Double-Blind Comparison of Sertraline, Imipramine, and Placebo in the Treatment of Dysthymia: Psychosocial Outcomes

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Objective: *The purpose of this study was to determine the effects of antidepressant pharmacotherapy on mood symptoms and psychosocial outcomes in dysthymia.* *Method:* *In a multicenter, double-blind, parallel-group trial, 416 patients with a diagnosis of early-onset primary dysthymia (DSM-III-R) of at least 5 years' duration without concurrent major depression were randomly assigned to 12 weeks of acute-phase therapy with sertraline, imipramine, or placebo. The psychosocial outcome measures used in the study were the Global Assessment of Functioning Scale, the Social Adjustment Scale, the Longitudinal Interval Follow-up Evaluation psychosocial ratings, and the Quality of Life Enjoyment and Satisfaction Questionnaire.* *Results:* *Sertraline and imipramine were significantly better than placebo in improving psychosocial outcomes as measured by the first three instruments. The Quality of Life Enjoyment and Satisfaction Questionnaire scores demonstrated significant improvements from baseline, and both active treatments produced significantly greater improvements than placebo. Significantly fewer patients discontinued sertraline (6.0%) than discontinued imipramine (18.4%) because of adverse events.* *Conclusions:* *Pharmacotherapy is an effective treatment for dysthymia in terms of psychosocial functioning as well as depressive symptoms, even when the dysthymia is long-standing.*

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Dysthymia, a chronic depressive disorder, is usually characterized by an insidious, often early, onset (1, 2). It is distinct from unresolved or partially remitted major depression; the onset of dysthymia must not be the result of the continuance of a major depressive episode. The Epidemiologic Catchment Area study (3) estimated the lifetime prevalence of dysthymia in the U.S. population to be approximately 3%. More recent results have indicated that the prevalence of dysthymia is higher than previously thought and that most patients with this condition are undertreated (4–6). The National Comorbidity Survey (5) indicated that the lifetime prevalence of dysthymia was 4.8% for men and 8.0% for women.

Despite a generally milder level of depressive symptoms, the early onset and chronic course of dysthymia may result in even greater impairments in both social and occupational functioning than those found with more episodic forms of major depression (7–10). Cassano et al. (10) used the Social Adjustment Scale to compare patients with acute or chronic depression and found greater social maladjustment in the dysthymic patients. The Medical Outcomes Study (8) found that patients with dysthymia (with and without concurrent major depression) had significantly lower functional status and well-being than patients with only depressive symptoms, as well as a high prevalence of poor general medical health and impaired physical functioning. Most recently, a study of over 1,000 primary care patients (9) found that those with dysthymia had substantial impairment in health-related quality of life and exhibited greater impairments in physical functioning, role functioning, and social functioning than patients with major depression.

Whereas studies of the efficacy of antidepressant therapy have traditionally concentrated primarily on symptom reduction and/or syndrome remission, more

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recent trials have recognized the importance of evaluating the effects of treatment on the psychosocial functioning and quality of life of patients with major depression (11, 12). The present study was undertaken to determine the effects of treatment with either sertraline or imipramine on both mood symptoms and psychosocial outcomes for a large group of patients with DSM-III-R-defined, early-onset primary dysthymia without concurrent major depression.

METHOD

This was a double-blind, placebo-controlled parallel trial in patients randomly assigned to acute-phase treatment that was carried out at 17 university-affiliated centers in the United States. Four hundred sixteen patients with a DSM-III-R diagnosis of early-onset primary dysthymia entered the study. An additional requirement for inclusion in the study was that the current episode of dysthymia had lasted at least 5 years, without a depression-free period exceeding 2 consecutive months. Subjects were also required to have a score of 12 or more on the Hamilton Depression Rating Scale (13) (29 items) at the end of the 7-day placebo run-in period. The age range of the subjects was 25–65 years.

The exclusion criteria included pregnancy or lactation, concurrent major depressive disorder, history of drug or alcohol dependency or abuse within the previous 6 months, serious risk of suicide, a primary diagnosis of panic disorder or generalized anxiety disorder, and a lifetime diagnosis of bipolar disorder, obsessive-compulsive disorder, or any psychotic disorder. Also excluded were patients who had failed to respond to adequate trials of at least two antidepressant medications or an adequate trial of imipramine or had participated in a previous trial of sertraline.

After complete description of the study to the subjects, written informed consent was obtained.

Four patients left the study before receiving double-blind medication. The 412 patients who completed the single-blind placebo run-in period and still met the above-listed entry criteria were randomly assigned to once-daily double-blind treatment with either sertraline (starting dose of 50 mg/day, titrated to a maximum of 200 mg/day), imipramine (starting dose of 50 mg/day, titrated to a maximum of 300 mg/day), or placebo. All patients received four identical capsules each time medication was given, in order to maintain the blind conditions. Patients who had not responded and were not experiencing dose-limiting side effects were permitted upward dose titration of imipramine and sertraline in 50-mg/week increments after 1 week and 4 weeks, respectively.

Both clinician-rated and self-rated depression and psychosocial rating instruments were used. The clinician-rated instruments were the Hamilton depression scale (the 29-item version containing the core 17 items and supplemental items to assess atypical depressive symptoms), the Longitudinal Interval Follow-up Evaluation psychosocial ratings (14), the Montgomery-Asberg Depression Rating Scale (15), and the Global Assessment of Functioning Scale (DSM-IV). Among the self-rated scales were the Hopkins Symptom Checklist (16), the 30-item Inventory for Depressive Symptomatology, self-report version (17, 18), the Social Adjustment Scale, self-rated version (19), and the Quality of Life Enjoyment and Satisfaction Questionnaire (20).

All ratings were performed at baseline, before initiation of the double-blind medication trials. Ratings on the Clinical Global Impression scale and the Hamilton depression scale were repeated weekly and biweekly, respectively, and the psychosocial ratings were repeated at the end of 8 and 12 weeks of treatment. Patients who discontinued treatment before week 12 were administered all rating scales at the time of discontinuation.

The statistical analyses performed have been described in detail elsewhere (21). Briefly, all clinical data were analyzed with the use of SAS statistical software, version 6 (22). The intent-to-treat efficacy group (N=410) consisted of the patients who had a baseline evaluation and at least one efficacy evaluation while on the double-blind medication regimen, and the group examined for safety and toleration (N=412) had received at least one dose of double-blind medication.

The treatment groups were examined for homogeneity at baseline with analysis of variance (ANOVA) models that included main effects of treatment group and center and the group-by-center interaction for continuous data. Chi-square tests for homogeneity at baseline were computed, as appropriate, for demographic characteristics. Frequency distributions were used to characterize the patients with respect to age at entry into the study, age at the first major depressive episode, frequency of previous episodes of major depression, age at onset of dysthymia, and duration of the current dysthymic episode.

An alpha level of 0.05 for significance was assumed throughout the efficacy analysis, and two-sided statistical tests were performed. The primary measures of efficacy for assessments with continuous data were the changes from baseline to endpoint (defined as the last observation while the patient was on the double-blind acute-phase medication regimen). The F statistics from either ANOVA models or, if assumptions were met, analysis of covariance models, with baseline values as the covariates, were used as the overall tests of significance to evaluate the treatment group and center main effects and the group-by-center interactions. Significant main effects were further explored with unpaired t tests. The significance of the within-group changes from baseline and the between-group differences in rates of response and remission was assessed with paired t tests and chi-square tests, respectively.

The incidence of adverse events was summarized for the active treatment groups with respect to the World Health Organization body-organ system, and the significance of between-group differences in rates was assessed with Fisher's two-sided exact test.

RESULTS

Table 1 presents demographic and clinical data for the 410 patients treated. Of these, 134 received sertraline, 136 received imipramine, and 140 received placebo. The patients were predominantly white, female, and middle-aged. At baseline they were generally mildly depressed (mean baseline 17-item Hamilton depression scale score=12.9, SD=3.9, range=12.7–13.4). The mean duration of dysthymia was 30 years, with an average age at onset of 12 years. Fifty-one percent of the group reported superimposed episodes of major depression since the onset of dysthymia.

A total of 310 patients in the intent-to-treat group completed 12 weeks of treatment. The percentages of patients in each group who completed the trial were 84.3% (N=113) for sertraline, 66.9% (N=91) for imipramine, and 75.7% (N=106) for placebo, with the sertraline group having a significantly higher percentage of completers than the imipramine group (p=0.004). The percentages of patients who discontinued treatment because of insufficient response were 2.2% (N=3) for sertraline, 3.7% (N=5) for imipramine, and 6.4% (N=9) for placebo. A significantly greater proportion of patients in the imipramine group (18.4%, N=25) discontinued treatment because of adverse events than did so in the sertraline group (6.0%, N=8) (p=0.001) and the placebo group (3.6%, N=5) (p<0.001).

The mean dose at the time of initial response (CGI improvement score ≤2) was 89.5 mg/day (SD=51.5) for sertraline and 159.7 mg/day (SD=8.08) for imipramine. At initial response, the modal or most frequently administered dose was 50 mg/day for sertraline and 100

TABLE 1. Demographic and Clinical Characteristics of 410 Patients With Dysthymia

Characteristic	Value	
	N	*%*
Demographic		
Female sex	266	65
Race		
Caucasian	390	95
Black	9	2
Asian	2	0.5
Other	9	2
	Mean	*SD*
Age (years)	42	9
Clinical		
Duration of illness (years)	29	11
Age at onset of dysthymia (years)	12	5
Duration of current dysthymic episode (years)	30	11
	N	*%*
Prior history of major depression	218	53
Lifetime episodes of major depression		
None	202	49
One	92	22
Two or more	116	28
DSM-III-R axis I comorbidity (>5%)		
Panic disorder[a]	29	7
Social phobia[a]	42	10
Generalized anxiety disorder	45	11
Substance abuse[a,b]	191	47
DSM-III-R axis II comorbidity		
Cluster A	44	11
Cluster B	48	12
Cluster C	193	47

[a]Lifetime prevalence.
[b]Includes abuse of or dependency on alcohol, cannabis, sedatives, stimulants, opioids, cocaine, and hallucinogens.

mg/day for imipramine, while the median daily doses were 50 mg and 150 mg, respectively. The mean final dose was 139.6 mg/day (SD=58.5) for sertraline and 198.9 mg/day (SD=91.2) for imipramine.

Antidepressant Response

The results for response to antidepressants are fully detailed in a previous report (21). Satisfactory clinical response was defined as having a CGI score of 1 or 2 (very much or much improved). According to this criterion, the proportion of patients classified as responders was 59.0% (N=79) for sertraline, 64.0% (N=87) for imipramine, and 44.3% (N=62) for placebo ($p<0.02$ for sertraline versus placebo, and $p<0.001$ for imipramine versus placebo).

Full remission was defined more stringently: patients had to no longer meet the DSM-III-R criteria for dysthymia (i.e., not have two or more clinically significant symptoms) *and* to have a score of 0 on Hamilton depression scale item 1 (depressed mood). The proportions of patients classified as having a full remission were 49.5% (N=66) for sertraline, 43.5% (N=59) for imipramine, and 27.8% (N=39) for placebo. Both active treatments were significantly superior to placebo ($p<0.05$).

Psychosocial Response

Improvement in overall psychosocial functioning (table 2) was demonstrated by increases in Global Assessment of Functioning Scale scores from baseline to treatment endpoint. Both sertraline and imipramine improved these scores significantly more than placebo. A significantly greater proportion of the sertraline-treated patients (61%) and the imipramine-treated patients (58%) than the placebo-treated patients (45%) achieved final Global Assessment of Functioning Scale scores of 71 or more, a score cutoff indicating no more than slight impairment in social, occupational, or school functioning (20) ($p=0.01$ for sertraline versus placebo, and $p=0.05$ for imipramine versus placebo).

All three treatments produced significant improvement in psychosocial functioning from baseline as measured with the Social Adjustment Scale; sertraline- and imipramine-treated patients had significantly more improvement in total Social Adjustment Scale scores than patients given placebo (table 2). In addition, both sertraline and imipramine produced significant improvements in family relationships (membership in family unit) ($p<0.001$ for both active treatments versus placebo) and marital relationships (marital role score) ($p<0.001$ for both active treatments versus placebo). Sertraline and imipramine also improved parental role function ($p=0.01$ and $p=0.15$, respectively, versus placebo).

For several domains reflecting role functioning and relationships measured by the Longitudinal Interval Follow-up Evaluation, the sertraline and imipramine groups showed greater improvement than the placebo group. These included patients' and clinicians' assessments of social adjustment and overall satisfaction. Quality of life, as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire, improved significantly from baseline in all three groups; both active treatment groups had significantly greater improvement than the placebo group, with no significant differences between imipramine and sertraline.

When psychosocial functioning was compared for patients achieving symptom remission and those failing to achieve remission, there were notable differences (table 3). Although both groups achieved significant improvement on all three scales, the patients with remission had larger improvements than those without remission.

The mean Social Adjustment Scale scores of the patients with and without remission were also compared with those of the community-sample and acutely depressed groups studied by Weissman et al. (23). The community group consisted of 482 individuals randomly drawn from the general population of an urban area, while the acutely depressed group consisted of 191 outpatients with a total score of 7 or more on the Raskin Depression Scale. At baseline in the present

TABLE 2. Changes From Baseline in Ratings of Psychosocial Functioning of Patients With Dysthymia Treated With Sertraline, Imipramine, or Placebo

	Sertraline Group			Imipramine Group			Placebo Group			Overall Analysis of Variance		
Measure	N	Baseline Score	Change From Baseline Score	N	Baseline Score	Change From Baseline Score	N	Baseline Score	Change From Baseline Score	F	df	p
Global Assessment of Functioning Scale	127			126			130			5.59	2, 364	0.004
Mean		63.54	10.99[a]		62.56	12.21[b]		63.17	7.55			
SD		7.95	11.54		7.83	11.77		8.25	10.42			
Social Adjustment Scale total score	123			122			123			6.53	2, 316	0.002
Mean		2.28	–0.37[c]		2.28	–0.34[b]		2.23	–0.17			
SD		0.40	0.39		0.44	0.42		0.42	0.35			
Patient's rating of social adjustment[d]	110			107			114			3.88	2, 285	0.02
Mean		3.52	–0.97[a]		3.64	–1.06[b]		3.54	–0.67			
SD		0.81	1.14		0.83	1.22		0.77	1.00			
Clinician's rating of social adjustment[d]	110			107			114			2.82	2, 285	0.03
Mean		3.25	–0.86		3.33	–1.02[b]		3.26	–0.71			
SD		0.73	0.93		0.75	1.06		0.74	0.85			
Overall satisfaction[d]	110			107			115			4.67	2, 329	0.005
Mean		3.29	–0.96[c]		3.32	–0.73		3.27	–0.53			
SD		0.71	1.03		0.69	1.16		0.65	0.92			
Quality of Life Enjoyment and Satisfaction Questionnaire total score	106			102			105			5.24	2, 294	0.006
Mean		42.5	7.7[a]		42.8	7.7[b]		43.6	4.2			
SD		6.4	8.8		8.1	9.6		6.7	8.0			

[a]p<0.05, sertraline versus placebo.
[b]p<0.01, imipramine versus placebo.
[c]p<0.01, sertraline versus placebo.
[d]Longitudinal Interval Follow-up Evaluation scale.

study, the scores of both the patients who achieved remission and those who did not were close to the scores of the acutely depressed patients in the Weissman et al. study. However, at last observation carried forward, the psychosocial functioning scores of the patients with remission had improved to meet or nearly meet the levels of the community group. Moreover, among the patients who were responders (i.e., had CGI scores of 2 or lower) and had a final Social Adjustment Scale total score less than or equal to the mean total Social Adjustment Scale score of the Weissman et al. community group, 82% had received active medication, while 18% had been treated with placebo (p<0.04).

DISCUSSION

The results of this study indicate that both sertraline and imipramine were more effective than placebo in improving scores on measures of psychosocial functioning of patients with dysthymia. Although previous studies have assessed the effect of treatment on social impairment in episodic major depression (24–26), few have systematically evaluated the effects of treatment for dysthymia on psychosocial impairment. The findings of this study are consistent with those of earlier trials indicating impairment in major social roles (i.e., work, family life, intimate relationships, and social and leisure time) associated with dysthymic disorder (12, 27–32).

There has been a long-standing controversy regarding whether mild chronic depression represents a mood disorder or underlying character pathology. The favorable response of psychosocial functioning to 12 weeks of pharmacotherapy in the present study suggests that the social dysfunction experienced by these patients is a symptom of a mood disorder rather than a trait-related manifestation of character pathology. This hypothesis is supported by the findings of Agosti et al. (27), who evaluated 61 chronically depressed outpatients (25% with major depression, 31% with dysthymia, 44% with double depression) receiving treatment with either phenelzine, imipramine, *l*-deprenyl, or placebo. Significant improvement from baseline in psychosocial functioning as measured by the Longitudinal Interval Follow-up Evaluation scale was seen in the patients receiving active treatment; specifically, responders showed improvement in the areas of work functioning, household functioning, relationship with relatives, frequency of sexual relations, and life satisfaction. Because of this improvement in functioning and quality of life, as well as the reduction in depressive symptoms seen with pharmacotherapeutic treatment, the authors suggested that psychosocial impairment in at least some of these patients was a result of their depression. A related conceptual issue is the extent to which psychosocial impairment and quality of life are influenced by the depressive state. Clearly, these are somewhat interdependent and overlapping behavioral factors that can be expected to

TABLE 3. Change From Baseline Score to Score at Last Observation on Psychosocial Measures of Patients With and Without Remission of Dysthymia After Antidepressant Treatment

	Quality of Life Enjoyment and Satisfaction Questionnaire			Social Adjustment Scale			Longitudinal Interval Follow-up Evaluation[a]		
Group	N	Mean	SD	N	Mean	SD	N	Mean	SD
Patients with remission[b]	127			148			133		
Baseline score		44.00	6.94		2.17	0.39		3.48	0.80
Adjusted change score[c]		11.69	7.12		–0.49	0.35		–1.55	0.88
Patients without remission[b]	183			213			196		
Baseline score		42.38	7.12		2.33	0.43		3.61	0.82
Adjusted change score[c]		2.52	6.97		–0.17	0.35		–0.43	0.88

[a]Social adjustment factor from the scale.
[b]Defined as no longer meeting the DSM-III-R criteria for dysthymia *and* having a Hamilton depression scale item 1 (depressed mood) score of 0.
[c]Least squares adjusted mean change from the analysis of covariance. All within-group and between-group p values=0.0001.

be intercorrelated. From a clinical standpoint, it seems sensible to pay attention to all three areas when assessing changes with treatment.

The beneficial effects of antidepressant therapy on social adjustment in this trial are consistent with results of earlier studies of psychosocial functioning of patients with chronic depression. Kocsis et al. (30, 33) followed a small group of 39 patients with DSM-III dysthymia (all but two of whom also presented with a concurrent major depressive episode) who either failed to complete (N=19), responded to (N=11), or failed to respond to (N=9) 6 weeks of treatment with imipramine. Those who responded to imipramine treatment showed significant improvement in overall social functioning compared with nonresponders. At the end of an average follow-up of 40 months, the patients who had responded to imipramine had significantly better (i.e., lower) scores on the Social Adjustment Scale than the patients who either failed to complete or did not respond to imipramine treatment, and the social functioning of the responders was comparable to that of the community control group of Weissman et al. (23, 31). Stewart et al. (32), in a study of 189 chronically depressed patients, found that those who responded to treatment in a 6-week trial of phenelzine, imipramine, and placebo reported significantly improved social functioning compared to nonresponders, but only 28% of the responders rated themselves as functioning as well as or better than the mean of social functioning for community control subjects.

The positive effect of antidepressant treatment on impaired work functioning in this study is particularly important, especially with the increasing emphasis on cost-benefit relationships. Because the patients in this study were generally mildly depressed, the need for antidepressant treatment and the potential benefit might be questioned, particularly by third-party payers under changing health care reimbursement systems. However, it is relevant that more than one-half of the economic cost of depression in the United States is estimated to be derived from indirect costs due to absenteeism or impaired work functioning. According to the estimates of Greenberg et al. (34), the economic costs of depression related to reduced work productivity could be more than $20 billion. As these authors pointed out, this figure may even be an underestimation, because there are no practical methods for measuring reduction in productivity at work. Tollefson et al. (35) reported that work impairment improved with increasing duration of antidepressant therapy in 454 outpatients with major or minor depression treated for up to 2 months, while Mintz et al. (36) reviewed 10 studies to evaluate the effects of treatment of depression on work impairment and found that although work recovery on the average took considerably longer than symptom remission, it steadily improved with increasing duration of treatment and reached maximum improvement at about 4–6 months.

It should be noted that in this 12-week study, role functioning and social relationships appeared to show more improvement than did participation in leisure activities. These results may reflect the length of observation. The patients in this study, who had a mean duration of dysthymia of 30 years or more, may have needed longer than 6–12 weeks of response to an antidepressant to achieve full improvement in psychosocial functioning.

The posttreatment improvement in depressive symptoms and functional impairment was apparent from the patient's perspective as well as the clinician's. This is reflected in the quality of life assessment. In all three treatment groups, there was significant improvement from baseline in quality of life as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire. The scores on the questionnaire indicated overall improved satisfaction with work, relationships with family members and friends, leisure activities, and physical well-being. At study endpoint, both active drug groups showed significantly greater improvement in questionnaire total scores than the placebo group.

When improvement in overall global functioning was assessed from the clinician's perspective, it was also meaningful. With the use of a cutoff score of 71 on the Global Assessment of Functioning Scale (indicating only mildly impaired functioning such that an untrained observer would not regard the patient as impaired or "sick"), a significant treatment-related effect was demonstrated. Significantly more sertraline- and imipramine-treated patients achieved this level of

global improvement in functioning than patients who received placebo.

In conclusion, this study of patients with primary early-onset dysthymia without concurrent major depression demonstrates that both social dysfunction and symptoms of depression can be effectively treated with antidepressant medications. Given the prevalence of dysthymia and its associated vocational and social morbidity, the positive results of this 12-week trial in patients with illness of nearly 30 years' duration are extremely encouraging.

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