Sertraline Versus Imipramine Treatment of Comorbid Panic Disorder and Major Depressive Disorder

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Objective: To evaluate the efficacy and tolerability of sertraline and imipramine in patients with comorbid panic disorder and major depressive disorder.

Method: Outpatients meeting a DSM-IV diagnosis of panic disorder and concurrent major depressive disorder were randomized in a 2:1 ratio to 26 weeks of double-blind treatment with either sertraline, in daily doses of 50 to 100 mg, or imipramine, in daily doses of 100 to 200 mg. Primary outcome measures were panic attack frequency (derived from patient diaries) and the Montgomery-Asberg Depression Rating Scale (MADRS).

Results: 138 patients were treated with sertraline (76% female; mean age = 40 years) and 69 with imipramine (70% female; mean age = 40 years). The symptoms of both major depressive disorder and panic disorder responded significantly and equivalently to both drugs. Endpoint improvement with sertraline versus imipramine, respectively, on the MADRS was 11.1 ± 10.8 versus 11.2 ± 10.4, and on the Clinical Global Impressions-Improvement scale (CGI-I) was 2.1 ± 1.3 versus 2.4 ± 1.6. Among study completers, CGI-I responder rates were 88% with sertraline and 91% with imipramine. Treatment outcome was concordant for both diagnoses in approximately 70% of patients and discordant in approximately 30%. Overall, sertraline was significantly better tolerated with significantly fewer discontinuations due to adverse events (11% vs. 22%; $\chi^2 = 4.39$, df = 1, p = .04).

Conclusion: Both sertraline and imipramine were found to be highly effective treatments for both major depressive disorder and panic disorder, with sertraline showing significantly greater tolerability and compliance during long-term treatment than imipramine.

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Panic disorder (PD) and major depressive disorder (MDD) exhibit one of the strongest comorbid associations among mood and anxiety disorders. The most extensive recent epidemiologic survey,[1] which is broadly consistent with previous research,[2] reported a lifetime prevalence of 3.4% for panic disorder and 16.9% for MDD. It was estimated that 56% of lifetime PD patients would develop an episode of MDD at some point. Conversely, it was estimated that 22% of lifetime MDD patients would develop PD, representing a 6.8-fold increased risk of developing PD compared with individuals never diagnosed with depression.[1] The World Health Organization Collaborative Study, conducted in 14 countries worldwide, estimated that the odds ratio of an MDD diagnosis among PD patients was 12.2, perhaps reflecting the higher rates of PD-MDD comorbidity in the primary care setting in which the study was conducted.[3,4]

PD-MDD comorbidity is clinically important because it has been associated with greater illness severity,[5–11] higher chronicity and poorer long-term prognosis,[8,12,13] poorer quality of life and psychosocial functioning,[4,7,10,11,14,15] and generally poorer response to treatment.[5,7,11,16–19] In addition to the markedly greater psychosocial impairment associated with comorbid PD-MDD, there is also a greater than 4-fold increased suicide attempt risk compared with PD alone.[11]

Despite the high prevalence and negative clinical implications of PD-MDD comorbidity, we are unaware of any double-blind, controlled trial prospectively designed to include patients meeting DSM criteria for both disorders. Most studies that examine the influence of comorbidity on treatment response do not report on patients suffering from full Axis I comorbidity, but instead include patients meeting Axis I criteria for the index illness (MDD or PD) and who suffer from subsyndromic manifestations of the comorbid illness. One of the few exceptions is a study reported by Keller and colleagues[19] that compared alprazolam with imipramine. Patients were required to meet DSM-III-R criteria for both panic disorder and some form of depression, but 48% of patients met criteria for depression not otherwise specified or dysthymia, and not MDD. The results of this study were partially positive, with imipramine demonstrating significant antidepressant efficacy but not a significant antipanic efficacy by the end of 16 weeks of study treatment.

The selective serotonin reuptake inhibitor (SSRI) sertraline is efficacious in the acute and long-term treatment of both major depression[20–23] and panic disorder[24–27] on the basis of the results of multiple double-blind, placebo-controlled studies.

Recently, a pooled analysis found sertraline to have both antipanic and antidepressant efficacy in patients meeting criteria for panic disorder who also suffered from subsyndromic depressive symptomatology.[28] The tricyclic antidepressant (TCA) imipramine has been found to have efficacy in MDD[29] and (separately) in PD[30] based on extensive research over more than 3 decades. Also, as noted above, imipramine is the only antidepressant to have demonstrated some degree of efficacy in a large trial of depression-PD comorbidity.[18]

The current report presents results from an international, multicenter, double-blind 26-week study comparing the efficacy and tolerability of sertraline and imipramine in outpatients suffering from full Axis I comorbid panic disorder and major depressive disorder.

METHOD

Study Subjects

To enter the study, all the patients were required to meet the following inclusion criteria: (1) be a man or woman between the ages of 18 and 65 years, inclusive; fertile women were required to have a negative pregnancy test at baseline and to be practicing a medically acceptable form of contraception for at least the previous 3 months; (2) meet DSM-IV criteria for both panic disorder with or without agoraphobia or specific phobia and current major depressive episode; (3) have a minimum of 4 panic attacks during the 4 weeks prior to screening, with at least 1 of these panic attacks required to be a full, spontaneous, or unexpected attack; and (4) have a baseline Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 20.

Patients were excluded from study entry for any of the following reasons: (1) presence of a primary Axis I diagnosis other than panic disorder (with or without agoraphobia or specific phobia) or major depressive disorder; (2) report of 50 or more full or limited symptom panic attacks per week in the 4 weeks prior to screening or during the screening period; (3) significant suicidality; (4) any history of seizure disorder, organic brain disorder, anorexia nervosa, or psychotic disorder; (5) drug or alcohol abuse or dependence within 6 months before screening; (6) use of any benzodiazepine at a dose of 1.5 mg of alprazolam or its equivalent on any day for 3 weeks prior to screening (doses of less than 1.5 mg of alprazolam or its equivalent were permitted as long as the stable dose had been taken for 3 months or longer); (7) treatment with the following drugs in the following time periods prior to screening: depot neuroleptics, 7 months; monoamine oxidase inhibitors or TCAs, 2 weeks; fluoxetine, 5 weeks; (8) presence of any acute or unstable medical condition or use of any medication that is known to interact with either sertraline or imipramine; (9) report of a history of nonresponse to sertraline or imipramine (or patients in whom either drug was contraindicated); and (10) among women, current pregnancy or lactation.

The study was conducted at 18 sites in 6 countries: Finland, Hungary, Israel, United Kingdom, South Africa, and Belgium. The study was approved by the Institutional Review Board monitoring each site. After a complete description of the study to the patients, written informed consent was obtained in accordance with the Helsinki Declaration of 1975 (1983 revision).

Study Design

Patients underwent a screening evaluation followed by a 1-week single-blind placebo lead-in period to ensure adequate current panic severity, defined as the occurrence of at least 1 full panic attack (situational or unexpected), and to exclude early placebo responders. Patients who continued to meet study entry criteria at the end of the lead-in period, and whose MADRS scores had not improved by 25% or greater, were then randomized to 26 weeks of double-blind treatment in a 2:1 ratio with daily doses of either sertraline (50–100 mg) or imipramine (100–200 mg).

Consistent with the clinically recommended titration schedule for PD, sertraline was initiated at a dose of 25 mg/day for 1 week, followed by 50 mg/day for 4 weeks. Patients unable to tolerate the 50-mg dose were discontinued from the study. For patients reporting insufficient therapeutic response, sertraline could be titrated to 100 mg/day at any visit from week 5 to week 14, after which the only change in dosage could be a reduction to 50 mg due to intolerable side effects.

On the basis of research reporting early hyperstimulation,[31] imipramine was initiated at a dose of 25 mg/day and increased, on a weekly basis, to 50 mg, then 100 mg, then 150 mg. Patients reporting insufficient therapeutic response on imipramine treatment could have their dosage titrated to 200 mg/day at any visit from week 5 to week 14, after which the only change in dosage could be a reduction to 100 mg due to intolerable side effects. Compliance with treatment was assessed by means of pill counts.

No concomitant psychotherapy (e.g., cognitive, behavioral, or other structured psychotherapy) was permitted during the course of the study. For example, investigators were not permitted to make recommendations that patients enter phobic or panic-provoking situations as part of a behavioral intervention program.

Patients were permitted to enter the study if they were on long-term, low-dose benzodiazepine therapy (defined as a daily dose ≤ 1.5 mg of alprazolam or its equivalent for at least 3 months prior to study entry). They were required

to maintain this low-dose regimen throughout the study. In addition, patients who have previously taken intermittent ("as needed") doses of benzodiazepines for insomnia were permitted to continue such intermittent use, if necessary and on a restricted basis: ≤ 3 times in any given week, and never on the night prior to an evaluation visit. Patients who exceeded these limits were discontinued from the study.

Efficacy and Tolerability Assessments

Safety and efficacy data were obtained at baseline and at the end of study weeks 1, 2, 3, 5, 7, 10, 14, 18, 22, and 26 (or the final visit if patients discontinued prematurely).

Two primary efficacy measures were used: (1) the MADRS,[32] a 10-item scale that rates symptoms of depression on a 7-point severity scale; and (2) a patient-completed Panic Diary for concurrently recording relevant information concerning the occurrence of panic attacks, such as frequency, severity, time of onset, duration, and whether the attack was situational or unexpected. The patients were required to record on a checklist the symptoms they experienced during an attack. The investigator was required to classify each panic attack as expected versus unexpected, and full versus limited symptom. A limited symptom panic attack consisted of an episode of panic that manifested as only 1 to 3 of the DSM-IV criteria panic symptoms. At each efficacy visit, the Panic Diary was reviewed with the patient and the information was systematically recorded.

Secondary efficacy measures consisted of (1) the Clinical Anxiety Scale (CAS),[33] a 6-item, investigator-rated measure that rates generalized and anticipatory anxiety on a 5-point severity scale; (2) the Clinical Global Impressions-Severity of Illness and -Improvement scales (CGI-S and CGI-I),[34] 2 investigator-rated measures that provide 7-point ratings of the global severity of illness and global improvement with treatment; (3) the agoraphobia subscale of the Marks Fear Questionnaire,[35] in which patients rate on a 9-point scale the severity of their avoidance of their self-described "main phobia" as well as 5 standard phobic situations; and (4) the patient-rated Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[36] used to assess an individual's perceived quality of life and satisfaction across multiple domains. The short form of the Q-LES-Q consists of 16 items rated by the patient on a 5-point Likert scale. The maximum total score on the first 14 items is 70. The last 2 items provide a global satisfaction rating and a rating of satisfaction with medication treatment. The scale is scored as a percent of the total possible score. The Q-LES-Q scale was completed at baseline and at study weeks 14 and 26.

Adverse events, volunteered or observed, were recorded and classified in terms of onset, duration, severity, cause (as judged by the investigator), action taken, and outcome. Blood pressure, heart rate, temperature, and body weight were obtained at the screen visit (day 1) and during each study visit thereafter. Laboratory tests (electrolytes, liver function tests, hematology, and a urinalysis, including a benzodiazepine screen) were performed at the screen visit and at week 28 (or at study endpoint if the patient discontinued prematurely). A urine pregnancy test was performed at the screening visit in premenopausal women.

Statistical Analyses

The safety analysis included all patients who took at least 1 dose of medication during the double-blind phase and provided any follow-up safety data; patients who had a baseline and at least 1 post-randomization efficacy evaluation were included in the intent-to-treat efficacy analysis. All intent-to-treat subjects who had been on the double-blind medication for more than 182 days (26 weeks) or had successfully completed the full course of treatment were included in a completer analysis. All statistical tests were 2-sided and were performed at the .050 level of significance with no adjustments made for multiple comparisons.

Baseline characteristics. Baseline efficacy assessments and demographic characteristics including age and weight were compared between patients receiving sertraline and imipramine using an analysis of variance model with terms for treatment and center. The sex of patients and the presence of agoraphobia were compared between the 2 treatment groups using a center-stratified Cochran-Mantel-Haenszel (CMH) test.

Efficacy. Observed values (for the CGI-I) and changes from baseline (for other efficacy parameters) were analyzed for between-treatment comparisons at all scheduled visits and at endpoint. Continuous variables were analyzed using an analysis of covariance (ANCOVA) model with effects of treatment, center, baseline measurement, and treatment-by-baseline interaction. Because some sites enrolled fewer than 10 patients, individual sites in each country were pooled and center was defined by country (total = 6 centers). There was no significant treatment-by-country interaction effect on any outcome measure at endpoint. Additionally, a repeated-measures random regression analysis was performed for MADRS score, panic attack frequency, and CGI-I score, with model terms of treatment, center, week, benzodiazepine usage indicator variable, baseline, week square, and treatment-by-week interaction.

Because panic attack frequency was not normally distributed, it was logarithmically transformed for the purposes of the analysis. Prior to logarithmic analysis of the data, the value 0.5 was added to each baseline and endpoint count for numbers of panic attacks and limited symptom attacks. This value is the minimum weekly average number of attacks over 2 weeks and was added to allow logarithmic transformation of data for patients with

zero attacks. The variable analyzed for numbers of panic attacks and limited symptom attacks is log ([endpoint attacks + 0.5]/[baseline attacks + 0.5]).

Categorical measures such as responder (CGI-I score ≤ 2) rates were analyzed using CMH methods with centers as strata. A survival analysis (Kaplan-Meier analysis) was performed on the time-to-response variable to test between-treatment difference on response curve over time.

For change from baseline analyses, only the patients with nonmissing observations at both baseline and at least 1 follow-up visit were included.

Adverse events. If a patient reported multiple episodes of the same adverse event, the event was counted only once in the computation of incidence rates of adverse events. Treatment-emergent adverse events reported at a rate ≥ 10% in each treatment group were compared between sertraline and imipramine using the CMH method.

RESULTS

Patient Characteristics

Patient characteristics at baseline were similar in both treatment groups (Table 1). The patients were predominantly female, typically in their 30s or 40s, experiencing full-symptom panic attacks on a daily basis, and suffering from moderate-to-severe major depression. Thirty-three percent of patients treated with sertraline and 39% of patients treated with imipramine reported that their current episode of MDD was ongoing for more than 2 years.

Study Treatment and Patient Disposition

The mean ± SD dose used by patients at study endpoint was 65.4 ± 24.8 mg of sertraline and 144.2 ± 54.0 mg of imipramine. Eighty-seven patients (63%) taking sertraline and 39 patients (57%) taking imipramine used a benzodiazepine during the course of the study ($\chi^2 = 0.821$, df = 1, p = .365). Of the 138 patients randomized to sertraline, 81 patients (59%) completed the full 26 weeks of study treatment, 15 patients (11%) discontinued due to adverse events, 10 patients (7%) discontinued due to lack of efficacy, 21 patients (15%) withdrew consent or were lost to follow-up, and 11 patients (8%) discontinued for miscellaneous other reasons. Of the 69 patients randomized to imipramine, 32 patients (46%) completed the full 26 weeks of study treatment, 15 patients (22%; $\chi^2 = 4.39$, df = 1, p = .04 vs. sertraline) discontinued due to adverse events, 3 patients (4%) discontinued due to lack of efficacy, 12 patients (17%) withdrew consent or were lost to follow-up, and 7 patients (10%) discontinued for miscellaneous other reasons. Among patients stopping study treatment prematurely, 41% of patients taking sertraline and 39% of patients taking imipramine met CGI-I responder criteria (as defined by a CGI-I score ≤ 2) at the time of premature study discontinuation.

Table 1. Baseline Demographic and Clinical Information on Study Sample[a]

Variable	Sertraline N = 138	Imipramine N = 69
Female, N (%)	105 (76)	48 (70)
Age, y	40.3 ± 10.4	40.3 ± 9.8
Range, y	19–64	22–60
History of recurrent major depression, N (%)	93 (67)	44 (64)
Panic disorder, agoraphobia subtype, N (%)	82 (59)	43 (62)
Duration of current major depression, y	3.1 ± 4.4	3.5 ± 4.3
Duration of panic disorder, y	7.4 ± 9.4	7.3 ± 8.4
Weekly frequency of full panic attacks	7.1 ± 8.8	7.0 ± 9.8
MADRS total score	28.5 ± 5.4	28.7 ± 5.4
CGI-S score	4.9 ± 0.8	5.0 ± 0.8

[a]Values shown as mean ± SD unless otherwise noted. Sample size for baseline efficacy measures: sertraline, N = 135; imipramine, N = 68.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, MADRS = Montgomery-Asberg Depression Rating Scale.

Treatment Response

Primary outcome measures. Sertraline and imipramine produced equivalent levels of improvement on both a priori primary outcome parameters at study endpoint, the MADRS and weekly frequency of full panic attacks (Table 2). Sertraline showed a trend significant early efficacy advantage in reducing depressive symptoms (week 3 MADRS score, p = .054). For both drugs, a substantial proportion (≥ 43%) of the overall antidepressant effect achieved during 26 weeks of treatment occurred in the first 3 weeks (Table 2).

The time course of improvement in the symptom severity of MDD and PD is illustrated in Figure 1 in which the visit-by-visit MADRS total score is graphed against the y-axis on the left side of the figure, while mean weekly frequency of full panic attacks is graphed against the y-axis on the right side of the figure. Figure 2 illustrates the extent of early response (CGI-I ≤ 2), as well as response at the end of 26 weeks of treatment based on both a completer analysis and the more conservative last-observation-carried-forward (LOCF) endpoint analysis. As can be seen, there were no significant between-drug differences in overall efficacy.

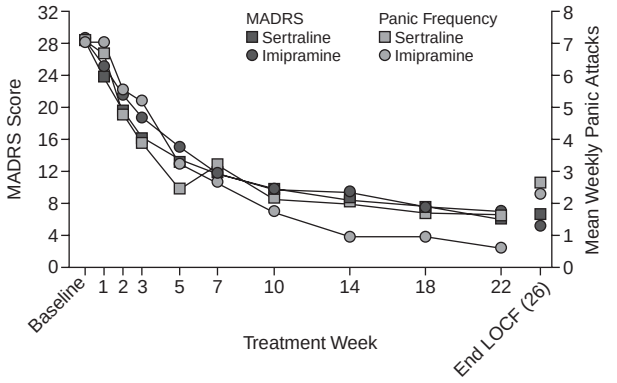
Results of a repeated-measures random regression analysis performed on MADRS score, panic attack frequency, and CGI-I score showed similar results. For the MADRS, the adjusted mean ± SE score over the 26-week treatment period was 14.0 ± 0.6 for sertraline and 14.7 ± 0.7 for imipramine (difference in least squares mean = –0.66, 95% CI = –2.09 to +0.77; p = .366). For panic attacks, the adjusted mean ± SE weekly frequency (log transformed) over the 26-week treatment period was 0.42 ± 0.09 for sertraline and 0.45 ± 0.11 for imipramine (difference in least squares mean = –0.03, 95% CI = –0.27 to +0.21; p = .796). For the CGI-I, the adjusted mean ± SE score over the 26-week treatment period was 2.41 ± 0.08 for sertraline and 2.57 ± 0.10 for imipramine (difference in least squares mean = –0.16, 95% CI = –0.36 to +0.04;

Table 2. Efficacy Measures During 26 Weeks of Treatment With Sertraline vs. Imipramine (intent-to-treat sample)

	Sertraline		Imipramine	
Measure	Mean	SD	Mean	SD
MADRS total score				
Baseline	28.5	5.4	28.7	5.4
Week 3	16.2*	8.5	18.6	8.4
Week 14	8.8	7.1	9.4	8.5
Week 26	6.5	7.4	5.3	6.4
Endpoint	11.1	10.8	11.2	10.4
Full panic attack frequency				
Baseline	7.1	8.8	7.0	9.8
Week 3	3.9	7.6	4.2	7.4
Week 14	2.0	5.2	1.9	5.6
Week 26	2.0	9.0	0.7	1.9
Endpoint	2.9	9.7	2.3	6.6
Fear Questionnaire, agoraphobia subscale score				
Baseline	21.3	13.0	23.1	15.9
Week 3	18.5	14.0	19.8	16.2
Week 14	10.3	12.7	12.8	14.9
Week 26	8.3	11.2	9.3	12.2
Endpoint	12.7	14.1	14.3	16.0
Clinical Anxiety Scale score				
Baseline	15.8	3.4	15.6	3.6
Week 3	10.2	4.8	11.1	4.9
Week 14	6.0	4.4	6.7	5.2
Week 26	4.9	3.8	3.9	3.7
Endpoint	7.1	5.2	7.1	6.0
CGI-Severity score				
Baseline	4.9	0.8	5.0	0.8
Week 3	3.8	1.1	4.1	1.1
Week 14	2.7	1.2	2.8	1.3
Week 26	2.0	1.2	2.2	1.2
Endpoint	2.8	1.6	3.0	1.6
CGI-Improvement score				
Week 3	2.6	1.0	2.8	1.1
Week 14	1.9	1.0	1.8	1.0
Week 26	1.5	0.8	1.4	0.7
Endpoint	2.1	1.3	2.4	1.6
Q-LES-Q overall score				
Baseline	52.2	13.1	51.6	13.1
Week 26	74.2	14.0	74.5	17.5
Endpoint	69.6	16.3	69.0	19.4

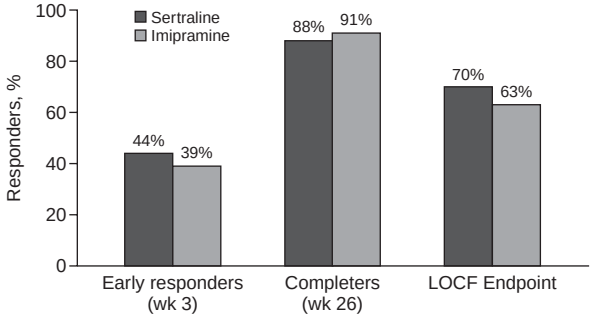
*p = .054 on test of difference in least squares means between treatment groups.
Abbreviations: CGI = Clinical Global Impressions scale, MADRS = Montgomery-Asberg Depression Rating Scale, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

Figure 1. Time Course of Improvement in MADRS Scores and Panic Attack Frequency Over 26 Weeks of Treatment[a]



[a]No significant between–treatment group difference on repeated-measures analysis of covariance.
Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 2. CGI-I Responder Status (CGI-I score ≤ 2)[a]



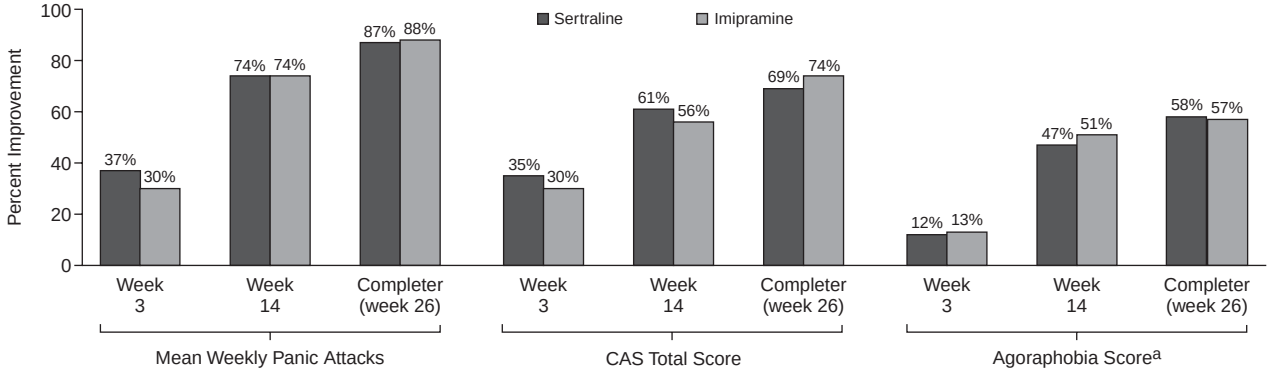
[a]No significant between–treatment group difference.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, LOCF = last observation carried forward.

p = .119). Sertraline showed significantly more rapid improvement than imipramine in CGI-I scores in the first 3 to 5 weeks of treatment: mean ± SE CGI-I scores at week 1 for sertraline versus imipramine = 3.24 ± 0.08 versus 3.47 ± 0.10 (p = .028); week 2, 3.06 ± 0.08 versus 3.29 ± 0.10 (p = .032); week 3, 2.90 ± 0.08 versus 3.12 ± 0.10 (p = .037); and week 5, 2.61 ± 0.08 versus 2.81 ± 0.10 (p = .052).

To determine whether concomitant benzodiazepine therapy significantly and independently contributed to treatment response, we performed 2 separate stepwise regression analyses, using both change in panic attack frequency and endpoint CGI-I score as dependent variables. The analysis included the following variables in the model: age, gender, study drug, baseline MADRS score, baseline panic attack frequency, duration of panic disorder, agoraphobia subtype, benzodiazepine use (yes/no), and baseline Q-LES-Q total score. The partial R-square for concomitant benzodiazepine therapy was 0.012 in the stepwise analysis of panic attack change and 0.015 in the stepwise analysis of endpoint CGI-I score. Thus, concomitant benzodiazepine therapy accounted for less than 2% of the variance in treatment outcome, and other variables also contributed minimally (< 5%).

Secondary outcome measures. The efficacy of both study treatments was observed consistently across all secondary outcome measures (Table 2). Once again, no significant efficacy advantage was found for either sertraline or imipramine. In addition to the reduction in the frequency of full-blown panic attacks, there was a 57% reduction in limited symptom attacks with sertraline and a 65% reduction with imipramine. The mean severity of limited symptom panic attacks at baseline (on a 10-point

Figure 3. Percent Improvement From Baseline in Panic Attack Frequency, Non-Panic Anxiety (CAS total score), and Agoraphobia Score[a]



[a]Agoraphobia subscale of the Fear Questionnaire.
Abbreviation: CAS = Clinical Anxiety Scale.

severity scale) was moderate: 5.0 ± 1.6 versus 5.2 ± 2.0 for sertraline and imipramine, respectively. Interestingly, while both drugs significantly reduced the frequency of limited symptom attacks, when a breakthrough attack occurred it had approximately the same severity as during pretreatment: the mean percent change in attack severity at endpoint was –6.3% for sertraline and +2.6% for imipramine.

In addition to improvement in panic attacks, patients reported improvement in 2 other key clinical outcome dimensions of panic disorder (Table 2): phobic avoidance, as measured by the agoraphobia subscale of the Fear Questionnaire, and generalized/anticipatory anxiety, as measured by the Clinical Anxiety Scale. Finally, treatment with both drugs was associated with equivalent improvement in quality of life as measured by the Q-LES-Q total score (Table 2).

Temporal progression of clinical improvement. Examination of week 3 data in terms of mean percent improvement from baseline suggested a temporal pattern to clinical improvement. Depressive symptoms showed a 42% versus 35% reduction from baseline at 3 weeks in MADRS total score for sertraline and imipramine, respectively. This level of improvement was marginally higher than the early (week 3) improvement observed in panic attack frequency: 37% versus 30% reduction in full panic attack frequency for sertraline and imipramine, respectively. Figure 3 shows the progression of improvement for 3 of the anxiety outcome dimensions: panic attack frequency, generalized anxiety as measured by the CAS, and phobic avoidance. As can be seen, phobic avoidance showed the greatest lag in treatment response.

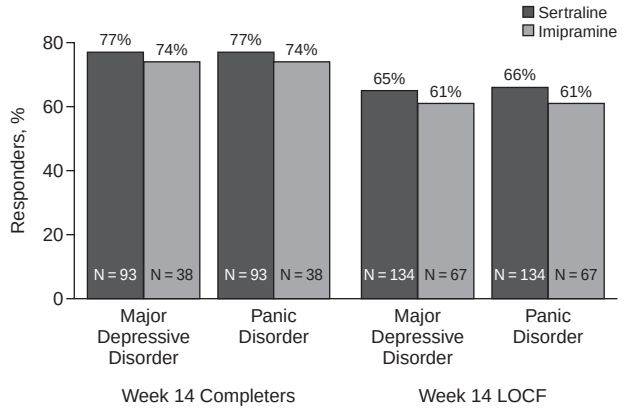
Overall time to response was evaluated using a Kaplan-Meier analysis, with response defined as a CGI-I score ≤ 2 (much or very much improved). The estimated median time to response was 35 days for both sertraline and imipramine (log-rank $\chi^2 = 0.004$, df = 1, p = .950).

Concordance and discordance of antidepressant and antipanic response. The degree to which depression and panic disorder treatment response were coupled versus uncoupled was examined by analyzing respective responder rates for each disorder at week 14. Week 14 was chosen, post hoc, as an acute phase milestone because it was the assessment timepoint that was closest to the most frequent endpoint of many recent panic disorder treatment studies. Additionally, the only available PD-MDD comorbidity study utilized a 16-week acute treatment period.[19] For major depression, the criterion for response was defined as achieving a greater than 50% reduction in the baseline MADRS score. For panic disorder, the criterion for response was defined as achieving a greater than 75% reduction from baseline in panic attack frequency. Using these criteria, sertraline and imipramine showed equivalent efficacy, based on both an LOCF and a completer analysis (Figure 4; it should be noted that use of the more stringent remission criterion, complete blockade of panic attacks, reduced the PD responder rates by a consistent 12%–13% for each drug).

Based on the improvement criteria cited above, antidepressant and antipanic response were usually, but not always, concordant. For example, at week 14, concordant antipanic and antidepressant response was 63% with sertraline and 60% with imipramine; concordant nonresponse was 7% with sertraline and 13% with imipramine; and discordant response (in which response was achieved in 1 disorder but not the other) was 30% with sertraline and 27% with imipramine.

Tolerability of treatment. Treatment with sertraline was significantly better tolerated than treatment with imipramine, with significantly fewer patients reporting severe adverse events (23% vs. 42%, $\chi^2 = 7.86$, df = 1, p = .005) and significantly fewer patients discontinuing due to adverse events (11% vs. 22%; $\chi^2 = 4.39$, df = 1,

Figure 4. Major Depressive Disorder and Panic Disorder: Response at Week 14[a,b]



[a]Major depressive disorder response: > 50% reduction in MADRS score; panic disorder response: > 75% reduction in panic frequency.
[b]No significant between–treatment group difference.
Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

p = .04). There were 2 adverse events with significantly (p < .05) higher rates in patients treated with sertraline compared with imipramine: nausea (30% vs. 16%; $\chi^2 = 4.64$, df = 1, p = .03) and diarrhea (15% vs. 4%; $\chi^2 = 5.30$, df = 1, p = .02). In contrast, there were 5 adverse events with significantly higher rates in patients treated with imipramine compared with sertraline: dry mouth (55% vs. 13%; $\chi^2 = 41.2$, df = 1, p < .001), dizziness (26% vs. 10%; $\chi^2 = 8.95$, df = 1, p = .003), sweating (23% vs. 8%; $\chi^2 = 9.39$, df = 1, p = .002), constipation (17% vs. 2%; $\chi^2 = 15.85$, df = 1, p < .001), and tremor (19% vs. 9%, $\chi^2 = 4.46$, df = 1, p = .03).

The mean change from baseline to endpoint in weight was +0.44 lb (0.20 ± 3.1 kg) in patients treated with sertraline and +1.61 lb (0.72 ± 3.71 kg) in patients treated with imipramine (t = –1.19, df = 176, p = .235).

The mean change from baseline to endpoint in seated heart rate was –0.73 b.p.m. in patients treated with sertraline and +5.34 b.p.m. in patients treated with imipramine (t = –3.35; df = 180; p = .001). The mean change from baseline to endpoint in seated diastolic blood pressure was –1.76 mm Hg in patients treated with sertraline and +0.40 mm Hg in patients treated with imipramine (t = –1.58; df = 179; p = .116). The mean change from baseline to endpoint in seated systolic blood pressure was –1.62 mm Hg in patients treated with sertraline and –0.75 mm Hg in patients treated with imipramine (t = –0.93; df = 179; p = .356).

DISCUSSION

The current study is the first large, double-blind trial that we are aware of to evaluate the efficacy of antidepressants in the treatment of patients meeting full DSM-III/IV criteria for PD-MDD comorbidity. The results found both sertraline and imipramine to have significant and equivalent efficacy in the treatment of both MDD and PD. Approximately 90% of study completers on both drugs met CGI-I responder criteria at week 26 (CGI-I score of 1 or 2), and approximately two thirds were responders based on the more conservative LOCF endpoint analysis (Figure 2). The most notable difference between the drugs was the greater tolerability of sertraline compared with imipramine, with a notably lower side effect burden and significantly fewer patients discontinuing due to adverse events (11% vs. 22%; p < .05). This is an important clinical issue in the long-term management of comorbid PD-MDD.

Onset of response appeared to be rapid in the current study, with 44% of patients taking sertraline and 39% of patients taking imipramine achieving CGI-I responder status by week 3 (Figure 2). Also, perhaps unexpectedly, improvement in depression did not lag behind improvement in PD (Figure 1). Instead, week 3 improvement on the MADRS was 42% and 35% for sertraline and imipramine, respectively, which was marginally higher than the respective 37% and 30% reduction observed by week 3 in mean weekly panic frequency (Table 2). These results are especially notable since previous studies[7,18] have suggested that the time course of response in patients suffering from PD-MDD comorbidity is delayed.

The mean endpoint dose of sertraline and imipramine, respectively, was 65.4 ± 24.8 mg and 144.2 ± 54.0 mg. These are relatively modest doses, lower than the mean daily doses used in most studies designed to evaluate the treatment of MDD or PD without the presence of comorbidity.[21–28] The degree of illness severity among the current treatment sample (easily exceeding ICD-10 severity criteria) and the chronicity of current illness (Table 1) both increase the likelihood that use of higher doses may have further improved patient outcomes. It has been established that sertraline has a relatively flat dose-response curve for both PD[24] and MDD.[20] The results of the current study also found sertraline to achieve high response rates despite use of relatively low doses (mean endpoint dose = 65.4 ± 24.8 mg).

Despite these good response rates, the presence of comorbidity may be an indication that more aggressive dosing might optimize response. In a previous report[28] of 2 fixed-dose studies, a significantly higher response rate was found among patients suffering from PD with subsyndromic depression who were treated with 100 mg or 200 mg of sertraline compared with 50 mg. Similarly, a higher daily dose of sertraline (mean = 160 mg) has also been shown to have significant efficacy in a double-blind, placebo-controlled MDD–obsessive-compulsive disorder (OCD) comorbidity treatment study.[37] It should be noted that use of a flexible dosing design that permits rapid titration may have resulted in a higher than necessary end-

point sertraline dose. These preliminary findings regarding the treatment of comorbidity suggest that treatment response, and the achievement of remission, might have been even greater in the current study if higher doses had been employed.

Response to both study drugs showed a similar temporal pattern (Figure 3) that was consistent with previous research.[18,24,25] By week 3, substantial and equivalent improvement (in the range of 35%–40% reduction from baseline) had occurred in the core symptoms of PD and MDD. Improvement in anticipatory anxiety, as measured by the CAS, showed somewhat less improvement by week 3, while there was a significant lag in improvement in phobic avoidance.

Future research is needed to evaluate whether higher doses of either sertraline or imipramine might further optimize treatment response in comorbid PD and MDD, especially in terms of hastening improvement in phobic avoidance or in treating the residual symptoms noted at treatment endpoint.

Another question of both conceptual and clinical interest is whether, and to what extent, there can be a discordance of treatment response in patients suffering from comorbid PD-MDD, and if so, if it is more likely that MDD or PD would fail to respond.[38] This issue was evaluated in the current study using week 14 data, since attrition was less of a confounding variable than at the 26-week endpoint. The results suggest that at the end of acute treatment, 70% of patients treated with sertraline and 73% of patients treated with imipramine showed a concordance of treatment outcome, with the majority being concordant for response in both MDD and PD. Discordance of outcome was evenly divided among both diagnoses. These results suggest that treatment response in patients suffering from comorbid PD-MDD is not simply a nonspecific or global phenomenon, but may, at times, be discordant. Again, the results of the current study provide no information as to whether patients who are discordant would have achieved a response in both illnesses if further dose titration was permitted. How to optimally manage treatment-resistant depression or panic disorder in the face of treatment response in the comorbid illness is a topic in need of research.

The clinical impact of PD-MDD comorbidity can be measured by comparing baseline quality of life in the current sample with what has previously been reported among patients suffering from PD or MDD without full current comorbidity. The baseline Q-LES-Q score in the current sample was 52, significantly lower than the baseline Q-LES-Q score of 67 reported in PD studies[23–26] and the score of 57 reported in a study of major depression.[39] In the current study, treatment with both sertraline and imipramine was associated with significant improvement (i.e., an increase) in the Q-LES-Q total score to a mean week 26 score of 74.2 for sertraline and 74.5 for imipramine. While this improvement is significant, it lags behind the degree of improvement in quality of life typically reported after treatment of PD and MDD without comorbidity. This suggests that patients with comorbid PD-MDD either may need longer-term treatment to achieve a complete quality of life response or may benefit from use of higher doses. Future research is needed to provide information on this issue.

Several important limitations of the current study should be noted. First and foremost was the lack of placebo control. However, the degree of chronicity of illness and the extent of comorbidity observed in the current treatment sample, as well as the length of study treatment, all increase the likelihood that a true drug response is being observed. Second, structured assessment of the presence of comorbidity was not performed, so we are unable to comment on the extent, or the influence, of additional Axis I comorbidity. Third, the dosing for each drug may have been lower than it should have been in light of the degree of comorbidity, chronicity, and illness severity in the current patient sample. This is especially true for imipramine, for which no measurements were obtained to ensure that an adequate plasma level had been achieved. Fourth, low doses of benzodiazepines (< 1.5 mg per day of alprazolam or its equivalent) were permitted, as long as dosing was stable for at least 3 months. In fact, 60% of patients were taking stable low-dose benzodiazepine therapy. Permitting concomitant medication use served to increase the generalizability of study results to clinical practice. The results of a stepwise regression analysis indicated that permitting concomitant therapy constituted only a trivial confounding variable, accounting for less than 2% of the variance in treatment response. Finally, the overall attrition rate of 45% reduced the sample size and therefore the power to perform additional subgroup analyses. Taken together, these study limitations suggest that caution should be exercised in drawing inference about efficacy.

CONCLUSION

The results of the current study of PD-MDD comorbidity, the first of its kind, suggest that sertraline and imipramine are effective treatments of both disorders, even when they co-occur. Improvement in the core symptoms of both PD and MDD occurred rapidly with both drugs, with 3-week CGI-I responder rates of 44% on sertraline and 39% on imipramine, despite the degree of comorbidity, illness severity, and chronicity in the current patient sample. Sertraline was significantly better tolerated and was associated with higher rates of long-term treatment compliance.

The efficacy of sertraline in PD-MDD, combined with its previously demonstrated efficacy when MDD occurs comorbidly with OCD[37] and posttraumatic stress disorder,[40] establishes sertraline as one of the most well-studied

SSRIs for the treatment of comorbid affective and anxiety disorders. Given the high frequency of affective/anxiety comorbidity in the primary care setting,[3,4] additional randomized controlled trials targeting comorbidity should be a high priority.

Drug names: alprazolam (Xanax and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), sertraline (Zoloft).

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