analysis, which showed that percentage of improvement on all 3 scales was superior with fluvoxamine as compared with imipramine and placebo (p ≤ .02). However, it is difficult to compare the results of this study with others because response to therapy was defined differently.

Studies in Psychotic Depression

Psychotic depression is a very severe form of depression. Patients with this disorder suffer a high rate of hospitalization, a long duration of functional impairment, and a high risk of suicide.[39] Approximately 10% to 25% of patients with major depression have psychotic depression. Mood-congruent delusions share common themes in depression, such as inadequacy, guilt, and persecution. Mood-incongruent delusions do not appear to relate to depressive themes on the surface and may be associated with a poorer prognosis and a need for prolonged neuroleptic treatment.[12]

Combined therapy with an antidepressant and an antipsychotic is the treatment of choice for psychotic depression. The superiority of combined therapy over a TCA alone has been demonstrated in hospitalized patients who met Research Diagnostic Criteria for major depression, psychotic subtype.[40] Patients treated with the combination of amitriptyline and perphenazine had a significantly higher response rate (78%, p < .01) than the response rate of patients treated with either amitriptyline alone (41%) or perphenazine alone (19%).

Although combined SSRI-antipsychotic therapy has not been studied extensively, it appears to be effective for the treatment of psychotic depression in studies conducted to date. Thirty patients with mood-congruent delusions who met DSM-III-R criteria for major depression with psychotic features were enrolled in a 5-week open trial of fluoxetine and perphenazine.[41] Seventy-three percent of patients achieved a 50% reduction in HAM-D and BPRS scores and a final HAM-D score less than 12. It is promising that 5 of 8 patients who had relapsed previously while receiving a TCA-antipsychotic combination regimen responded to combined therapy with fluoxetine. Combined SSRI-antipsychotic therapy also possesses an advantage in terms of tolerability because it avoids the additive anticholinergic toxicity of a TCA combined with an antipsychotic.[41,42]

Studies in Geriatric Depression

Three studies have compared SSRIs with TCAs in elderly patients with severe or melancholic depression, most of whom also suffered from medical illness. In a retrospective review of elderly depressed inpatients with cardiac disease who had participated in clinical drug trials over a 10-year period, 22 patients (mean age = 73 years) who had received fluoxetine were compared with 42 patients who had received nortriptyline (mean age = 70 years).[10] The duration of fluoxetine therapy was 6 weeks, with at least 5 weeks at a dose of 40 mg/day. The duration of nortriptyline therapy was at least 4 weeks, with doses adjusted to maintain a plasma concentration between 50

and 150 ng/mL. Response to therapy was defined as a return to baseline functioning, at least 2 weeks of therapy in the community without requiring an adjustment in antidepressant therapy, and a final HAM-D score of less than 8. The mean baseline HAM-D score was 28 in patients who received nortriptyline and 26 in patients who received fluoxetine. Among patients who completed the studies, the response rate was significantly greater in those treated with nortriptyline than in those treated with fluoxetine (82% versus 28%, respectively; $p < .001$). The response rate in the subgroup of melancholic patients who received at least 4 weeks of therapy also was greater with nortriptyline (83%, 20/24) than with fluoxetine (10%, 1/10; $p < .001$).

Generalizability of these findings with nortriptyline must be tempered by a number of study limitations. First, antidepressant efficacy was not the primary outcome measured in the studies evaluated. In addition, the nonrandomized assignment of comparison groups suggests the possibility of other, unidentified, between-group differences influencing outcome. Finally, the patient population targeted was atypical (i.e., elderly, hospitalized males with cardiac disease).

Contrasting results were demonstrated in another retrospective review of hospitalized geriatric patients (mean age = 75 years) in which the responses to SSRIs (N = 29) and TCAs (N = 23) were compared.[43] Response to therapy was defined as a GAS score of more than 50 or a 20-point score increase. Response rates were similar for SSRIs (41%) and TCAs (39%). Although the TCA group contained significantly more patients with psychotic depression (35% versus 7%; $p < .05$), this difference did not affect response rates.

The comparative efficacy of SSRIs and TCAs in severe geriatric depression has been confirmed in another double-blind, multicenter, randomized trial comparing paroxetine with clomipramine in patients older than 60 years.[44] Patients received paroxetine, 30 mg/day (N = 40; mean baseline HAM-D score = 27.9), or clomipramine, 75 mg/day (N = 39; mean baseline HAM-D score = 27.5), for 6 weeks. A decline in HAM-D score of 50% or greater was achieved by 65% of paroxetine-treated patients and by 72% of clomipramine-treated patients (not significant [p value not reported]).

Summary: SSRIs Versus TCAs

Using several different definitions of severity, the findings from these studies support equivalent efficacy for SSRIs and TCAs. SSRIs are also effective in the treatment of severe depression. In comparative studies using a 50% or greater decline in HAM-D scores as an endpoint, response rates for SSRIs have ranged from 53% to 64%, and response rates for TCAs have ranged from 43% to 70%.

At least for paroxetine, there appears to be a dose-response relationship for the treatment of melancholia, with higher response rates observed in patients receiving more than 20 mg/day. Because a daily dose of 20 mg has been identified as the optimal dose of paroxetine for patients with less severe depression,[37] these data suggest that higher doses of SSRIs may be required for the treatment of melancholic depression. Further research is needed to define optimal doses for this subpopulation.

TOLERABILITY OF SSRIs VERSUS TCAs IN SEVERE DEPRESSION

Differences in adverse-event profiles between SSRIs and TCAs in patients with severe depression are similar to those observed in less severely ill patients. In the studies reviewed herein, a number of adverse anticholinergic (e.g., dry mouth, constipation, sweating) and cardiovascular (e.g., postural hypotension, vasodilatation) effects were significantly more common with TCAs than with SSRIs.[15,17,18,44] In some cases, these adverse effects led to higher dropout rates in patients receiving TCAs.[8,9,30,38] In other trials, the SSRI was better tolerated, although significance was not achieved.[16,21,28,30] The most frequently reported adverse events associated with SSRI therapy were agitation, insomnia, somnolence, dry mouth, sweating, constipation, nausea and vomiting, and headache.

VENLAFAXINE, MIRTAZAPINE, NEFAZODONE, AND BUPROPION IN SEVERE DEPRESSION

Venlafaxine is an antidepressant that blocks reuptake of both norepinephrine and serotonin at higher doses. To date, 2 studies have evaluated the use of venlafaxine in hospitalized patients with severe melancholic depression.

Guelfi and colleagues[45] conducted a multicenter clinical trial evaluating the effects of venlafaxine in melancholic patients with initial Montgomery-Asberg Depression Rating Scale (MADRS) scores of at least 25. Mean MADRS and HAM-D scores at baseline were approximately 35 and 28, respectively. After a 4-day placebo washout, patients were randomly assigned to receive placebo (N = 47) or venlafaxine (N = 46) titrated to 150 to 375 mg/day as tolerated for 4 weeks. At day 28 of the double-blind portion of the trial, twice as many venlafaxine-treated patients achieved a 50% decline in MADRS scores as did placebo-treated patients (65% versus 28%, respectively; $p < .001$). The trend was the same for the HAM-D total score and CGI improvement scores. Discontinuation rates because of unsatisfactory response occurred in 40% of placebo recipients and in 9% of venlafaxine recipients ($p < .001$). Nausea and sweating were the most common adverse events associated with venlafaxine.

Clerc and coworkers[25] compared the efficacy of venlafaxine to that of fluoxetine in hospitalized melancholic patients. Baseline MADRS and HAM-D scores were

similar to those in the previous study.[45] After a 4-day washout, 33 patients received venlafaxine, 200 mg/day, and 34 patients received fluoxetine, 40 mg/day, for 6 weeks. After 4 weeks, a 50% decline in MADRS score occurred significantly more often in the venlafaxine group than in the fluoxetine group (76% versus 47%, respectively; $p = .024$). Significantly more patients receiving venlafaxine also experienced a 50% reduction in HAM-D score (76% versus 41% fluoxetine; $p = .006$). The CGI improvement score also was significantly better in patients who received venlafaxine (76%) than in those who received fluoxetine (47%; $p = .024$). However, with the response rate in fluoxetine patients increasing to 50% by week 6, this difference was no longer significant. The dropout rate was 18% for venlafaxine and 35% for fluoxetine.

Thus, venlafaxine appears to be a useful agent for the treatment of severe depression. In one study, venlafaxine was associated with a more rapid response in severe depression than fluoxetine. That study also demonstrated that a moderate dose offered efficacy comparable to that of fluoxetine; however, further studies are needed to confirm this finding and to compare venlafaxine with TCAs in melancholic depression.

Mirtazapine is a new antidepressant that enhances both noradrenergic and serotonergic transmission.[46] Postsynaptic 5-HT_2 and 5-HT_3 receptors are blocked. Mirtazapine has been compared with active controls (e.g., TCAs, trazodone) and placebo in both inpatients and outpatients with severe depression[46]; one comparative study with fluoxetine has recently been published.[26]

In one study, 150 severely depressed outpatients were randomly assigned to receive mirtazapine, amitriptyline, or placebo for 6 weeks.[27] Mean HAM-D and MADRS scores were ≥ 26.6 and ≥ 36.4, respectively, at baseline. At week 6, response (≥ 50% reduction in HAM-D score) was evident in 70% of patients receiving mirtazapine, 58% of patients receiving amitriptyline, and 33% of patients receiving placebo ($p \leq .05$ active versus placebo). Dry mouth, constipation, and dyspepsia were significantly more common in amitriptyline-treated patients (80%, 24%, and 20%, respectively) than in mirtazapine- (54%, 8%, 0%, respectively; $p \leq .05$) or placebo-treated patients (30%, 6%, 0%, respectively; $p \leq .05$). Although the rate of dry mouth in the mirtazapine group was relatively high (54%) in this sample, the rate of the anticholinergic cluster does not differ from placebo rates in other samples. Somnolence occurred significantly more often in both active treatment groups (56%, amitriptyline; 46%, mirtazapine) than in placebo recipients (22%; $p \leq .05$).

Results of a 6-week, European multicenter trial demonstrated a faster response with mirtazapine than fluoxetine.[26] In this trial, 133 depressed inpatients and outpatients (baseline HAM-D score = 26.1) received either mirtazapine (mean dose = 39.8 mg/day) or fluoxetine (mean dose = 23.8 mg/day).

The reduction in the HAM-D score from baseline was numerically greater in mirtazapine-treated patients than in fluoxetine-treated patients at each time point. The decrease in the mirtazapine group reached statistical significance at week 3 and week 4 ($p \leq .05$). The 4-point difference in the week 6 HAM-D score between the mirtazapine-treated group (–14.2 points) and the fluoxetine-treated group (–10.3 points) was not statistically different ($p = .054$), but was considered clinically important. The proportion of responders (≥ 50% reduction HAM-D) was significantly better at week 4 in the mirtazapine group.

Similar numbers of patients withdrew from the study because of adverse events (mirtazapine, 10.6%; fluoxetine, 13.4%). Patients receiving fluoxetine more often reported headache (17.9%) and nausea (10.4%) than mirtazapine-treated patients (9.1% and 3.0%, respectively). Events more commonly reported by mirtazapine recipients than by fluoxetine recipients included dry mouth (18.2% and 4.5%, respectively) and blurry vision (7.6% and 1.5%, respectively).

Nefazodone is a new antidepressant that antagonizes postsynaptic 5-HT_2 receptors and weakly inhibits presynaptic serotonin and norepinephrine reuptake. Its general antidepressant actions have been demonstrated in several large trials.[18–20] Nefazodone has performed comparably to fluoxetine, sertraline, and paroxetine in head-to-head trials with these agents (references 47 and 48 and data on file, Bristol-Myers Squibb, Princeton, N.J.; 1997).

Nefazodone's efficacy in more severely ill patients was tested in a placebo-controlled 6-week study of patients hospitalized for depression.[24] Baseline 17-item HAM-D total scores averaged above 27. The nefazodone group was superior to the placebo group on all efficacy measures, including the HAM-D, the MADRS, the CGI, and the overall response rate.

Bupropion is an antidepressant chemically unrelated to other antidepressants.[49] Its mechanism of action is unknown, but is likely related to noradrenergic or dopaminergic functioning. It has no direct effect on serotonergic function. The efficacy of bupropion in more severely depressed patients was tested in 2 separate 4-week placebo-controlled studies of depressed inpatients in the late 1970s.[22,23] In one study performed at a single hospital, HAM-D reductions were significantly larger in the bupropion than the placebo group by day 11 and continued to be larger throughout the study. In the other study (which was a multicenter study), bupropion was significantly more effective than placebo at the end of the study. Mean HAM-D endpoint scores were 14.9 for bupropion and 19.6 for placebo. The CGI improvement scale–determined response rates were significantly better for bupropion (61%) than for placebo (28%).[22]

COMBINATION THERAPY FOR SEVERE DEPRESSION

Because down-regulation of β-receptors occurs more rapidly with combination SSRI-TCA therapy than with monotherapy,[50] a combination regimen may be helpful in reducing the latency to antidepressant response for some patients with severe depression. Some reports provide evidence for the benefit of this approach,[51,52] although data in severely depressed patients are very limited.

Included in one retrospective, uncontrolled report were 3 severely depressed patients (baseline HAM-D score ≥ 32) considered treatment-resistant by virtue of having failed at least 3 courses of heterocyclic and monoamine oxidase inhibitor antidepressant therapy, often with adjuvant lithium or ECT.[53] Patients also had failed open-label fluoxetine treatment (mean dose = 73 mg/day). After combination treatment with a heterocyclic antidepressant (amoxapine or trazodone) and fluoxetine (40 to 80 mg/day) for at least 9 weeks, mean HAM-D scores in the 3 severely depressed patients were 2, 14, and 16, which represented reduction of at least 50%. When SSRI-TCA therapy is prescribed, plasma TCA levels must be monitored closely because hepatic metabolism of TCAs can be inhibited by some SSRIs.[54]

ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy is another alternative for the treatment of severe psychotic or melancholic depression and is especially appropriate for patients who are suicidal or intolerant of or resistant to antidepressant therapy. This modality would be useful for patients with renal, cardiac, or hepatic impairment that precludes antidepressant use. Although early studies suggested that melancholic depression predicted a good response to ECT, more recent research has not confirmed this finding.[55] In a study that included patients with a baseline mean HAM-D of 33.2, response rates ranged from as high as 86% in patients who had not received adequate antidepressant therapy to as low as 50% in patients with treatment-resistant depression.[56] Maintenance antidepressant therapy is usually required to prevent relapse of depression; ECT can also be used for maintenance therapy. A thorough medical examination is required to evaluate the risk of cardiovascular and neurologic adverse effects with ECT, as well as anesthesia risks.[57] Temporary confusion and memory impairment are the most common adverse events observed.

THE ISSUE OF RESPONSE TO TREATMENT

Many of the outcomes reported in this article appear lower than often quoted response rates of 58% for active drug and 36% for placebo.[58] The higher figures are not well justified.

CONCLUSION

Overall, TCAs and SSRIs appear to have comparable efficacy for the treatment of severe and melancholic depression. The SSRIs are better tolerated, without significant adverse anticholinergic and cardiovascular effects. There are some indications that higher doses of SSRIs may be required for the treatment of severe depression; further research is needed to define the optimal dose. Venlafaxine and mirtazapine appear to be effective in a limited number of trials for patients with severe melancholic and severe depression, respectively. Nefazodone has comparable efficacy to the SSRIs and is effective in hospitalized depressed patients. Bupropion is also effective for severe depression. For truly resistant cases or for selected patients with severe depression, ECT and combined antidepressant therapy may be useful alternatives. Combined antidepressant-antipsychotic therapy should be considered for patients with psychotic depression.

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

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