Treatment of Dysthymia With Sertraline: A Double-Blind, Placebo-Controlled Trial in Dysthymic Patients Without Major Depression

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Background: The selective serotonin reuptake inhibitor sertraline has been shown to be efficacious and well tolerated for the treatment of major depressive disorder. Relatively few trials, however, have examined the role of pharmacotherapy in dysthymia without concurrent major depression. The current investigation focuses on the use of sertraline for the treatment of dysthymia.

Method: In this 12-week, multicenter, double-blind study, 310 patients with a DSM-III-R diagnosis of dysthymic disorder without concurrent major depression were randomly assigned to receive either sertraline (N = 158) or placebo (N = 152). Sertraline was initiated at a dose of 50 mg daily, with titration permitted to a maximum of 200 mg daily. The primary evaluation criteria were the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version (SIGH-SAD), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales.

Results: Mean percentage reductions for the intent-to-treat population in SIGH-SAD scores were 44.6% for the sertraline-treated group and 33.2% for the placebo-treated group ($p = .03$); MADRS scores, 43.6% and 33.0% ($p = .02$); and CGI-S scores, 32.8% and 22.8% ($p = .02$). A significantly greater proportion of the sertraline-treated group was classified as responders (defined for HAM-D and MADRS scores as a 50% score reduction and for CGI-I as a score of 1 or 2 by the final visit) and remitters (SIGH-SAD score ≤ 8) relative to the placebo-treated group by the final visit. In addition, sertraline-treated patients experienced greater improvements in all 9 domains of the Battelle Quality of Life Questionnaire than placebo-treated patients did, with a significant difference observed in favor of sertraline in 8 of the 9 domains. The life satisfaction and social interaction quality of life domains showed significantly greater response in sertraline responders compared with placebo SIGH-SAD responders. Sertraline was well tolerated. Thirteen percent of the sertraline-treated group versus 8% of the placebo-treated group withdrew from therapy owing to adverse events ($p = .14$).

Conclusion: Sertraline is efficacious and well tolerated in the short-term treatment of dysthymia without concurrent major depression.

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Dysthymia is a common and debilitating psychiatric condition. The National Comorbidity Survey conducted in the United States found lifetime prevalence rates for DSM-III-R–defined dysthymia of 6.4%.[1] Up to 68% of dysthymic patients have lifetime comorbid major depression[2] and therefore meet the criteria for double depression.[3] Dysthymia is also commonly associated with anxiety disorders. For example, 26% of dysthymic patients also meet the criteria for panic disorder.[3]

Relatively few trials have examined the role of pharmacotherapy in "pure" dysthymia (dysthymia without concurrent major depression). Although as many as 15 published studies have demonstrated the effectiveness of the monoamine oxidase inhibitors (MAOIs), the tricyclic antidepressants (TCAs), and the selective serotonin reuptake inhibitors (SSRIs) in the treatment of dysthymia,[4–18] some of these trials are limited by small sample size, absence of a placebo arm, inadequate duration or dosage of treatment, and heterogeneity of patient population.

Interpretation of the results of studies that included patients with concomitant major depression is difficult, as major depression may resolve without improvement of the underlying dysthymia.[19] Of the 15 studies (excluding this report) available at the time of publication, only 9 were conducted in "pure" dysthymic populations[4,6,9,10,12–16] (Table 1).

Sertraline is an SSRI that has been shown to be both efficacious and well tolerated in the treatment of major depressive disorder.[20,21] It has also been shown to be effec-

Table 1. Clinical Trials Conducted in Populations of Subjects With "Pure" Dysthymia[a]

Study	N	Diagnosis/Severity	Duration	Results
Ravindran et al[16] (1999)	80	DSM-III-R/ HAM-D > 12 after washout	12 wk	Sertraline + gCBT ≥ sertraline > gCBT = placebo
Vanelle et al[15] (1997)	140	DSM-III-R/ HAM-D > 16	6 mo	Fluoxetine > placebo
Thase et al[14] (1996)	416	DSM-III-R/ early onset	12 wk	Sertraline = imipramine > placebo
Bakish et al[4] (1993)	50	DSM-III/ HAM-D > 13	7 wk	Imipramine > placebo Ritanserin > placebo
Hellerstein et al[6] (1993)	32	DSM-III-R/ early onset	8 wk	Fluoxetine > placebo
Nardi et al[12] (1992)	315	DSM-III-R/ at least moderate severity	8 wk	Moclobemide > placebo Imipramine > placebo
Bersani et al[9] (1991)	30	DSM-III/ HAM-D > 20	5 wk	Ritanserin > placebo
Stewart et al[10] (1989)	57	DSM-III/ HAM-D ≥ 10	6 wk	Phenelzine > imipramine > placebo
Stewart et al[13] (1985)	18	DSM-III/ HAM-D ≤ 18	6 wk	Desipramine = placebo

[a]Abbreviations: gCBT = group cognitive-behavioral therapy, HAM-D = Hamilton Rating Scale for Depression.

tive in the prevention of relapse and recurrence of major depressive disorder[21,22] and in the management of chronic major depression.[23] The placebo-controlled efficacy and tolerability of sertraline in the treatment of dysthymia have recently been demonstrated in a large, double-blind, multicenter, comparative study with imipramine[14] and in a smaller single-center study.[16] In the current investigation, we present the results of a large, multicenter, parallel-group, double-blind, placebo-controlled study of sertraline for the treatment of dysthymia.

METHOD

This was a 12-week, double-blind, multicenter, placebo-controlled study to determine the efficacy, safety, and tolerability of sertraline in the treatment of dysthymic disorder. Participating study centers were located in Canada, France, Italy, Spain, Sweden, and the United Kingdom. Following a 1-week washout period, patients were randomly assigned to receive either a flexible dose of sertraline, 50 to 200 mg daily, or placebo equivalent.

Patient Selection

Study participants were selected from outpatients aged 18 years or over. Both men and women were enrolled. Those with stable medical conditions were admitted to the study provided they were not taking psychotropic agents or any other medication likely to interact with sertraline. The institutional review boards approved the protocol at all centers. Written informed consent was obtained after the study procedures had been fully explained to subjects.

For inclusion in the study, patients had to meet the DSM-III-R criteria for dysthymic disorder. Those with a concomitant diagnosis of major depressive disorder were excluded. Eligible patients also needed to have met the criteria for dysthymia for a duration of ≥ 5 years. In addition, patients had to have a total score of ≥ 12 on the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders Version (SIGH-SAD)[24] at the end of the washout period. Patients whose total HAM-D score had declined by ≥ 25% from the screening visit to the end of the washout phase were excluded from the study, as were patients with a Clinical Global Impressions-Improvement scale (CGI-I)[25] score of 1 or 2. Other exclusion criteria included pregnancy, clinically significant medical conditions, a diagnosis of schizophrenia or other psychotic or paranoid disorder, a principal diagnosis of an anxiety disorder within the previous 6 months, or previous use of sertraline.

Study Design

Once informed consent had been obtained, subjects were enrolled in the study for the screening visit. Patients entered a 1-week washout phase during which they received single-blind placebo. For patients receiving prior MAOI or fluoxetine treatment, the washout period was extended to 2 and 5 weeks, respectively, owing to the prolonged elimination of these drugs.

At the end of the washout, patients were randomly assigned to receive either placebo or an initial 50-mg daily dose of sertraline. Treatment was continued for 12 weeks, and dose escalation was carried out according to treatment response and tolerability. Dose escalation of sertraline was permitted in 50-mg increments, at 2-week intervals, to a maximum of 200 mg daily. Dose reduction was permitted in the event of intolerable side effects.

Efficacy Evaluation

Patients were evaluated at screening, baseline, and weeks 1, 2, 4, 6, 8, and 12. Physician-rated evaluation measures included the SIGH-SAD,[24] the Hamilton Rating Scale for Anxiety (HAM-A),[26] the Clinical Global Impressions-Severity of Illness scale (CGI-S) and the CGI-I,[25] and the Montgomery-Asberg Depression Rating Scale (MADRS).[27] Patient-rated measures included the Hospital Anxiety and Depression Scale subscales for anxiety and depression (HAD-A and HAD-D)[28] and the Battelle Quality of Life Scale (BQOLS),[29] which comprises a set of 9 health-related quality of life dimensions.

An intent-to-treat (ITT) analysis was carried out on all patients who received at least 1 dose of double-blind

Table 2. Baseline Demographic Characteristics of the Study Population[a]

Characteristic	Sertraline (N = 158)	Placebo (N = 152)
Gender		
Male, N (%)	54 (34.2)	49 (32.2)
Female, N (%)	104 (65.8)	103 (67.8)
Age, y, mean ± SD	46.0 ± 12.94	44.2 ± 12.41
18–44 y	(N = 71)	(N = 81)
45–64 y	(N = 74)	(N = 62)
≥ 65 y	(N = 13)	(N = 9)
White, N (%)	126 (79.7)	121 (79.6)
DSM-III-R dysthymia onset, N (%)		
Early (< 21 y)	60 (38.0)	62 (40.8)
Late (≥ 21 y)	98 (62.0)	90 (59.2)
Age at onset, y, mean ± SD	29.1 ± 12.85	27.8 ± 13.26
Duration of illness, y, mean ± SD	17.0 ± 10.50	15.9 ± 9.92
Baseline 17-item HAM-D score, mean ± SD	19.2 ± 6.98	18.6 ± 6.62

[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

therapy and had at least 1 efficacy evaluation. The primary efficacy variables included the SIGH-SAD, CGI, and MADRS scores. Treatment responses were defined as a SIGH-SAD or MADRS reduction of total score of 50% or more or a CGI-I score of 1 or 2. Remission was defined as a score of ≤ 8 on the SIGH-SAD.

Safety Assessment

Adverse events reported by the patient or observed by the investigator were classified according to severity (mild, moderate, or severe), onset, action taken, and outcome.

Statistical Methods

Study endpoint analysis (in which patients discontinuing prior to the last study visit had their last observation carried forward to subsequent timepoints) in the ITT patient population was the primary analysis of efficacy in this study. Patients were included in this analysis if they had received at least 1 dose of double-blind medication and at least 1 follow-up efficacy assessment in addition to baseline. All patients who received at least 1 dose of double-blind medication were included in the safety analysis.

Cochran-Mantel-Haenszel tests were used to test the significance for the treatment response rate between 2 treatment groups and dropouts due to lack of efficacy. Cochran-Mantel-Haenszel tests were also used for the remission comparison between 2 treatment groups. Fisher exact tests were used to compare adverse-event profiles. Analysis of covariance (ANCOVA) methods were used to compare the mean change of efficacy measurements from baseline. Analysis of variance (ANOVA) was used where no baseline data were collected (the CGI-I, for example). Both ANCOVA and ANOVA models included treatment, country, and treatment-by-country interaction as the main effects. The baseline was included as covariate in the ANCOVA model as well. All tests of hypotheses were carried out with a 2-sided significance level of .05.

RESULTS

Patient Characteristics

A total of 322 patients entered the trial, of which 12 withdrew during the washout phase. A total of 310 patients were randomly assigned to receive either sertraline (N = 158) or placebo (N = 152). All 310 randomized patients were analyzed for safety and included in the ITT analyses of efficacy. The baseline characteristics of the patients entering the study are summarized in Table 2. The 2 populations were closely comparable in all demographic variables.

The mean scores of efficacy measures at baseline are summarized in Table 3. The 2 populations were once again closely comparable at baseline with respect to all parameters of efficacy and quality of life.

Withdrawals

In the ITT population, the mean duration of treatment was 73.8 days in the sertraline group (range, 2–109 days) and 73.7 days in the placebo group (range, 1–103 days). In total, 121 patients receiving sertraline and 114 patients receiving placebo completed the study.

Thirty-seven patients (23.4%) in the sertraline group and 38 (25.0%) receiving placebo withdrew from double-blind treatment. The most common reason for withdrawal in the placebo group was inadequate response to treatment. A higher proportion of patients withdrew from the placebo-treated group than the sertraline-treated group owing to inadequate response to treatment, although this difference only approached statistical significance (N = 20, 12.5% vs. N = 10, 6.3%, respectively; p = .062). In the sertraline group, the most common reason for withdrawal was adverse events (N = 21, 13.3% vs. N = 12, 7.9% for placebo; NS).

Efficacy

Patients in the sertraline group exhibited significantly greater reductions in the SIGH-SAD, MADRS, CGI-S, HAD-D, and HAD-A scores relative to the placebo group (see Table 3).

The number of treatment responders was significantly higher in the sertraline group than in the placebo group. For the sertraline group, the percentages of responders at the final visit were 51.9%, 53.2%, and 60.1% according to HAM-D, MADRS, and CGI-I scores, respectively; for the placebo group, the percentages of responders were 33.8%, 37.5%, and 39.5% according to HAM-D, MADRS, and CGI-I scores (p = .001, p = .006, and p < .001, respectively).

Table 3. Physician- and Patient-Rated Efficacy Variables at Baseline and Final Visit (intent-to-treat population)[a]

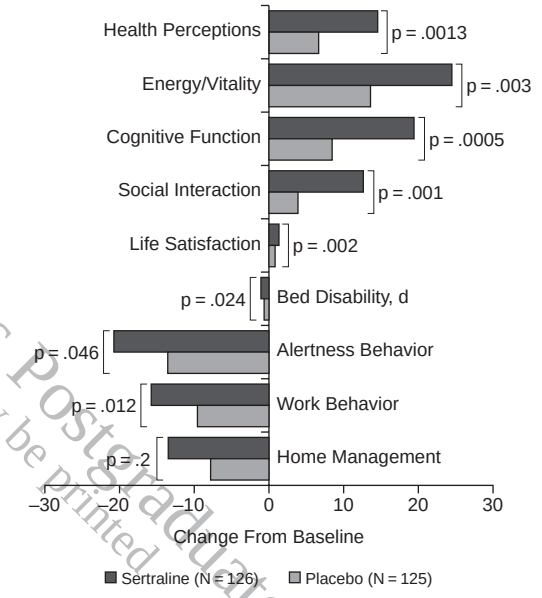
	Sertraline				Placebo				
Scale	N	Baseline	Final Visit	Change From Baseline (%)	N	Baseline	Final Visit	Change From Baseline (%)	p Value[b]
SIGH-SAD	154	27.66	14.97	–12.68 (–44.6)	148	26.93	17.46	–9.47 (–33.2)	.03
MADRS	158	23.46	12.71	–10.75 (–43.6)	152	23.10	15.26	–7.84 (–33.0)	.02
CGI-S	158	4.17	2.77	–1.40 (–32.8)	152	4.18	3.17	–1.01 (–22.8)	.02
HAM-A	150	19.65	10.64	–9.01 (–41.2)	147	19.00	12.29	–6.71 (–30.5)	.08
HAD-D	150	12.16	7.37	–4.79 (–35.9)	144	11.53	9.40	–2.13 (–11.8)	.003
HAD-A	150	12.21	8.20	–4.01 (–29.6)	144	12.09	9.57	–2.52 (–15.3)	.004

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAD-A = Hospital Anxiety and Depression Scale-Anxiety, HAD-D = Hospital Anxiety and Depression Scale-Depression, HAM-A = Hamilton Rating Scale for Anxiety, MADRS = Montgomery-Asberg Depression Rating Scale, SIGH-SAD = Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version.
[b]p Values based on the analysis of absolute mean change from baseline.

The number of remitters was also significantly greater in the sertraline group than in the placebo group (33.8% vs. 21.6%; p = .02). It could be hypothesized that a greater differential response in more severely ill patients could drive the greater response to active treatment relative to the placebo group. Factorial analyses of the absolute change from baseline on the SIGH-SAD adjusted by the baseline severity (defined on the 17-item HAM-D) were performed. The sample was dichotomized using total 17-item HAM-D severity criteria of ≥ 18 (158/302 patients; 52%) and ≥ 23 (83/302 patients; 27%). No significant treatment-by-severity interaction was demonstrated using either severity definition (≥ 18, F = 1.21, df = 1290, p = .2724; ≥ 23, F = 0.02, df = 1290, p = .8898)

Analysis of the BQOLS scores showed significant within-group improvements at endpoint relative to baseline in both the sertraline and placebo groups (Figure 1), with numerical advantages for the sertraline group in all ratings. The greater improvement seen with sertraline treatment was significant in 8 of the 9 domains (life satisfaction, bed disability days, energy/vitality, cognitive function, social interaction, health perception, alertness behavior, and work behavior). In addition, each treatment group was divided on the basis of responder status on the SIGH-SAD. Statistically significant baseline-to-endpoint differences were seen in favor of sertraline-treated patients relative to placebo-treated patients. In responding patients, significant differences were seen on social interaction (sertraline baseline = 50.2, endpoint = 71.0; placebo baseline = 49.9, endpoint = 56.39; p = .0416) and life satisfaction scores (sertraline baseline = 2.80, endpoint = 5.07; placebo baseline = 2.66, endpoint = 4.75; p = .0417). In addition, a trend in the same direction was noted for energy/vitality scores (sertraline baseline = 27.4, endpoint = 63.1; placebo baseline = 25.27, endpoint = 58.5; p = .0931). Similar quality of life results were obtained when responder status on the MADRS was used.

Figure 1. Improvement in Battelle Quality of Life Scale Scores Following Treatment With Sertraline or Placebo (intent-to-treat population)[a]



[a]All items show greater improvement with sertraline relative to placebo.

Tolerability

In total, 119/158 patients (75.3%) receiving sertraline experienced adverse events during the trial, compared with 98/152 (64.5%) of those receiving placebo (p = .047). The most common adverse events (frequency > 5%) occurring during double-blind therapy are listed in Table 4. Overall, 91% of the adverse events in the sertraline group were classified as mild to moderate, and 1.3% of patients reported adverse events classified as serious, compared with 2.6% in the placebo group.

Dose

The mean ± SD final daily dose of double-blind medication was 127.8 ± 53.4 mg in the sertraline group and 139.8 ± 55.3 mg equivalent in the placebo group. In sertraline responders (≥ 50% reduction in MADRS total score), the mean ± SD final daily dose was 114.3 ± 5.12

Table 4. Most Common Adverse Events During Double-Blind Therapy (frequency > 5%)

	Sertraline (N = 158)		Placebo (N = 152)	
Adverse Event	N	%	N	%
Autonomic				
Dry mouth	17	10.8	10	6.6
Increased sweating	22	13.9	3	2.0
Central/peripheral nervous system				
Dizziness	20	12.7	6	3.9
Headache	48	30.4	51	33.6
Tremor	22	13.9	1	0.7
Gastrointestinal				
Abdominal pain	21	13.3	9	5.9
Constipation	10	6.3	5	3.3
Diarrhea	20	12.7	11	7.2
Dyspepsia	28	17.7	15	9.9
Flatulence	17	10.8	6	3.9
Nausea	33	20.9	27	17.8
Vomiting	9	5.7	6	3.9
General				
Back pain	8	5.1	9	5.9
Fatigue	11	7.0	4	2.6
Influenza-like symptoms	9	5.7	8	5.3
Psychiatric				
Anxiety	13	8.2	5	3.3
Insomnia	35	22.2	25	16.4
Somnolence	18	11.4	11	7.2
Reproductive				
Ejaculation disorder (male)	5	9.3	0	0.0
Respiratory				
Pharyngitis	8	5.1	6	3.9
Upper respiratory tract infection	10	6.3	7	4.6

mg; in nonresponders, it was 142.5 ± 6.58 mg. The dosages in responders and nonresponders were statistically significantly different ($p < .05$). The modal dose at initial response among both sertraline and placebo patients was 50 mg daily.

DISCUSSION

The principal finding of this double-blind, placebo-controlled study was that sertraline was an effective and well-tolerated treatment for dysthymia. Significantly greater improvements in both physician- and patient-rated evaluation criteria, including HAM-D, MADRS, CGI-S, HAD-A, and HAD-D scores, were observed in the group receiving sertraline compared with placebo during the 12-week period of the trial. Furthermore, a significantly higher proportion of responders and remitters was found in the sertraline group compared with the placebo group.

This study confirms the results of an earlier study[14] of sertraline in dysthymia, which also documented the superior efficacy of this agent relative to placebo. As in that earlier study, it is important to note that, despite an average illness duration of greater than 15 years, response rates in excess of 50% were evident in patients administered short-term treatment with active medication. Paralleling Thase and colleagues'[14] study, the modal (most frequent) dose of sertraline at the time of initial response was 50 mg daily. It is not clear if the higher doses used later in this acute-phase clinical trial actually had additional therapeutic effects.

In addition to affording symptomatic relief and control of the disease process, a major aim of therapeutic intervention should be to improve quality of life. This is especially true for the treatment of psychiatric disorder. The "true" value of a drug therapy cannot be assessed without including the patient's own evaluation of the outcome of treatment. Outcome measures commonly used in depression studies, such as the HAM-D, do not examine the full impact of treatment on broader aspects of patient well-being in which important differences between therapies may be apparent. Other domains of functioning, broadly conceptualized as quality of life, are increasingly being recognized as valid outcome measures. In all 9 domains of the BQOLS, the improvement with sertraline was greater than with placebo; this difference was statistically significant for 8 dimensions.

In the 12-week Ravindran et al.[16] study, the BQOLS dimensions measuring health perceptions, energy/vitality, cognitive functioning, alertness, social interaction, and life satisfaction among dysthymic patients at baseline were significantly impaired relative to nondepressed control subjects. All of these dimensions improved significantly in the sertraline-treated group relative to the placebo group. Furthermore, responders to drug treatment had superior life satisfaction, social interaction, and energy/vitality quality of life scores compared with sertraline nonresponders. The scores for the responders to drug treatment approached those of the nondepressed control subjects. Responders to placebo, however, showed no significant improvement in these quality of life dimensions compared with nonresponders.

Interestingly, responders to sertraline in our study demonstrated greater (statistically significant or a trend approaching statistical significance) quality of life improvement relative to placebo responders in these same domains (life satisfaction, social interaction, and energy/vitality). The quality of life in responders to sertraline approached that found in the nondepressed control group assessed by Ravindran et al.[16] The quality of life of sertraline-treated patients whose mood and anxiety disorders responded to treatment has been shown to be significantly greater than that of placebo-treated patients showing the same response on symptom rating scales.[30] The sertraline-treated patients reported here add to the findings that suggest that there is something unique about a symptomatic response to drug treatment that is not apparent in patients responding to placebo.

Sertraline was well tolerated by most patients. The 23.4% dropout rate was comparable with that found in dysthymia studies of fluoxetine[6] and other SSRI studies. The principal side effects with sertraline relative to placebo were headache, insomnia, sweating, dizziness, tremor, gas-

trointestinal symptoms, and ejaculatory delay in men. The frequency and severity of these effects were low and typical of SSRI therapy in studies of depression. Tolerability is an important consideration in the treatment of dysthymia, given the increasing recognition that this chronic condition requires long-term therapeutic intervention.

The baseline HAM-D scores in this study were higher than those seen in previous large-scale studies of "pure" dysthymia[14,15] and indicate that the severity of dysthymic illness in this particular patient population may have been higher than in some comparable studies, although patients with a DSM-III-R diagnosis of concurrent major depression and dysthymia were specifically excluded from the study. However, factorial analyses using 2 definitions of severity did not reveal that higher depressive symptom scores at baseline were associated with a significantly greater magnitude of symptom improvement.

In recent years, the placebo response in clinical trials of depressed patients has been increasing.[31,32] The placebo response rates in our study exceeded 30% for the HAM-D, MADRS, and CGI-I, despite the elimination of fast placebo responders during the single-blind phase of this study. The term *placebo response* is potentially misleading. The benefit in the placebo group response is not due to an inert sugar pill, but rather to a nonspecific treatment response, whereas the additional benefits in the sertraline group are due to the specifics of active treatment. Spontaneous remission, regression to the mean (as patients tend to present for treatment when their symptoms are at their worst), patient/physician expectations of treatment, and the healing effects of the structured clinical environment are just some of the factors that may influence treatment effects. Moreover, less severe forms of depression may be more likely to respond to the nonspecific treatment effects found in a clinical study.

Another reason for the relatively small drug-placebo differences found in this and other studies in pure dysthymia is the lower mean depressive symptom rating scale scores in patients with pure dysthymia relative to patients with major depression. Therefore, the possible decreases or changes in scores produced by effective treatment are correspondingly less. It is interesting to note the greater separation between active and placebo scores in the patient-rated variables compared with the physician-rated variables.

This is the third positive, large, placebo-controlled, double-blind study of sertraline in "pure" dysthymia. Now that the basic efficacy and safety of sertraline in dysthymia have been demonstrated, subsequent studies should address questions relating to the duration of treatment and the potential of educational and psychotherapeutic strategies to augment response and/or reduce relapse.

Drug names: desipramine (Norpramin and others), fluoxetine (Prozac), phenelzine (Nardil), sertraline (Zoloft).

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