Editorial

Pros and Cons of Prozac and Its Relatives

The past decade has witnessed a tremendous shift in how we treat patients who suffer from depressive or anxiety disorders. Selective serotonin reuptake inhibitors (SSRIs) have become first-line agents for patients with major depression, dysthymia, panic disorder, obsessive-compulsive disorder, social phobia, etc., and their U.S. sales top $6 billion annually. The effects of these agents on our social fabric have perhaps been even greater, with brand names of specific drugs (e.g., Prozac) commonly used in English parlance. In fact, there are many in the lay population who worry we may be becoming too "dependent" on these agents to maintain our mental health.

Fluoxetine (Prozac), the original SSRI in this country, remains the leader of the pack in dollar sales. In spite of its widespread use, there are many academics who question whether it is as effective as the older tricyclic antidepressants or monoamine oxidase inhibitors (MAOIs) in a number of special circumstances—e.g., severe depression, atypical depression. Four articles in this issue of the *Journal* highlight some features and limitations of the wide-scale use of SSRIs, particularly fluoxetine.

The study of Robinson et al. on poststroke depression and recovery indicates that fluoxetine is not effective for these patients and is consistent with the previous observations by Roose et al. (1) of depressed patients with heart disease. In the Robinson et al. study, fluoxetine was not more effective than placebo in poststroke depression, whereas nortriptyline was highly effective. Neither drug was effective in aiding recovery in nondepressed patients. Taken together, these studies suggest that norepinephrine reuptake blockade is important in elevating depressive affect in some elderly subjects. Of interest is another recent study by Roose et al. (2), which demonstrated that both nortriptyline and paroxetine were effective in depressed patients with ischemic heart disease, suggesting that the observation of Nemeroff's group (3, 4) that paroxetine may block norepinephrine reuptake in addition to acting on the serotonin transporter may be clinically valid. Thus, all SSRIs may not enjoy equal efficacy in specific populations. A direct head-to-head comparison of paroxetine and fluoxetine in depressed patients with vascular disease (cardiac or cerebrovascular) would be of considerable interest to the field.

Patients with atypical depression were shown several years ago to be more responsive to MAOIs than to imipramine or placebo (5, 6). The article by McGrath and colleagues in this issue indicates equivalent efficacy of fluoxetine and imipramine for this disorder and thus suggests that fluoxetine may be less effective than an MAOI in atypical depression. Unfortunately, since we do not have such comparison data, we cannot be certain of this conclusion, and, as the authors point out, for practical reasons (e.g., the safety of MAOIs) we are unlikely to ever have these data. Thus, in fluoxetine for atypical depression we have an agent that has clear efficacy (McGrath et al.), is safe and easy to use, but may not be the most effective medication available. Here too a head-to-head trial of fluoxetine versus phenelzine would be highly informative for clinical practice. Even if fluoxetine turned out to be not as effective as an MAOI in atypical depression, its relative efficacy as compared to placebo and its tolerability and wide safety margin still make it a useful agent in this disorder.

Indeed, these advantages for fluoxetine and the other SSRIs largely explain their success to date. The earlier agents—tricyclic antidepressants and MAOIs—were

problematic in regard to their side effects and smaller safety margins. SSRIs have allowed for a wider range of patients, including those with milder disorders, to be treated successfully and easily in the community. In a sense, they may be more broadly effective but may not be more effective for specific populations than older agents. Herein lie their advantages and their potential limitations.

The last two studies in this group point to the ease of use of SSRIs. Thompson and colleagues, using a variety of methods to assess compliance in primary care, found significantly greater consistency of use for fluoxetine than for the European tricyclic antidepressant dothiepin. The study used a medication event monitoring system—a computerized pill container—to assess how reliably patients took their medications. Using cruder assessments of pill-taking behavior, Thompson et al. noted no superiority of fluoxetine over dothiepin. In contrast, superior compliance for fluoxetine was determined with the more objective medication event monitoring system. Of particular importance was that the patients who were more compliant also demonstrated greater improvement than those who were not. Thus, taking one's medications helps (thank the Lord), and that is one of the things SSRIs allow for—i.e., greater surety in compliance.

A result of the extensive use of SSRIs is highlighted in the article by Mamdani and colleagues. Using an Ontario database on drug utilization, they found that since the introduction of SSRIs into Canada, the utilization and costs of antidepressants for the elderly have increased dramatically. Exploring prescriptions of antidepressants from 1993 to 1997, they noted an increase in the prevalence of antidepressant use by the elderly from 9.3% to 11.5%, with SSRIs growing from 9.6% of antidepressant prescriptions to 45.1% over that period. The increase in total expense was due largely to a switch from almost entirely generic tricyclic antidepressants to the SSRIs. This increase occurred despite the fact that generic fluoxetine became available in Canada in 1995. While the increased use of SSRIs and the resultant higher costs may be of concern to health care economists, such costs must be weighed against such potential benefits as 1) better efficacy and restoration of function, because the agents are often better tolerated (a point questioned by Mamdani and colleagues in their article) and patients are understandably more compliant with their treatment (see preceding discussion), and 2) the potential savings in emergency room visits and stays in the intensive care unit associated with overdoses. Further large-scale studies on the cost-benefit ratio would aid in assessing the value of switching from tricyclic antidepressants to SSRIs. (As Mamdani et al. argue, such studies should be performed with nortriptyline, a secondary tricyclic antidepressant with fewer side effects than a tertiary agent, such as amitriptyline.) Still, the increased prescriptions of SSRIs suggest that there is at least a reasonable level of satisfaction with this class of agents in the elderly, and although this study did not focus on fluoxetine, the data are in keeping with the findings from a large-scale study of geriatric depression (7), in which fluoxetine was significantly more effective than placebo.

Perhaps no other class of antidepressants has affected our practice in the same way or to the same degree as the SSRIs. Today, 12 years since their introduction, we still need further studies on the similarities and differences among members of the class in both efficacy and tolerability, as well as further data on the relative efficacy and safety of the SSRIs versus tricyclic antidepressants or MAOIs for special populations. Such studies not only will help us to understand better how we can best use these agents but also will assist in laying a template for assessing new classes of antidepressants and anxiolytics in the future.

REFERENCES

1. Roose SP, Glassman AH, Attia E, Woodring S: Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. Am J Psychiatry 1994; 151:1735–1739

2. Roose SP, Laghrissi-Thode F, Kennedy JS, Nelson JC, Bigger JT Jr, Pollock BG, Gaffney A, Narayan M, Findel MS, McCafferty J, Gergel I: Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. JAMA 1998; 279:287–291
3. Owens MJ, Morgan WN, Plott SJ, Nemeroff CB: Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. J Pharmacol Exp Ther 1997; 283:1305–1322
4. Owens MJ, Knight DL, Nemeroff CB: Paroxetine binding in the rat norepinephrine transporter in vivo. Biol Psychiatry (in press)
5. Quitkin FM, Stewart JW, McGrath PJ, Liebowitz MR, Harrison WM, Tricamo E, Klein DF, Rabkin JG, Markowitz JS, Wager SG: Phenelzine versus imipramine in the treatment of probable atypical depression: defining syndrome boundaries of selective MAOI responders. Am J Psychiatry 1988; 145:306–311
6. Quitkin FM, McGrath PJ, Stewart JW, Harrison W, Tricamo E, Wager SG, Ocepek-Welikson K, Nunes E, Rabkin JG, Klein DF: Atypical depression, panic attacks, and response to imipramine and phenelzine: a replication. Arch Gen Psychiatry 1990; 47:935–941
7. Flint AJ: Pharmacologic treatment of depression in late life. Can Med Assoc J 1997; 157:1061–1067

ALAN F. SCHATZBERG, M.D.

Address reprint requests to Dr. Schatzberg, Department of Psychiatry, Stanford University Medical Center, 3rd Floor, 401 Quarry Rd., Stanford, CA 94305-5717; afschatz@leland.stanford.edu (e-mail).