Double-blind Switch Study of Imipramine or Sertraline Treatment of Antidepressant-Resistant Chronic Depression

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Background: Although various strategies have been proposed to treat antidepressant nonresponders, little controlled research has been published that examines prospectively the use of switching to an alternate antidepressant.

Methods: This was a multisite study in which outpatients with chronic major depression (with or without concurrent dysthymia), who failed to respond to 12 weeks of double-blind treatment with either sertraline hydrochloride (n=117) or imipramine hydrochloride (n=51), were crossed over or switched to 12 additional weeks of double-blind treatment with the alternate medication. Outcome measures included the 24-item Hamilton Rating Scale for Depression and the Clinical Global Impressions–Severity and Improvement scales.

Results: The switch from sertraline to imipramine (mean dosage, 221 mg/d) and from imipramine to sertraline (mean dosage, 163 mg/d) resulted in clinically and statistically significant improvements. The switch to sertraline treatment was associated with fewer adverse effect complaints and significantly less attrition owing to adverse effects. Although sertraline treatment also resulted in significantly higher response rates in the intent-to-treat samples (60% in the sertraline group and 44% in the imipramine group), neither the intent-to-treat remission rates nor the response and remission rates among study completers differed significantly. Moreover, after considering the effect of attrition, there were no significant treatment effects on the more comprehensive generalized estimating equation analyses of the continuous dependent measures.

Conclusions: More than 50% of chronically depressed antidepressant nonresponders benefited from a switch from imipramine to sertraline, or vice versa, despite a high degree of chronicity. As in the initial trial, sertraline was generally better tolerated than imipramine. Switching to a standard antidepressant of a different class is a useful treatment strategy for antidepressant nonresponders and could be considered a standard of comparison for future studies of novel alternate strategies.

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SUBJECTS AND METHODS

SUBJECTS

This protocol was part of a multiphase, collaborative research program studying chronic depressive disorders. A full description of the study design, rationale, and methods has been previously published. Briefly, outpatients aged 21 to 65 years were eligible to enroll at 1 of 12 centers if they met DSM-III-R criteria for chronic major depressive disorder (ie, current major depressive episode of ≥2 years in duration) or “double depression” (ie, a current major depressive episode superimposed on an antecedent dysthymic disorder). The findings of the main study have been described elsewhere.

Intake diagnoses were based on interviews using the Structured Clinical Interview for DSM-III-R12 and Structured Clinical Interview for DSM-III-R Personality Disorders. Patients were excluded if they had organic mental syndromes, bipolar disorder or cyclothymia, schizophrenia or other psychotic disorder, obsessive compulsive disorder, or schizotypal, antisocial, or severe borderline personality disorder. Those with principal current diagnoses of panic, generalized anxiety, or post-traumatic stress disorders were also excluded. Patients were not eligible if they had abused alcohol or other drugs within 6 months or had experienced bulimia or anorexia nervosa within 1 year of intake. Patients considered to be an immediate suicide risk, to have medical contraindications to antidepressant therapy, or to have significant, unstable general medical disorders were also excluded. Patients who had not responded previously to minimally adequate trials of sertraline or imipramine (ie, at least 4 weeks of ≥50 mg of sertraline or ≥150 mg of imipramine daily) were ineligible. Patients could not have been treated with anxiolytic or other antidepressant medication within 2 weeks, monoamine oxidase inhibitors within 3 weeks, fluoxetine hydrochloride within 1 month, electroconvulsive therapy within 3 months, or depot neuroleptics within 6 months. Psychotherapy was permitted during the study only if it had been ongoing for at least 3 months before intake.

INITIAL TREATMENT TRIAL

After providing written informed consent, a complete medical history, physical examination, electrocardiography, and laboratory screening battery were completed to confirm medical eligibility. Patients began a 1-week, single-blind placebo lead-in, during which the only psychotropic medications permitted were chloral hydrate or temazepam, used sparingly for severe insomnia. Patients whose Clinical Global Impressions–Improvement (CGI-I) score was 3 or higher and whose score on the 24-item Hamilton Rating Scale for Depression (HAM-D)13 was 18 or higher at the end of the lead-in period were randomized to double-blind treatment with either sertraline (n=426) or imipramine (n=209). This 2:1 proportion was used because responders to sertraline, but not imipramine, could subsequently participate in a placebo-controlled maintenance-phase trial.

All patients were seen initially for 6 weekly visits, followed by visits every other week for the balance of the 12-week trial. Imipramine was started at 50 mg/d and titrated by 50 mg/d per week, as tolerated, up to a maximum of 300 mg/d. Sertraline was also initiated at 50 mg/d, but a dosage increase was not permitted until the end of week 3. Thereafter, weekly increases of 50 mg/d were possible, if indicated and tolerated, up to a maximum of 200 mg/d. Therefore, maximum dosages of either study drug could be reached by week 6. Patients who could not tolerate at least 50 mg/d of either study medication were withdrawn from the trial. Mean±SD dosages of 141±59 mg/d of sertraline and 200±82 mg/d of imipramine were achieved at the end point of the initial acute-phase trial.

ASSESSMENT OF RESPONSE

Vital signs and adverse events (volunteered or observed) were assessed at each visit. The principal dependent measures, the CGI-I (Improvement) and the 24-item HAM-D, were obtained at each visit. Secondary measures included the CGI-S (Severity), Montgomery-Åsberg Depression Rating Scale,16 Cornell Dysthymia Scale,17 and self-report 21-item Beck Depression Inventory. All clinical ratings were completed by a blinded, independent evaluator. A satisfactory therapeutic response (hereafter referred to as response) was noted if the final CGI-I and sertraline received at the end point of the second trial were 221±84 mg/d and 163±48 mg/d, respectively.

ATTRITION AND TOLERABILITY

Thirty-four patients dropped out, including 10% (5/51) of those switched to sertraline treatment and 23% (29/117) of those switched to imipramine treatment (χ² = 4.94, P = .03). This difference was largely the result of a significantly greater number of patients discontinuing imipramine because of intolerable adverse effects (9% vs 0%; Fisher exact test, P = .04).

Adverse effects reported during the first and second antidepressant trials are summarized in Table 2. Anticholinergic adverse effects, including dry mouth, constipation, and urinary complaints, were significantly more common in the group that switched to imipramine. There were also significantly more complaints of sweating, dizziness, and

SAMPLE CHARACTERISTICS

Fifty-one patients were switched from imipramine to sertraline, and 117 sertraline nonresponders were switched to imipramine. These groups did not differ significantly on any relevant characteristic (Table 1). There was, however, a trend for women to be overrepresented in the group switched from imipramine to sertraline (78% vs 62%; χ² = 3.50, P = .06). The mean±SD dosages of imipramine and sertraline received at the end point of the second trial were 221±84 mg/d and 163±48 mg/d, respectively.
score was 1 or 2, there was at least a 50% reduction in total HAM-D score to a final score of 15 or lower, and the CGI-S score was 3 or lower (ie, the patient was no more than mildly ill). Patients not meeting these criteria were considered nonresponders. A full remission was defined as a final HAM-D score of 7 or lower and a CGI-I score of 2 or lower.

ACUTE-PHASE OUTCOME

Among the 635 randomized patients, 302 completed the 12-week acute-phase trial as responders (205 for sertraline and 97 for imipramine). Two hundred seven completed the study as nonresponders. One hundred twenty-six patients discontinued the study prematurely (76 in the sertraline-treated group and 50 in the imipramine-treated group), of whom 22 patients were responders at the time of study discontinuation (15 in the sertraline-treated group and 7 in the imipramine-treated group) and of whom 12 patients discontinued before the first evaluation after randomization (5 in the sertraline-treated group and 7 in the imipramine-treated group). There was no difference in response rates between treatments in the intent-to-treat samples (32% in the sertraline group and 51% in the imipramine group).10 Of the 311 nonresponders, attrition was significantly greater from imipramine (41% [43/105]) than sertraline (30% [61/206]) (χ²₁=4.02, P=.045).

SWITCH PROTOCOL

Two hundred seven nonresponders completed the initial trial. The 62 imipramine nonresponders received a mean±SD final dosage of 235±66 mg/d (range, 100-300 mg/d). The 145 sertraline nonresponders received a mean±SD final dosage of 158±57 mg/d (range, 30-200 mg/d). In both cases, nonresponders received significantly higher mean±SD dosages than responders (205 sertraline responders: 144±53 mg/d, F₁,106=6.23, P=.01; 97 imipramine responders: 218±72 mg/d, F₁,119=4.30, P=.04).

Nonresponders were tapered off study medication over 1 to 2 weeks, with the double blind maintained. After at least 1 week of not taking any study medications, patients who continued to meet nonresponse criteria and who gave renewed written informed consent were crossed over to the alternate medication. Visits, assessments, medication dosing, and outcome definitions for the switch study followed the same protocol as that used in the initial acute-phase trial.

STATISTICAL ANALYSES

Categorical analyses (eg, adverse effects, attrition, and response rates) were performed using Fisher exact probability test, simple χ² tests, McNemar test (for within-subject comparisons), or Cochran-Mantel-Haenszel χ² test, as appropriate. The latter test was stratified by study site and depression subtype. All statistical tests used 2-tailed probability values, with unadjusted significance levels of P ≤ .05.

Response and remission rates are reported at the end point for the intent-to-treat sample and for study completers. The original data analysis plan called for analyses of covariance of the continuous dependent measures for the intent-to-treat sample, using the last observation carried forward method, and the completers sample. The availability of more sophisticated statistical methods, coupled with a significant, nonrandom difference in study completion rates, led us to pursue a different analytic strategy. Tabulated results of the more conventional analyses of covariance are available from one of us (M.E.T.).

To combine information for continuous outcome measures from all patient visits in a single analysis, repeated-measures models were fit using generalized estimating equation (GEE) methods.19,20 An independent correlation model was assumed for the analyses reported herein. Separate GEE models were fit for each dependent measure, using data from all available visits and including main effects for medication group and week of treatment. Because missing data were not randomly dispersed (eg, virtually all missing data were the result of premature attrition, which was associated with poorer outcomes), we also included completion status as a main effect in the GEE analyses. Although repeated-measures analysis of such data could lead to biased results (ie, informative censoring), adjustment for completion status may partially reduce this risk.21 Score statistics based on GEE empirical SEs were used to quantify main effects and interaction terms (in the context of repeated-measures models), controlling for baseline severity, study site, and type of depression.

somnolence in the imipramine group. Diarrhea and insomnia were significantly more common among the group that switched to sertraline therapy. Other common adverse effects, including headache, nausea, fatigue, and sexual dysfunction, were comparable in both groups.

Comparing adverse effect reports between the 2 treatment phases revealed that patients who switched from sertraline to imipramine experienced significant reductions in 3 adverse effects, but significant increases in 8 adverse effects (columns 2 through 4 of Table 2). In contrast, the switch from imipramine to sertraline resulted in statistically significant reductions in 7 adverse effects, but no significant increase in any adverse effect columns 5 through 7 of Table 2).

RESPONSE AND REMISSION RATES

Response status could not be determined for 1 patient. The sertraline intent-to-treat response rate was 60% (30/50), while the imipramine intent-to-treat response rate was 44% (52/117) (χ²₁=4.90, P=.03). Remission rates were 32% for sertraline and 23% for imipramine (χ²₁=2.28, P=.13). Among the 134 completers, response rates were 63% in the sertraline group and 55% in the imipramine group (χ²₁=1.96, P=.16). Remission rates also did not differ significantly among completers (35% for sertraline and 30% for imipramine; χ²₁=0.94, P=.33).

ANALYSES OF CONTINUOUS MEASURES

Mean scores at baseline and end point and mean change scores for continuous clinical outcome measures are presented in Table 3. Results of the repeated-measures GEE analyses indicated that the patients in both treatment groups improved significantly across time, and completers improved significantly more than noncompleters on all measures. After averaging across the study
weeks and adjusting for number (percentage) unless otherwise indicated. HAM-D indicates Hamilton Rating Scale for Depression.

**Table 1. Demographic and Clinical Characteristics of Study Group***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 168)</th>
<th>Sertraline → Imipramine (n = 117)</th>
<th>Imipramine → Sertraline (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD) age, y</strong></td>
<td>40.5 (10.2)</td>
<td>40.9 (9.8)</td>
<td>39.6 (11.1)</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>112 (66.7)</td>
<td>72 (61.5)</td>
<td>40 (78.4)</td>
</tr>
<tr>
<td><strong>White ethnicity</strong></td>
<td>156 (92.9)</td>
<td>109 (93.2)</td>
<td>47 (92.2)</td>
</tr>
<tr>
<td><strong>Employed</strong></td>
<td>129 (76.8)</td>
<td>91 (77.8)</td>
<td>38 (74.5)</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>53 (31.5)</td>
<td>39 (33.3)</td>
<td>14 (27.5)</td>
</tr>
<tr>
<td>Divorced or separated</td>
<td>46 (27.4)</td>
<td>32 (27.4)</td>
<td>14 (27.5)</td>
</tr>
<tr>
<td>Never married</td>
<td>59 (35.1)</td>
<td>42 (35.9)</td>
<td>17 (33.3)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (5.4)</td>
<td>4 (3.4)</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>38 (22.6)</td>
<td>27 (23.1)</td>
<td>11 (1.6)</td>
</tr>
<tr>
<td>Some college</td>
<td>60 (35.7)</td>
<td>41 (35.0)</td>
<td>19 (37.3)</td>
</tr>
<tr>
<td>College graduate or more</td>
<td>67 (39.9)</td>
<td>47 (40.2)</td>
<td>20 (39.2)</td>
</tr>
<tr>
<td><strong>Major depressive disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age of onset, y</td>
<td>24.4 (12.3)</td>
<td>24.8 (12.6)</td>
<td>23.6 (11.8)</td>
</tr>
<tr>
<td>Mean (SD) duration of current episode, y</td>
<td>6.1 (7.1)</td>
<td>5.6 (7.6)</td>
<td>7.3 (5.7)</td>
</tr>
<tr>
<td>Recurrent</td>
<td>100 (59.5)</td>
<td>69 (59.0)</td>
<td>31 (60.8)</td>
</tr>
<tr>
<td>Chronic major subtype</td>
<td>84 (50.0)</td>
<td>54 (46.2)</td>
<td>30 (58.8)</td>
</tr>
<tr>
<td><strong>Dysthymia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double depression subtype</td>
<td>84 (50.0)</td>
<td>63 (53.8)</td>
<td>21 (41.2)</td>
</tr>
<tr>
<td>Mean (SD) age of onset, y</td>
<td>16.2 (13.0)</td>
<td>16.4 (12.8)</td>
<td>15.6 (13.8)</td>
</tr>
<tr>
<td>Mean (SD) initial acute phase HAM-D</td>
<td>25.3 (5.3)</td>
<td>25.4 (5.3)</td>
<td>25.1 (5.3)</td>
</tr>
<tr>
<td>Mean (SD) week-12 acute phase HAM-D</td>
<td>21.7 (6.0)</td>
<td>21.7 (6.1)</td>
<td>21.6 (5.8)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) unless otherwise indicated. HAM-D indicates Hamilton Rating Scale for Depression.

weeks and adjusting for completion status, baseline value, site, and depression type, there were no significant differences between the medication groups for each outcome. In addition, when the effect of attrition was considered, there were no significant week-by-medication group interactions, indicating that the groups did not differ in their pattern of symptomatic improvement over time.

**COMMENT**

This double-blind switch study provides further evidence that chronic depressions are responsive to antidepressant monotherapy after nonresponse to a vigorous 12-week initial trial. Overall, more than 50% of the patients who began treatment with a second antidepressant responded. These results are particularly noteworthy as the patients had a mean duration of more than 6 years of continuous major depressive disorder.

As in the initial trial,10 sertraline was significantly better tolerated than imipramine. The better tolerability of sertraline was reflected by a significantly lower attrition rate owing to adverse effects and a greater reduction in adverse effect burden following the switch to the alternate antidepressant. The difference in tolerability also helped to explain a significantly higher intent-to-treat response rate in the sertraline group, although a smaller difference in intent-to-treat remission rates was not statistically significant.

Overall, we observed response rates that were similar to those in earlier published studies2,22-25 of switching across antidepressant classes. Response to the second medication was maximized in the present study by providing 12 weeks of pharmacotherapy (rather than the customary 4-6 weeks) and by permitting imipramine and sertraline dosages to be increased gradually, if tolerated, to the highest levels permitted within the manufacturers’ therapeutic indications.

Compared with augmentation strategies for antidepressant nonresponders, switching antidepressant classes has the advantages of simplicity and parsimony (eg, lower cost and little risk of drug-drug interactions). Given the tolerability problems observed in the group that switched from sertraline to imipramine, it may be more useful to switch within the selective serotonin reuptake inhibitors class26,27 or to a dissimilar newer antidepressant (eg, bupropion hydrochloride, mirtazapine, nefazodone hydrochloride, reboxetine, or venlafaxine hydrochloride).3 Augmenting the initial antidepressant with lithium salts,28,29 thyroid hormone,29 pindolol,30 or buspirone hydrochloride31 is also an option. Although it is unlikely that the augmentation strategies would have produced better outcomes than those observed in the present study, some clinicians favor them because of quicker implementation. Combining antidepressants (eg, adding sertraline to imipramine, or vice versa) is another widely used approach, although there is the potential for drug-drug interactions and there are no large, well-controlled, prospective studies of this strategy.12

Despite a favorable antidepressant response rate observed following the switch of antidepressants, low percentages of patients who began the second treatment trial (32% in the sertraline group and 23% in the imipramine group) achieved full remission. In other words, about one half of the responders had significant residual symptoms after 12 weeks of pharmacotherapy. Such patients are unlikely to have robust social recoveries,32 and they

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are at high risk for subsequent relapse. It is likely that patients with chronic depression warrant longer acute-phase trials. Indeed, 42% of the patients who responded but did not remit during the initial trial converted to full remission during continuation therapy. Evidence from another recent study of chronic depression suggests that the combination of psychotherapy and pharmacotherapy also increases the likelihood of remission.

Our study has several methodological limitations that affect interpretation of the results. The first limitation is...
the lack of a placebo control group, which precludes more
definitive assessment of the true magnitude of the treat-
ment effects. We decided against using a placebo-
controlled design because of concerns about withholding
active treatment from chronically depressed antidepress-
ant nonresponders. Most investigators studying treatment-
resistant depression have made the same choice.3 However,
placebo has been used in several studies29-31 of
augmentation strategies, and nonspecific response rates of
10% to 20% are typically observed. Kocsis and col-
leagues32 similarly found a placebo response rate of only
13% in their study of imipramine as the initial treat-
ment of chronic depression. If it is assumed that 20% of our pa-
tients would have responded to placebo, the effects of sertraline and imipramine would have been statistically
significant.

A second methodological problem is that switch-
ing the antidepressants of only the nonresponders is not
representative of a true crossover design, which would
require that responders also switch medications. Be-
cause the nonresponders are no longer necessarily rep-
resentative of the initial randomized samples, we can-
not rule out that the 2 switch groups differed in some
meaningful way. Confidence in the validity of compar-
ing these groups is strengthened by the lack of signifi-
cant differences in the sociodemographic and clinical char-
acteristics, as well as a virtual lack of predictors of
differential response in the main trial.38 Nevertheless, with-
out rerandomization of nonresponders to alternate treat-
ments, our comparative results should be viewed as
tentative.

A third limitation is the exclusion of more compli-
cated and comorbid patients from the main trial. Be-
cause such patients tend to be overrepresented among
antidepressant nonresponders,1,2 the generalizability of
our findings is somewhat attenuated. However, there is
no reason to assume that excluded patients would have
responded preferentially to one or the other of the study
medications.

Finally, it could be argued that the slower dose-
titration schedule of imipramine during the first weeks
of the protocol, while necessary, might have biased the
results in favor of sertraline. However, because rapidity
of response did not differ between the treatments and be-
cause all imipramine-treated patients received up to 6
weeks of therapy at maximal dosage, it is unlikely that
speed of titration affected the final results. Faster titra-
tion of imipramine also may have exaggerated the toler-
ability problems observed with this medication.

To our knowledge, this is the largest double-blind
study of switching antidepressants conducted to date.
Given the magnitude of the problem of antidepressant
nonresponse and the large number of controlled studies
of antidepressants under way at any given time, it is puz-
zling that switch designs are not more widely. There
is an impression that these studies are too difficult to con-
duct, because of perceived problems such as subject re-
flux, attrition, and inability to maintain the double blind.
We experienced no such difficulties (eg, more than 80%
of patients consented to the switch study), and our pa-
tients’ outcomes were as good as those observed in the
initial trial. Furthermore, the costs of a switch study are
small compared with those of the parent trial. The pub-
lic health importance of treatment-resistant depression
provides a strong justification for broader use of the switch
designs, which would facilitate the study of promising
strategies for antidepressant nonresponders.

The findings of this study illustrate the value of
switching to an antidepressant of a different class after
the failure of first-line pharmacotherapy. Switching non-
responders to an alternate antidepressant monotherapy
is a straightforward strategy that could be considered an
ethical standard of comparison for future studies of treat-
ment-resistant depression.

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