Antidepressant Selection in the Postgenomic Era

The term selective serotonin reuptake inhibitors (SSRIs) implies a common mechanism of action for these agents; hence, the assumption by pharmacy managers and health care planners that they are all clinically equivalent. Extensive clinical case report data belie this assumption, however, as individuals may have differing responses to the different SSRIs, and the average profile of response in terms of symptoms and side effects may differ between agents; however, there are little empirical data bearing on this issue, as few studies have directly contrasted SSRIs in empirical clinical trials.

In this issue, Stahl and colleagues compare sertraline and citalopram in a well-designed, double-blind, controlled trial. They employed a range of assessment instruments including the Hamilton Depression Rating Scale, the Montgomery–Asberg Depression Rating Scale, and the Clinical Global Impressions Scale. They noted a significant improvement with sertraline at week 12, whereas improvement with citalopram began at weeks 2 to 4. Also, a significant anxiolytic effect of the citalopram, but not the sertraline, was demonstrated in comparison to a placebo. As investigators note, there have been quite variable results in previous comparisons of SSRIs. In a previous double-blind, multicenter study comparing sertraline and citalopram with 308 patient completers, but without a placebo trial, there were no statistically significant differences in rate of side effects between the two agents, although there was an absolute increase in citalopram-induced sexual dysfunctional symptoms that did not reach statistical significance. In this study, the patients in the sertraline groups used significantly more sedatives and hypnotics than those in the citalopram group, whereas there was a slight but nonsignificant increase in response in the citalopram group as well as a higher dosage of citalopram employed (Ekselius et al 1997). In a comparison of citalopram and fluoxetine, citalopram also showed a significantly better response at 2 weeks, demonstrating an earlier onset of recovery (Patris et al 1996), whereas another report from this group suggested greater reduction of anxiety symptoms with citalopram, as compared to fluoxetine (Bougerol et al 1997).

Given the discrepant or variable results between different multicenter trials regarding comparisons between SSRIs, the investigators interpret these results in the context of different populations responding differentially to one SSRI as compared with another. A number of studies suggest that patients who were intolerant of (Brown and Harrison 1995; Thase et al 1997; Zarate et al 1996) or failed to respond to (Joffe et al 1996; Thase et al 1997) an initial SSRI trial may respond to a second trial with a different SSRI. Thus, the investigators are probably right in stating that these results support a differential response to SSRIs in different populations rather than the conclusion that one SSRI is clearly superior to another in a generalizable fashion.

This conclusion, although not directly inferable from this study, has important practical and research implications. A trend for pharmacies or health care organizations to restrict SSRIs to one or two agents, under the assumption that they are all equivalently efficacious, may not be valid and would prevent access of patients to medications that might be effective for them when the SSRI chosen by the pharmacy is not. When cost control issues become paramount in clinical care, definitive empirical data that can correct these assumptions of equal efficacy for the SSRIs in all populations are clearly called for.

There are many reasons, of course, why antidepressants may differ in their efficacy. Differences in pharmacokinetics, including drug metabolism; differences in pharmacologic effects; and differences in nontarget pharmacologic mechanisms that contribute to side effects and tolerability can contribute to differential responses. Thus, for example, agents that enhance dopaminergic activities, such as buproprion, would be expected to have a different profile of efficacy than the SSRIs. Similarly, mixed noradrenergic-serotonergic reuptake blockers such as venlafaxine would be expected to have some properties of the SSRIs with additional effects that more nearly mimic the actions of the tricyclics at higher doses, where noradrenergic effects are more prominent. A better understanding of differential efficacy of the antidepressants and the populations that are best served by the individual agents could have important implications for treatment interventions.

If this conclusion is true, however, it remains elusive as to how to define population differences that are relevant for treatment response. Up until now, demographic or clinical characteristic approaches to defining homogeneous populations that will respond to one rather than another antidepressant have been largely disappointing. But with the advent of new techniques of mapping the genotype permitting the identification of single nucleotide pairs that vary between individuals, the door is opened to identifying genetic differences in individuals that are relevant for medication responses. Indeed, this has resulted in a new field of “pharmacogenomics.” By identifying genetic differences between populations of responders to a particular medication and those who are nonresponders, the possibility of identifying those who would most benefit from a particular medication and those
who are most at risk for potentially deleterious side effects becomes potentially realizable.

This approach has been used with varying results to predict responses of individuals to atypical antipsychotics, particularly clozapine, but has not been widely applied to the SSRIs, with several exceptions. A polymorphism for the serotonin transporter gene promoter site has been identified, with the long (l) form resulting in more transporter being expressed than the short (s) form, which is associated with greater psychopathology (Lesch et al. 1994). In one study of 102 inpatients with major depressive disorder with psychotic features, patients homozygous for the s allele (s/s) demonstrated a worse antidepressant response to fluvoxamine than either those heterozygous (l/s) or homozygous (l/l) for the l allele (Smeraldi et al. 1998). In another study of 51 patients treated with paroxetine, patients homozygous for the l allele responded with more improvement from week 2 to week 6 than those with l/s or s/s genotypes, although at 12 weeks there were no differences in response between groups (Pollock et al., in press). Another study also showed a worse response to paroxetine in depressed patients with the s/s homozygote of the transporter (Zanardi et al., in press). Transporter polymorphisms have been related to response to fluoxetine as well as platelet serotonin transporter affinity (Rausch et al. 2000). The promoter polymorphism and an intronic polymorphism in the transporter gene were also associated with treatment response to fluoxetine or paroxetine in a Korean population (Kim et al. 2000). This polymorphism has also been associated with response to sleep deprivation (Benedetti et al. 1999). Although there have been inconsistencies between these initial studies, which require replication in larger series, these results suggest that a functional polymorphism at the promoter site of the serotonin transporter might influence both postsynaptic response and presynaptic serotonergic activity. With the advent of DNA chip technology, it may be possible to evaluate a panel of related serotonergic genes to determine those profiles that are associated with optimal drug response for any particular agent, pointing the way to a rational basis for pharmacologic selection.

Strain differences in animal models of antidepressant response (West and Weiss 1998) to antidepressants with differing mechanisms of action may enable a better understanding of the factors that confer differential response to antidepressants. It is not clear whether some of the pharmacologic effects of antidepressant administration such as downregulation of the serotonin transporter may differ in different genetic strains. These differences are not likely to be due to differences in transporter gene expression, but may be attributable to genes affecting regulation of the transporter (Benmansour et al. 1999).

Individual differences in the cytochrome P-450 system may also play a role in differential response to SSRIs. Although the pharmacogenetic differences and oxidation of the SSRIs themselves may not be of clear clinical relevance, the differential inhibition of the various cytochrome P-450 isozymes will alter the interactions with other drugs that patients may be taking that are metabolized by these isozymes, thus influencing their differential response (Brosen 1993).

Environmental variables such as diet or stress may also influence response to SSRIs. For example, patients with anorexia nervosa may not be responsive to SSRIs when ill as a consequence of inadequate supply of nutrients that are essential for normal serotonin synthesis and function (Kaye et al. 1998). Conceivably, then, factors including nutritional status, stress, and even social milieu (Raleigh et al. 1994) can affect responses to SSRIs. Trauma may influence responses of the serotonergic system and its relation to hypothalamic–pituitary–adrenal axis activity (Siever et al. 1998), and such differences might conceivably affect the response of antidepressant medication.

Whereas perhaps the choice of antidepressant type in a clinical situation will always be partially an art, there are clearly a lot of questions that could empirically be answered to bring more science into the process. There are few head-on-head studies to evaluate differential responses, even differing mechanisms of action, between
antidepressants, much less the more similar SSRIs. We know little of the potential genetic and environmental factors that might influence individual responses to specific antidepressants. The new science of pharmacogenomics can help us understand the genetic determinants of drug response, whereas the role of other environmental factors such as diet or social context needs to be more systematically studied. As the genome has now been largely mapped, these strategies then may afford us the prospect for a more rational pharmacotherapy in the next 100 years.

Larry J. Siever

Mount Sinai School of Medicine
1 Gustave L. Levy Place, Box 1230
New York NY 10029

References


