The Treatment of Chronic Depression, Part 2:

A Double-Blind, Randomized Trial of Sertraline and Imipramine

Martin B. Keller, M.D.; Alan J. Gelenberg, M.D.; Robert M. A. Hirschfeld, M.D.; A. John Rush, M.D.; Michael E. Thase, M.D.; James H. Kocsis, M.D.; John C. Markowitz, M.D.; Jan A. Fawcett, M.D.; Lorrin M. Koran, M.D.; Daniel N. Klein, Ph.D.; James M. Russell, M.D.; Susan G. Kornstein, M.D.; James P. McCullough, Ph.D.; Sonia M. Davis, Dr.P.H.; and Wilma M. Harrison, M.D.

Background: Chronic depression appears to be a common, frequently disabling illness that is often inadequately treated. Unlike episodic depressions with shorter illness duration, neither acute nor long-term treatment approaches for chronic depression have been well studied.

Method: 635 outpatients at 12 sites who met DSM-III-R criteria for chronic major depression or double depression were randomly assigned to 12 weeks of double-blind treatment with either sertraline (in daily doses of 50–200 mg) or imipramine (in daily doses of 50–300 mg). Efficacy and safety were assessed either weekly or every 2 weeks during the 12 weeks of acute treatment.

Results: Despite high rates of chronicity (mean duration of major depression = 8.9 ± 9.1 years; mean duration of dysthymia = 23 ± 13 years) and high rates of comorbidity, 52% of patients achieved a satisfactory therapeutic response to sertraline or imipramine (by a conservative, intent-to-treat analysis). Approximately 21% of the patients who had achieved a therapeutic response at week 12 had not done so at week 8, confirming the longer time to response in depressions with high chronicity. Patients treated with sertraline reported significantly fewer adverse events and were significantly less likely to discontinue treatment due to side effects than imipramine-treated patients (6.3% vs. 12.0%).

Conclusion: These results indicate that patients suffering from depression with high chronicity can achieve a good therapeutic response to acute treatment with either sertraline or imipramine, although sertraline is better tolerated.

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Received June 15, 1998; accepted August 31, 1998. *From the Department of Psychiatry and Human Behavior, Butler Hospital, Brown University, Providence, R.I. (Dr. Keller); the Department of Psychiatry, University of Arizona Health Sciences Center, Tucson (Dr. Gelenberg); the Department of Psychiatry and Behavioral Sciences, University of Texas Medical Branch at Galveston (Drs. Hirschfeld and Russell); the Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas (Dr. Rush); the University of Pittsburgh School of Medicine and Western Psychiatric Institute and Clinic, Pittsburgh, Pa. (Dr. Thase); the Department of Psychiatry, Cornell University School of Medicine, New York, N.Y. (Drs. Kocsis and Markowitz); the Department of Psychiatry, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Ill. (Dr. Fawcett); the Department of Psychiatry, Stanford University School of Medicine, Stanford, Calif. (Dr. Koran); the Department of Psychiatry, State University of New York at Stony Brook, N.Y. (Dr. Klein); the Department of Psychiatry, Medical College of Virginia, Virginia Commonwealth University, Richmond (Drs. Kornstein and McCullough); Quintiles, Inc., Research Triangle Park, N.C. (Dr. Davis); and Pfizer Inc and the College of Physicians and Surgeons, Columbia University School of Medicine, New York, N.Y. (Dr. Harrison).*

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Reprint requests to: Martin B. Keller, M.D., Box G-BH, Brown University, Providence, RI 02912-G-BH.

For more than a decade, research and clinical observations have shown that patients with depression have a substantial risk of experiencing a recurrent or chronic course of illness. Recent attempts to classify depression using longitudinal course modifiers have led to the inclusion in DSM-III-R and DSM-IV of 3 categories of chronic depressive disorder: chronic major depression, defined as a major depressive episode of at least 2 years' duration; dysthymia, defined as chronic depressive symptoms of lesser severity than those of major depression, persisting for 2 or more years; and what has come to be called "double depression," major depression superimposed on antecedent dysthymia.[1] Substantial evidence exists that the chronic depressions are common, disabling, costly, and suboptimally treated.[2,3] Moreover, unlike the treatment of recurrent or episodic depressions,[4–6] neither acute nor long-term treatment approaches for chronic depression have been well studied.

Recent reviews have highlighted emerging evidence indicating that pharmacotherapy is an effective acute phase treatment for dysthymia and double depression.[7,8] Although many of the early studies reviewed have methodological shortcomings, particularly with respect to the distinction between dysthymia and double depression, the findings of studies of older antidepressants are generally positive, as are those of subsequent studies of selective serotonin reuptake inhibitors (SSRIs) in dysthymia.[9–11] The efficacy and tolerability of SSRIs suggest a potential role for SSRIs in the treatment of chronic depression.

However, since chronic disorders probably warrant longer term treatments, particularly given the potential personal, societal, and mortality costs of chronic mood disorders,[3,12,13] it is imperative that we explore the benefit of continuation and maintenance strategies in these chronic disorders in studies of long-term design.[14] To date, only 1 maintenance study in chronic depression, a placebo-controlled trial demonstrating sustained efficacy of desipramine, has been completed.[15]

This study arose from the need for data to better inform management practices for chronic depression, and, in particular, to explore the outcomes of long-term treatment in these chronic disorders. To this end, a multidisciplinary collaborative group devised a series of studies emphasizing a longitudinal perspective to evaluate treatment outcome in acute, continuation, and maintenance phases for a well-defined group of patients with double depression and chronic major depression. The rationale for the design and methods is detailed in the previous article in this issue.[14]

METHOD

This article presents the treatment outcome, tolerability, and safety findings from the 12-week, double-blind acute phase study of 635 chronically depressed outpatients. Additional analyses from this phase are reported elsewhere in this issue. The results of the subsequent phases will be reported at a later date. This randomized, parallel-group, comparative multicenter trial enrolled only outpatients with DSM-III-R defined chronic major or double depression.

Sertraline, an SSRI, and imipramine, a tricyclic antidepressant (TCA), were selected as study treatments. Both have demonstrated prophylactic efficacy for prevention of relapse and recurrence of episodic major depression.[16,17] In addition, imipramine was shown to be effective in a randomized double-blind acute phase trial in chronic depression[18] and sertraline has been shown to be effective in a randomized double-blind trial of dysthymia.[11] The comparison of the 2 treatment groups enables further evaluation of long-term efficacy, tolerability, and safety of treatment with both major classes of antidepressant drugs.

After a complete medical and psychiatric history and physical examination, subjects accepted into the study began a 1-week single-blind placebo washout phase. All psychotropic treatment was discontinued during this time except for chloral hydrate or temazepam, both of which were allowed only for infrequent use for management of severe insomnia. Patients whose Clinical Global Impressions-Improvement (CGI-I) score was 1 or 2 (very much or much improved) and 24-item Hamilton Rating Scale for Depression (HAM-D)[19] score was < 18 at the end of the washout period were not entered into the double-blind phase of the study.

Patients were randomly assigned to double-blind antidepressant treatment with sertraline or imipramine in a 2:1 ratio, at a starting dose of 50 mg/day. The dose of imipramine was titrated weekly in 50-mg increments from week 2 up to a maximum of 300 mg/day by week 6. This slow titration reflected the need for a gradual dosage increase to avoid tolerability problems. Since sertraline, on the other hand, has been shown effective for many patients at the starting dose of 50 mg daily,[20] the first option to titrate sertraline was at the end of week 3. Thereafter, dose increases of 50 mg/day were permitted weekly to a maximum of 200 mg/day sertraline.

Patient Recruitment

At each of the 12 collaborating centers, subjects were recruited by referrals from physicians or mental health professionals, media advertising, and word of mouth. The rationale and procedures were explained to subjects entering the study, all of whom gave explicit written informed consent for acute phase treatment.

Men and women aged 21 to 65 years with either a diagnosis of DSM-III-R-defined chronic major depressive disorder (i.e., current major depressive episode ≥ 2 years with ≤ 2 cumulative months free of depressive symptoms), and who had not met DSM-III-R criteria for dysthymia within 2 months of the onset of the current major depressive episode, or with a diagnosis of double depression (concurrent major depressive episode superimposed on antecedent DSM-III-R dysthymia) were eligible for the study. Premenopausal women were required to be using adequate contraception.

Patients excluded from the study included those with any of the following DSM-III-R diagnoses: organic mental syndrome; current or lifetime diagnosis (DSM-III-R criteria) of bipolar disorder or cyclothymia, schizophrenia, or other psychotic disorder; obsessive-compulsive disorder; or antisocial, schizotypal, or severe borderline personality disorder. Other exclusion criteria included a principal DSM-III-R diagnosis of panic disorder, generalized anxiety disorder, or posttraumatic stress disorder within the past 6 months; DSM-III-R-defined anorexia nervosa or bulimia nervosa within the past year; or drug or alcohol abuse or dependence within the past 6 months. Patients deemed to be at immediate suicide risk and/or those who had medical contraindications to antidepres-

sant therapy or evidence of significant general medical disorder were also excluded.

The protocol criteria excluded patients requiring concomitant therapy with any psychotropic drug (other than chloral hydrate or temazepam, as noted above) and patients who had failed a previous adequate trial of sertraline or imipramine (i.e., ≥ 4 weeks of ≥ 50 mg of sertraline or ≥ 150 mg of imipramine daily). Subjects were ineligible if they had been treated with monoamine oxidase inhibitors within 3 weeks; any depot neuroleptic within 6 months; fluoxetine within 1 month; any regular daily neuroleptic, anxiolytic, or antidepressant medication within 2 weeks; or electroconvulsive therapy (ECT) within 3 months of beginning double-blind study medication. Concomitant medications without psychoactive properties were permitted. Psychotherapy was prohibited during the study unless it had been started at least 3 months before randomization and was unchanged during the study.

Diagnostic screening was undertaken at day 1 of the washout period using the Structured Clinical Interview for DSM-III-R (SCID-P, DSM-IV field trial version) to assess Axis I disorders and the SCID-II to assess personality disorders.[21,22] Return visits were scheduled at weekly intervals after initiation of medication for the first 6 weeks and every 2 weeks thereafter.

Routine laboratory tests, urine toxicology screen, and electrocardiograph (ECG) were performed at day 1 of the washout. Laboratory tests were repeated at the end of week 12 or when a patient was discontinued. Vital signs, adverse events (volunteered or observed), and symptoms were monitored at each subject visit throughout the 12-week trial. Subjects' adherence to prescribed doses was determined by pill counts and plasma drug concentrations at the end of week 12, or when the patient was discontinued prior to end of week 12. Analyses of plasma level–response relationships are ongoing and will be reported subsequently.

Rater Training Procedures

To ensure consistent protocol implementation, each site used the same detailed operating manual and participated in teleconferences every 2 weeks. All sites participated in investigator meetings that included training in the use of rating scales and consensus rating exercises. Details of these procedures are reported in Rush et al., part 1 of this series (p. 593).

Assessments

Clinician-rated scales included the following: 24-item HAM-D, CGI-Severity (CGI-S) and CGI-I scales, Montgomery-Asberg Depression Rating Scale (MADRS),[23] Global Assessment Scale (GAS), Schneiderian Traits Questionnaire,[24] Family History - Research Diagnostic Criteria (FH-RDC), Diagnostic Interview for Depressive Personality features (DID-P), Cornell Dysthymia Rating Scale (CDRS), and the Longitudinal Interval Follow-Up Evaluation (LIFE).[25] The CGI scale was completed by the treating physician. Investigators or trained raters completed other scales. Subjects completed the Beck Depression Inventory (BDI) and the following measures of psychosocial functioning, occupational functioning, and quality of life: Quality of Life Enjoyment and Satisfaction Questionnaire, Social Adjustment Scale (self-rated) (SAS-SR),[26] Patient Global Evaluation (PGE), and the Medical Outcomes Study (MOS) Health Status Questionnaire.[27]

All measures were obtained at baseline (end of washout), and, with the exception of the FH-RDC, Schneiderian Traits Questionnaire, and DID-P, at week 4 and week 12. The HAM-D, CGI, and CDRS were administered at additional visits throughout the study (HAM-D at weeks 1, 2, 4, 6, 8, 10, 12; CDRS at weeks 2, 4, 6, 8, 12; CGI at all visits).

Treatment response was defined a priori using the HAM-D and CGI as the major outcome variables. Full remission and satisfactory therapeutic response were identified as separate outcomes. Full remission was defined as both a CGI-I score of 1 or 2 (very much or much improved) and a total HAM-D (24-item) score of ≤ 7 at the last attended visit. An additional post hoc analysis defined full remission using the 17-item HAM-D in place of the 24-item scale, as suggested by Frank et al.[28] For satisfactory therapeutic response, the following criteria were required at the last attended visit: a CGI-I score of 1 or 2, a total HAM-D (24-item) score of ≤ 15, an improvement from baseline score of at least 50% on total HAM-D (24-item) score, *and* a final CGI-S score of ≤ 3 (mildly ill).

Data Analyses

Treatment groups were compared for discontinuation rates, and reasons for discontinuation, and adverse events with an (unadjusted) chi-square test. Between-treatment group comparisons for baseline and demographic characteristics were based on Cochran-Mantel-Haenszel chi-square tests for categorical variables, Cochran-Mantel-Haenszel mean score chi-square tests with modified ridit scores for ordinal categorical variables, and analysis of variance (ANOVA) for continuous variables (including CGI and PGE). All comparisons included adjustment for site and depression type (chronic vs. double), where applicable. Comparisons of depression types at baseline were based on similar methods, adjusting for site and treatment group. Depression types were also compared for dose of study drug at the last study visit for each treatment group with an ANOVA adjusting for site.

For each assessment, the endpoint was defined as the patient's last visit at which outcome assessments were obtained prior to study end or discontinuation, based on the last-observation-carried-forward (LOCF) principle. Changes from baseline to weeks 4, 12, and endpoint, as well as changes from week 4 to week 12, were tested for signifi-

Table 1. Patient Population and Discontinuations: Chronic Major and Double Depression[a]

	Chronic Major		Double Depression		Combined	
Condition	Sertraline	Imipramine	Sertraline	Imipramine	Sertraline	Imipramine
No. randomized	199	95	227	114	426	209
No. prematurely discontinued (%)	34 (17.1)	16 (16.8)	42 (18.5)	34 (29.8)**	76 (17.8)	50 (23.9)*
No. discontinued due to adverse events (%)	13 (6.5)	10 (10.5)	14 (6.2)	15 (13.2)**	27 (6.3)	25 (12.0)**
No. with severe[b] treatment-related[c] adverse events (%)	21 (10.6)	23 (24.2)***	28 (12.3)	18 (15.8)	49 (11.5)	41 (19.1)***

[a]Test of sertraline vs. imipramine (χ^2 test): *p ≤ .10, **p ≤ .05, ***p ≤ .01.
[b]Judged severe in the opinion of the investigator.
[c]Cause of adverse event identified by the investigator as study drug, uncertain, or concurrent drug.

cance within treatment groups via 1-sample t tests. Between-treatment group tests for changes from baseline were based on analysis of covariance (ANCOVA) models with adjustment for site, depression type, and baseline value.

Response and remission rates at endpoint were tested for treatment group differences with a Cochran-Mantel-Haenszel mean score chi-square test adjusting for site and depression type. Rates at endpoint were evaluated for all patients and for the subset of patients completing the study. Treatment groups were compared for changes in response rates from week 8 to week 12 with McNemar test and a Wald chi-square test for correlated binary data.

An interim analysis of response and discontinuation rates was performed when approximately two thirds of subjects had completed the acute phase so that projections of the maintenance phase sample size and the associated statistical power could be determined. If projections had indicated that the maintenance phase might be underpowered, we had planned to expand acute phase enrollment until the projected power was sufficient. If projections indicated sufficient power, we had planned to leave acute phase study enrollment unchanged. Since no changes to study conduct or subject treatment in the acute, continuation, or maintenance phases were contemplated, no adjustment was made to the nominal 5% type I error rate. The "blinded" analysis of the acute phase response and dropout rates revealed that no increase in the planned acute phase enrollments was necessary.

RESULTS

Patient Characteristics

Six hundred thirty-five patients entered the study: 294 with chronic major depression and 341 with double depression (Table 1). In accordance with the 2:1 randomization plan, 426 patients received sertraline and 209 imipramine. Five hundred nine patients (80.2%) completed acute phase therapy; 244 (83.0%) with chronic major depression and 265 (77.7%) with double depression. Of 126 patients (19.8%) who discontinued treatment prematurely, 76 (17.8%) were receiving sertraline and 50 (23.9%) were receiving imipramine ($\chi^2 = 3.3$, df = 1, p = .07). For double depression, the discontinuation rate for sertraline (42/227, 18.5%) was significantly lower than for imipramine (34/114, 29.8%) ($\chi^2 = 5.6$, df = 1, p = .02). For chronic major depression the discontinuation rates for sertraline (34/199, 17.1%), and imipramine (16/95, 16.8%) were virtually identical ($\chi^2 = 0.003$, df = 1, p = .96). Only 19 patients (3.0%) were lost to follow-up.

Tables 2 and 3 present the demographic and clinical characteristics of the combined chronic major and double depression groups. Details of patient characteristics, psychosocial functioning, chronicity, severity, and comorbidity of the 2 groups are compared and discussed in a manuscript that focuses on the validity of the nosological distinctions (McCullough JP, unpublished data).

The chronic major and double depression samples showed few differences in demographic characteristics, lifetime psychiatric history, or baseline depression severity scores. Baseline scores for psychosocial function measures—SAS-SR, LIFE, and MOS—showed comparable impairment in the chronic major and double depression groups. These measures are utilized as outcome measures reported by Miller et al.[29] (see the next article in this issue). There were no statistically significant baseline differences between the 2 medication groups, consistent with successful randomization.

Chronicity and Severity of Illness

The mean ± SD duration of the current major depressive episode was 107 ± 108.6 months (range, 24–575) in the chronic major group and 43 ± 77.2 months (range, 0.4–418) in the double depression group ($p < .001$). The mean duration of dysthymia was 23.4 ± 13.4 years. The majority of patients in both groups had been depressed for most of their adult lives, reporting a lifetime illness duration of 17.2 and 15.6 years in the chronic major and double depression groups, respectively. Most patients had moderate-to-severe illness as assessed by the pretreatment CGI-S (94% score ≥ 4) and a baseline mean total 24-item HAM-D score of 25.

Comorbidity

Almost one fourth (24.1%) of the chronic major and double depression groups had at least 1 lifetime comorbid

Table 2. Sociodemographic Characteristics[a]

Parameter	Combined Chronic Major and Double Depression Group (N = 635)[b]
Age (mean ± SD y)	41.1 ± 10.1
Sex	
Male	235 (37.0%)
Female	400 (63.0%)
Race	
White	577 (90.9%)
African American	25 (3.9%)
Other	33 (5.2%)
Educational level	
High school graduate	113 (17.9%)
Some college education	252 (40.0%)
College or university education	140 (22.2%)
Graduate or professional	100 (15.9%)
Occupational status (SAS-SR)	
Unemployed	127 (20.6%)
Employed[c]	491 (79.4%)
Marital status	
Married	241 (38.1%)
Single	162 (25.6%)
Divorced or separated	197 (31.1%)
Other	33 (5.2%)

[a]Abbreviation: SAS-SR = Social Adjustment Scale Self Report.
[b]Percentages are based on the number of patients providing data for each parameter.
[c]Includes worker for pay, housewife, student, and retired.

Table 3. Clinical Features of Combined Sample[a]

Parameter	N	Combined Chronic Major and Double Depression Groups (N = 635)
Duration of current episode of major depression (mo)		
Mean ± SD	629	72.3 ± 98.4
Range		0.4–575.4
Lifetime duration of illness (y)		
Mean ± SD	623	16.3 ± 11.4
Range		0.2–57.3
Age at onset of first major depressive episode (y)		
Mean ± SD	624	24.8 ± 12.1
Range		0–62
Age at onset of dysthymia (y)		
Mean ± SD	329	17.0 ± 13.1
Range		0–60
Number of patients with ≥ 1 previous episodes of major depression (%)	634	407 (64%)
Baseline assessments		
HAM-D total score (mean ± SD)	635	25.1 ± 5.1
CGI-S (mean ± SD)	635	4.2 ± 0.6
Mild, N (%)		41 (6.5%)
Moderate, N (%)		451 (71.0%)
Marked, N (%)		129 (20.3%)
Severe, N (%)		14 (2.2%)
CGI-I[b] (mean ± SD)	634	3.8 ± 0.6
BDI (mean ± SD)	618	24.6 ± 8.8
CDRS (mean ± SD)	635	40.7 ± 9.5
MADRS (mean ± SD)	634	25.5 ± 7.3

[a]Abbreviations: BDI = Beck Depression Inventory, CDRS = Cornell Dysthymia Rating Scale, CGI-I = Clinical Global Impressions-Improvement, CGI-S = Clinical Global Impressions-Severity, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.
[b]Based on change from screening level.

anxiety disorder. Social phobia (12.0%), simple phobia (6.0%), panic disorder (7.1%), and generalized anxiety disorder (5.2%) were the most common. There was also substantial lifetime comorbidity for alcohol and substance abuse and dependence, even though patients with alcohol or substance abuse or dependence in the past 6 months were excluded from the study. Over a third of patients (N = 220, 35%) reported a lifetime history of alcohol abuse or dependence or substance abuse or dependence, 29.4% reported a lifetime history of alcohol abuse or dependence, and 18.9% reported abuse of or dependence on substances other than alcohol. Over half of all subjects (50.7%) had at least 1 Axis II disorder. Avoidant (25.3%), obsessive-compulsive (18.1%), and self-defeating (16.0%) personality disorders were most frequently diagnosed.

Prior Treatment

Forty-three percent of the subjects had never received any previous antidepressant pharmacotherapy. Only 20% had received a prior adequate trial of antidepressant medication, defined as at least 150 mg/day of amitriptyline or 20 mg/day of fluoxetine or their equivalents taken for at least 4 weeks. Fifty-nine percent had received previous psychotherapy.

Study Treatments

The mean ± SD final dose was 141.0 ± 59.4 mg for sertraline and 200.2 ± 82.1 mg for imipramine. The doses for the chronic major depression and double depression groups respectively were 137.7 mg and 143.8 mg for sertraline and 207.4 mg and 194.3 mg for imipramine. These doses did not differ significantly (p = .810 for sertraline and p = .187 for imipramine).

Efficacy

Depression rating scale scores at baseline, week 4, 12, and endpoint are presented in Table 4. Efficacy variables demonstrated significant within-subject improvement (from baseline to endpoint) on all clinician-rated variables (HAM-D, MADRS, CGI, and CDRS) and all patient-rated variables (BDI, PGE, and pyschosocial functioning assessments).[29] Improvements in patient and physician parameters, as assessed by the CGI and PGE, were comparable.

At the endpoint, mean percentage improvements on the HAM-D and MADRS total scores (LOCF analyses) in the chronic major depression group were 47.6% (HAM-D) and 53.8% (MADRS) for sertraline and 46.7% (HAM-D) and 54.3% (MADRS) for imipramine. For the double depression group, corresponding figures were 44.1% (HAM-D) and 47.4% (MADRS) for sertraline and 41.9% (HAM-D) and 46.8% (MADRS) for imipramine. No statistically significant differences in efficacy parameters were observed between the 2 treatment groups, or between the chronic major and double depression groups

Table 4. Rating Scale Mean Scores at Baseline, Week 4, Week 12, Endpoint, and Change From Baseline Using Last Observation Carried Forward[a]

	Chronic Major		Double Depression		Combined	
Assessment	Sertraline (N = 199)	Imipramine (N = 95)	Sertraline (N = 227)	Imipramine (N = 114)	Sertraline (N = 426)	Imipramine (N = 209)
HAM-D (24 Item)						
Baseline	25.4	25.7	24.7	24.6	25.0	25.1
Week 4	17.6	16.9	17.0	16.3	17.3	16.6
Week 12	12.5	12.8	12.6	11.9	12.5	12.4
Endpoint	13.3	13.8	13.8	14.3	13.6	14.1
Change from baseline to endpoint	–12.1	–12.0	–10.9	–10.3	–11.5	–11.1
MADRS						
Baseline	26.2	26.7	24.7	24.8	25.4	25.7
Week 4	17.6	16.6	16.8	15.9	17.2	16.2
Week 12	10.9	12.1	12.0	11.7	11.5	11.9
Endpoint	12.1	12.5	13.0	13.3	12.6	12.9
Change from baseline to endpoint	–14.1	–14.5	–11.7	–11.6	–12.8	–12.9
CDRS						
Baseline	41.1	41.3	40.4	40.0	40.7	40.6
Week 4	27.6	27.8	27.9	26.3	27.8	27.0
Week 12	18.6	21.0	19.9	19.2	19.3	20.1
Endpoint	20.4	21.8	21.7	22.1	21.1	22.0
Change from baseline to endpoint	–20.7	–19.6	–18.9	–18.0	–19.7	–18.7
CGI-S						
Baseline	4.2	4.3	4.1	4.1	4.2	4.2
Week 4	3.2	3.4	3.3	3.3	3.2	3.3
Week 12	2.5	2.6	2.5	2.4	2.5	2.5
Endpoint	2.6	2.8	2.6	2.7	2.6	2.7
Change from baseline to endpoint	–1.6	–1.5	–1.5	–1.4	–1.6	–1.4
BDI						
Baseline	25.1	25.3	24.4	23.4	24.7	24.3
Week 4	17.2	17.7	17.2	16.1	17.2	16.8
Week 12	12.7	13.0	12.6	11.2	12.7	12.1
Endpoint	13.1	13.9	13.5	13.0	13.3	13.4
Change from baseline to endpoint	–12.0	–11.6	–11.2	–10.0	–11.6	–10.8
PGE-S						
Baseline	4.5	4.5	4.4	4.5	4.4	4.5
Week 4	3.2	3.2	3.4	3.5	3.3	3.3
Week 12	2.6	2.8	2.6	2.8	2.6	2.8
Endpoint	2.7	2.7	2.7	3.0	2.7	2.9
Change from baseline to endpoint	–1.8	–1.7	–1.7	–1.6	–1.8	–1.6

[a]All between-treatment comparisons for baseline and change from baseline to endpoint are nonsignificant ($p > .05$). All within-treatment comparisons between baseline, week 4, week 12, and endpoint and between week 4 and week 12 are significant ($p < .001$). Abbreviation: PGE-S = Patient Global Evaluation of Severity.

with the exception of the MADRS at baseline ($p = .047$) and change from baseline to endpoint ($p = .049$).

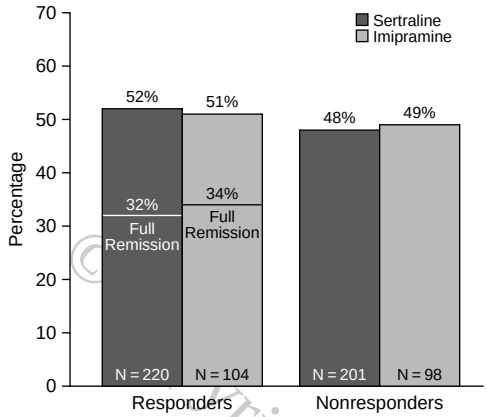
Response and Remission

Rates of full remission, satisfactory therapeutic response, and nonresponse reported for completers and for all randomized samples (intent-to-treat [ITT] analysis) are based on the 24-item HAM-D. We found no significant differences in response rates at endpoint between chronic major and double depression groups ($\chi^2 = 1.5$, $df = 1$, $p = .22$), or between sertraline and imipramine ($\chi^2 = 0.03$, $df = 1$, $p = .87$). Overall, over half of patients who completed the 12-week study achieved either full remission (36% sertraline group; 40% imipramine group) or a satisfactory therapeutic response (22% sertraline group; 21% imipramine group). ITT rates of response or remission were 52% for sertraline and 51% for imipramine (Figure 1). Full remission rates were higher when the 17-item HAM-D total score was used in place of the 24-item total score in calculating response (41% for the sertraline patients and 39% for the imipramine patients at endpoint, and 47% of completers for each group).

Time Course of Response

Five hundred patients had sufficient outcome data available at weeks 8 and 12 to permit their responder status to be categorized as either responder (satisfactory response or full remission) or nonresponder. Of these 500 patients, 193 were responders at *both* week 8 *and* week 12, 103 were responders at week 12 (but not at week 8), and 32 were responders at week 8 (but not at week 12). The remaining 172 patients were categorized as nonresponders at both week 8 and week 12. McNemar test of change between weeks 8 and 12 showed that significantly more patients switched from nonresponse at week 8 to response at week 12 than vice versa ($\chi^2 = 37.34$, $df = 1$,

Figure 1. Response Rates Following 12 Weeks of Treatment With Sertraline or Imipramine (Intent-to-Treat)[a]



[a]Response was defined for 623 patients.

Table 5. Treatment-Related Adverse Events[a]: Chronic Major and Double Depression Combined

Adverse Event	Sertraline (N = 426)	Imipramine (N = 209)
Nausea	131 (30.8%)	51 (24.4%)
Diarrhea	112 (26.3%)	13 (6.2%)***
Dyspepsia	67 (15.7%)	41 (19.6%)
Constipation	47 (11.0%)	71 (34.0%)***
Insomnia	115 (27.0%)	37 (17.7%)**
Somnolence	88 (20.7%)	58 (27.8%)*
Nervousness	42 (9.9%)	27 (12.9%)
Headache	168 (39.4%)	67 (32.1%)
Dizziness	74 (17.4%)	75 (35.9%)***
Tremor	34 (8.0%)	48 (23.0%)***
Dry mouth	148 (34.7%)	156 (74.6%)***
Sweating	60 (14.1%)	61 (29.2%)***
Fatigue	52 (12.2%)	28 (13.4%)
Micturition disorder	9 (2.1%)	25 (12.0%)***
Sexual dysfunction[b]	57 (13.4%)	25 (12.0%)

[a]Adverse events ≥ 10% incidence in either treatment group during treatment. Cause of adverse event identified by the investigator as study drug, uncertain, or concurrent drug.
[b]Includes delayed ejaculation, anorgasmia, impotence, and decreased libido.
*p = .05. **p = .01. ***p = .001.

p = .001). The percentage of patients with a satisfactory response or full remission was substantially larger at week 12 (59%) compared with week 8 (44%) ($\chi^2 = 42.1$, df = 1, p = .001). If response is defined as at least a 50% reduction in HAM-D score from baseline, comparisons of week 12 (61% responded) versus week 8 (48% responded) are similar ($\chi^2 = 31.45$, df = 1, p = .001) (Wald chi-square test for correlated binary data for both weeks' data).

Adverse Events

Significantly more imipramine-treated patients (12%) discontinued treatment because of adverse events than sertraline-treated patients (6%), ($\chi^2 = 5.9$, df = 1, p = .015). In the imipramine group, these adverse events accounted for 50% of discontinuations compared with 36% in the sertraline-treated patients (see Table 1). Significantly more patients experienced severe treatment-related adverse events in the imipramine group (20%) versus the sertraline group (12%; $\chi^2 = 7.6$, df = 1, p = .01). Tolerability appeared to vary with subtype of chronic depression. In the chronic major depression group, 11% of sertraline patients reported severe treatment-related adverse events versus 24% in the imipramine group ($\chi^2 = 10.4$, df = 1, p = .01). In the double depression group, this difference was less marked (12% vs. 16%; $\chi^2 = 0.7$, df = 1, p = .38).

Treatment-related side effects occurring in at least 10% of patients taking sertraline included nausea, diarrhea, dyspepsia, constipation, insomnia, somnolence, fatigue, dizziness, increased sweating, headache, sexual dysfunction, and dry mouth. In the imipramine group, side effects (≥ 10%) included dry mouth, headache, constipation, increased sweating, sexual dysfunction, nausea, dyspepsia, insomnia, somnolence, nervousness, dizziness, fatigue, tremor, and micturition disorder (Table 5).

In total, 302 responders (sertraline, N = 205; imipramine, N = 97) completed the acute study. Responders entered the 16-week continuation treatment phase or were tapered off medication and discontinued. Two hundred seven patients did not respond but completed the acute study; 168 patients (sertraline, N = 117; imipramine, N = 51) entered the crossover study, crossing double-blind to the alternative medication for 12 additional weeks. Responders completing the crossover study were also eligible to enter the continuation phase. A total of 307 patients, 209 in the sertraline group and 98 in the imipramine group, were enrolled directly into the continuation phase. Results of treatment outcome in the crossover and continuation phases will be reported in subsequent publications.

DISCUSSION

This study is the first controlled study to report results of treatment of chronic major and double depression with an SSRI. Results show efficacy for sertraline equivalent to that of imipramine, with better tolerance. With the exception of a small subgroup of patients reported by Kocsis et al.[15] (N = 14), no prior controlled, double-blind studies have specifically addressed the treatment of chronic major depression.

The size of the cohort in this study, as well as the 3-phase protocol design intended to facilitate the assessment of long-term outcome, provides the largest database to date on chronic major and double depression and their treatment. The acute phase has produced important results that, with appropriate reservations regarding their generalizability, suggest directions for clinical management and further study of chronic depression.

First, the demographic characteristics of individuals with chronic major depression and those with double depression are similar, as detailed elsewhere (McCullough JP, unpublished data). The demographics of the double depression sample appear comparable with those previously reported, suggesting that this study group is representative of patients presenting to tertiary centers.[30–33] This is also reflected in the low representation of nonwhite groups in the study. Whether this sample is representative of individuals in the general population with chronic depression cannot be determined.

The striking chronicity of both the chronic major and the double depression subjects is again consistent with previous reports. Patients in both groups had spent a significant proportion of their adult lives depressed. Although the extent of this chronicity cannot be generalized to community samples, the length of depressive episodes in nonresearch settings may be significantly underestimated by a failure to record a detailed history.[34]

That this chronicity significantly damaged the lives of these individuals is evident in the remarkable discrepancy between the educational achievements of these patients (77% had completed at least some college education) and their current employment status. The rate of patients who reported that they were unemployed was 20.6%, a rate considerably above the 5% to 6% national average at the time of study enrollment. An additional 23% were working 30 hours per week or less (LIFE), reflecting the socioeconomic impairment associated with chronic depression. For those who were employed, 31% were in a job that was below their educational level and training. The impact of depression on national productivity in the United States was estimated in 1993 to be $23.8 billion per annum in cost of time lost from work.[12] Chronic depression thus has a large social and economic cost as well as high personal cost.

Both groups had high Axis I lifetime comorbidity, particularly for panic disorder, social phobia, and alcohol abuse. This comorbidity rate corroborates previous reports. Keller and Sessa estimated that 75% of patients with double depression had anxiety symptoms, and studies of dysthymia have reported rates of 22% to 56% for comorbid anxiety disorders.[31] Future analyses will consider the effect of current and lifetime comorbidity on treatment response and outcome.

In spite of the severity and chronicity of this disorder, the current study shows that 43% of subjects had never received any antidepressant treatment. Although the exclusion criteria were relatively broad, and might have caused a selection bias that skewed this sample, these factors are unlikely to fully account for the degree of inadequate prior treatment. The high percentage of patients receiving either no previous pharmacotherapy treatment or inadequate doses is consistent with other studies,[18,31,35–38] and is distressing, particularly given the subsequent positive treatment response. This response rate to adequate pharmacotherapy is further evidence to refute the myth that chronic depressions are treatment resistant or characterological.

The key findings of this study underscore an important message. Despite an average lifetime chronicity of 16 years, 59% of patients with chronic major or double depression who completed (and 52% of those who began) 12 weeks of acute phase pharmacotherapy achieved a satisfactory response. When response was defined using the conventional definition of ≥ 50% reduction in HAM-D score from baseline to endpoint, for the ITT sample, 109 of 202 (54%) of imipramine-treated patients and 235 of 421 (56%) of sertraline-treated patients were responders ($\chi^2 = 0.4$, df = 1, p = .54). Using this definition of response, 58% of the chronic major depression group and 53% of the double depression group achieved treatment response. This response rate approximates the ITT response rates of around 50% to 58% (Agency for Health Care Policy and Research guidelines)[5] characteristically seen in more episodic forms of major depression.

In chronic depression, there are few studies in well-defined samples available for comparison. In dysthymia, open-label studies have reported a response around 45%, and controlled studies report a range between 13% and 60%.[7,18] A significantly superior response rate (45%) was reported[18] for 29 imipramine-treated outpatients with chronic depression (96% had double depression and 4% had "pure dysthymia") compared with 12% for the placebo-treated group (N = 25). In a recently published multicenter study of 416 subjects with pure dysthymia, full remission of symptoms (based on stringent criteria of no longer meeting DSM-III-R criteria for dysthymia and a score of 0 on HAM-D item 1) was achieved in 50% of sertraline and 44% of imipramine subjects compared with a significantly lower rate for placebo (28%) (ITT analysis [LOCF]).[11]

There are no comparable randomized, controlled studies of chronic major depression or double depression available for comparison. The studies conducted to date on double depression failed to include careful diagnostic assessments and do not clarify how many subjects were currently in an episode of major depressive disorder and how many had worsening of dysthymic symptoms. Frank et al. identified a cutoff of ≤ 7 on the 17-item HAM-D as the level that equated with full remission of depression,[28] and that criterion was used in this study to define full remission. At 12 weeks, 38% to 47% of patients who completed the study (depending on HAM-D scale used) and 32% to 40% of those randomized (ITT) achieved full remission. These remission rates are similar to those reported in studies of episodic major depression. There was a trend for partial responders to have had higher mean baseline scores compared with baseline scores for remitters at week 12. Subjects receiving either sertraline or imipramine showed substantial further improvement

between weeks 8 and 12, which suggests that an 8-week trial of medication may be insufficient in this population. This finding is consistent with previous evidence that patients with chronic depressions take longer to respond than do patients with shorter episodes of depression.[39–41] It will be interesting to follow this group through the continuation phase to evaluate whether patients with a satisfactory therapeutic response achieve full remission with more prolonged treatment.

The generally comparable efficacy outcome for sertraline and imipramine is an important finding given the tendency for TCAs to be perceived as potentially more powerful treatments in severe, chronic, and treatment-resistant depressions. The 2 treatments did differ in tolerability. A greater level of adverse events and discontinuations for adverse events was reported in the imipramine than the sertraline group, which may have important implications for patient compliance in long-term treatment of these chronic disorders.

The double-blind condition required that physicians rapidly titrate the doses of both sertraline and imipramine to ensure sufficient exposure to an adequate dose of imipramine. To accomplish this, and to maintain the blind, sertraline was titrated to the higher end of the usual therapeutic range. Nonetheless, treatment with sertraline was not associated with greater attrition than imipramine. This result is consistent with the notion that: (1) sertraline was well tolerated in the patient group, even in higher doses; (2) the blind was retained; and (3) chronically depressed patients may take longer to respond than those with briefer major depressive episodes. The dosing results of this study cannot shed light on whether lower or higher doses may be needed in some of these patients since doses were not fixed and escalation was required after 3 weeks for both groups if the patients had not had sufficient response (in the absence of dose-limiting side effects). The titration schedule allowed for achievement of maximum doses before sufficient time for a full response to the treatment.

Since we did not include a placebo cell for reasons previously cited,[14] one could question whether both groups responded equally to ineffective treatments (i.e., speculate that a pill placebo group would have done as well as either the imipramine or the sertraline group). We believe this *not* to be the case for several reasons: (1) a substantial number of patients failed to respond at 4 weeks but ultimately responded at 12 weeks (38%), in contrast to previous research that suggests that placebo effects generally occur in the first few weeks of treatment[42]; (2) there were only a few patients on imipramine (7 [4%]) or sertraline (9 [3%]) who responded by 4 weeks but who then *lost* the response at 12 weeks, also in contrast to previous research that suggests that placebo responders tend to have transient rather than sustained responses[42,43]; and (3) patients with more prolonged major depressive episodes (e.g., 1 vs. 6 months, 6 months vs. 2 years) tend to have lower placebo response rates than those with brief illness duration.[44,45]

CONCLUSION

The most important finding to emerge from this study is that both chronic major depression and double depression often respond to adequate pharmacotherapy. Improvement encompasses both symptomatic response and a significant improvement in psychosocial functioning and quality of life, as described in greater detail elsewhere in this issue.[29] Furthermore, sertraline, an SSRI, was equally effective and better tolerated than imipramine, a TCA. We recommend, therefore, a vigorous trial of antidepressants in chronic depressive disorders for at least 12 weeks at the highest tolerated dose necessary for a full response. Given the long-term tolerability and safety profile, SSRIs may represent a more logical initial treatment choice in chronic depressions. Results of the continuation and maintenance phases of this study should enable informed clinical decisions about longer term treatment in these groups. In addition, the crossover phase should provide important new data relevant to the treatment of patients who do not respond to an initial adequate trial of pharmacotherapy with a TCA or an SSRI. We hope that the findings of this study and subsequent recommendations for the treatment of chronic depression will be incorporated into treatment guidelines and widely communicated.

Drug names: amitriptyline (Elavil and others), chloral hydrate (Noctec), desipramine (Norpramin and others), fluoxetine (Prozac), imipramine (Tofranil and others), sertraline (Zoloft), temazepam (Restoril and others).

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