Editor's Note: This Commentary was intended to accompany the article by Drs. Posternak and Zimmerman that appeared in our February 2001 issue. We regret the omission, but are pleased to offer it to you now. Please also see: Posternak MA, Zimmerman M. Switching versus augmentation: a prospective, naturalistic comparison in depressed, treatment-resistant patients. J Clin Psychiatry 2001;62:135–142.

The Need for Clinically Relevant Research on Treatment-Resistant Depression

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It is increasingly well-recognized that the results of highly controlled randomized clinical trials (RCTs) provide an imperfect foundation for the practice of evidence-based medicine.[1] Such trials typically exclude too many people to be readily generalizable to the larger population of affected individuals. Moreover, the very controls that ensure the internal validity of an RCT, including the use of a placebo comparison group and "blinded" assessment of outcome according to reliable, standardized measures, have little ecological validity for practicing clinicians and their patients. The results of RCTs thus must be complemented by other types of data, including illustrative case series of more representative groups of patients. The recent report by Posternak and Zimmerman[2] on treatment-resistant depression is an example of the kind of research that can be performed in a small group practice. Although these efforts are to be applauded, loudly, it is still important to place the results of Posternak and Zimmerman within the context of what is known from RCTs of treatment-resistant depression. The limitations of the methods employed by Posternak and Zimmerman also need to be noted, taking into account the very real restrictions imposed by having to run a solvent clinical practice. Finally, I will offer some recommendations to enhance future practice-based research efforts.

STUDY FINDINGS

Posternak and Zimmerman[2] reported on a series of 74 outpatients with depressive disorders who were treated in their group practice at the Rhode Island Hospital between 1996 and 1999. All of the patients had either failed to respond to or relapsed after responding to an adequate trial of antidepressant medication. The treating psychiatrists either switched the patients to another antidepressant (N = 38) or added a second medication to augment the first antidepressant (N = 36). The relatively even number of patients treated with each strategy was not by design. Rather, it may be viewed as a behavioral indicator of the psychiatrists' belief that augmenting and switching strategies are comparably useful for antidepressant nonresponders. Forty-five patients (61%) were taking a selective serotonin reuptake inhibitor (SSRI) at the time of the decision to switch or augment. Fifteen patients were taking other newer antidepressants (bupropion, N = 5; venlafaxine, N = 5; nefazodone, N = 4; and mirtazapine, N = 1). Among the remainder, 12 patients were treated with tricyclic antidepressants (TCAs), and 2 patients were taking monoamine oxidase inhibitors (MAOIs) (phenelzine and moclobemide, 1 each). The selection of antidepressants appears to be representative of contemporary psychiatric practice, although moclobemide is not approved for general use in the United States.

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Overall, Posternak and Zimmerman[2] found that there was a small advantage for augmentation (as compared to the switching strategy) after 1 or 2 months of therapy. This difference (i.e., 56% vs. 45% response rate) was not statistically significant, which means that there is more than a 5% chance that the difference was due to a chance variation. Responders to both strategies had about 25% to 30% risk of relapse across the next 6 months of follow-up. Thus, only a small proportion of their patients with treatment-resistant depression (augment: 31% [10/32]; switch: 29% [10/35]) obtained sustained benefit as a result of the first, prospectively observed intervention.

Several other findings are noteworthy. First, 9 of the 18 "nonresponders" who received a second, prospective trial with a different switch or augmentation strategy subsequently responded. This suggests that 1 failed trial may not reduce the likelihood of response to a subsequent intervention.

Second, none of the 36 augmentation patients received lithium salts or thyroid hormone. This observation is consistent with recent survey data that indicate that psychiatrists are currently much more likely to pick novel strategies ahead of the better established (although perhaps passé) interventions.[3] Indeed, the vast majority—29 (81%)—of the augmentation patients in this series received a combination of 2 antidepressants.

Third, within the switch group, the patients who received a trial with a second SSRI did reasonably well (4 responders out of 8 trials). The group that was switched from an SSRI to a TCA also had a good outcome (6 of 9 responders), although only 2 of 5 patients switched from an SSRI to venlafaxine responded. Again, none of the between-group differences were statistically significant. Nevertheless, the more conservative within-class switch strategy (50% responders) was not a clear-cut loser when compared with the across-class switch (8 of 14 or 57% responders). The outcome of the within-class switch group also was not remarkably worse than that of the groups that received the more complex and expensive 2-antidepressant strategies.

Fourth, there was no apparent advantage for adding a TCA to an SSRI (6 of 9 responders) when compared with simply switching from an SSRI to a TCA (as noted above, 6 of 9 responders). As cost, complexity, and safety considerations all favor the simpler switch strategies, the findings of comparable benefits must be viewed as a small victory for pharmacologic Calvinism!

A final interesting observation pertains to the 10 patients who achieved partial responses. Seven (70%) of these patients subsequently relapsed, which was more than twice the relapse rate observed among the "full" responders. This observation provides further support for the position that a partial response is not an acceptable outcome and that further treatment efforts targeting persistent residual symptoms must be undertaken.

RESULTS OF RELEVANT CONTROLLED RANDOMIZED CLINICAL TRIALS

How do these findings compare with the results of RCTs? It is easy to review the relevant literature on controlled studies comparing switching versus augmenting strategies for antidepressant nonresponders: there are none. Qualitative reviews conclude that switching antidepressants after the history of 1 medication failure can be expected to yield short-term response rates of about 45% to 60%.[4,5] One might think that the simple question of whether it is better to switch outside of the class than to repeat a second trial, within class, would be resolved,[4] but again no properly controlled studies have yet been published. In 1 randomized trial of patients who had not responded to 2 prior antidepressant trials (about 75% had been treated unsuccessfully with at least 1 SSRI), venlafaxine therapy resulted in a significantly greater remission rate than treatment with a second SSRI, paroxetine.[6] However, in 3 open-label studies, SSRI nonresponders had response rates of 72%,[7] 63%,[8] and 51%[9] to a second SSRI trial. Meta-analyses of studies of lithium[10] and thyroid[11] augmentation, the 2 best-studied augmentation strategies, indicate that 40% to 50% response rates are likely. There are virtually no controlled studies of combining modern antidepressants, despite the frequency of use in contemporary practice. Moreover, in the 1 small published study, adding low doses of a TCA (desipramine, 25–50 mg) to fluoxetine was somewhat less effective than simply increasing the fluoxetine dose from 20 mg to 40–60 mg/day.[12] Although the data from controlled studies are indeed meager, the findings generally are consistent with those of Posternak and Zimmerman: more complex strategies are not necessarily better than simpler ones.

METHODOLOGICAL ISSUES

There are several important methodological issues that limit the impact of the Posternak and Zimmerman case series. One issue is nonrandom selection of treatments, which renders the findings vulnerable to potential biases in treatment selection. It is possible, for example, that different types of patients were chosen to receive augmentation versus switching strategies. If true, this bias could invalidate all across-strategy comparisons. Although the 2 groups did not differ significantly on sociodemographic and clinical variables, the augmentation group tended to be more severely depressed and the switch group included more patients with chronic depressive syndromes. Further, 53% of the augmentation group had relapsed or had a partial response to the index trial (compared with 32% of those switched), whereas 66% of the patients who were switched had failed the index trial (compared with 44% of the augmentation

group). Although these differences were not statistically significant, they are suggestive that the psychiatrists had implicit rules that governed selection of particular strategies.

Is it possible to conduct a randomized trial within a fee-for-service practice? Yes, I believe it is *with* explicit informed consent, assuming that people who decline to participate are not prejudiced against (with respect to their subsequent treatment) *and* providing that the treatment options being studied are reasonable and can be offered with equipoise. A randomized, yet fee-for-service study might use 1 relatively conservative option to represent a standard for comparison, against which a novel treatment could be available. In the case of Posternak and Zimmerman's patients, a within-class switch (e.g., fluoxetine → citalopram or nortriptyline → clomipramine) could have served as such a standard, with the SSRI + TCA combination being the "experimental" group.

The absence of statistically significant findings (despite 20+% differences, such as those noted above) points to a second and, frankly, more important limitation: the case series is too small. More confidence could be placed in the findings only if the investigators had studied a large enough group of patients to have adequate power to detect clinically meaningful (i.e., 15%–20%) differences. Although it may not have been practicable for Posternak and Zimmerman to have enrolled the 300 or more patients needed to make powerful comparisons (they treated 74 antidepressant nonresponders in 3 years), power could have been conserved by limiting the number of strategies compared (i.e., a single switch strategy versus a single augmentation). Such a decision to restrict treatment options would again require explicit informed consent, but the trade-off would be a greater likelihood that the results would be informative.

A third limitation concerns the lack of information about the patients' participation in psychotherapy. It cannot be assumed that patients with chronic,[13] severe/recurrent,[14] or antidepressant-resistant[15] depressive disorders obtain no benefit from psychotherapy. Further, it is very likely that participation in psychotherapy was not randomly distributed. This creates the possibility that favorable psychotherapy outcomes contributed to the unexplained (error) variance, which may have obscured detection of differences between the various pharmacotherapy strategies. Further studies would do well to keep track of this information.

A fourth limitation concerns the measurement of outcome. Posternak and Zimmerman faced real pressure to keep assessments at a minimum and necessarily collected data using only a few simple, face-valid, clinician-rated scales. The use of additional, patient-rated outcome measures would have strengthened the study without imposing prohibitive costs or unacceptable respondent burden. Measures such as the Inventory of Depressive Symptoms[16] and the Medical Outcomes Scale[17] would be strongly recommended for future studies.

A fifth issue pertains to the nature of the patients treated in the group practice of Posternak and Zimmerman. Although this group was not artificially restricted by exclusions due to medical or psychiatric comorbidities, nor by patients' refusal to accept random assignment, the study group was composed of patients who could afford treatment in a fee-for-service specialty practice. Thus, the study group was predominantly white and included few, if any, patients of lower socioeconomic status. Parallel practice-based studies conducted in community mental health centers, such as the Texas Medication Algorithm Project,[18] will be needed to ensure the representativeness of the findings.

The high prevalence of depression and the imperfect nature of our treatments virtually ensure that treatment-resistant depression will continue to be an important worldwide public health problem. There are many treatment options to consider, yet little empirical guidance to rank the likelihood of benefit. A large nationwide study, funded by the National Institute of Mental Health, is just underway, and within a few years the relative merits of several common switching and augmenting strategies can be addressed with more clarity (A. J. Rush, M. Fava, S. R. Wisniewski, et al. for the STAR*D Research Group. Manuscript submitted). But no study can answer all questions and new strategies will continue to emerge. The practice-based effectiveness study is a promising, yet often overlooked approach that can complement more highly controlled studies. Although the report of Posternak and Zimmerman provides no clear-cut answers, it is hoped that it can serve as both an example and an inspiration for future studies.

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