Debate and Discussion

In the Treatment of Depression, Does Selectivity of Action Matter?

Dr. Schatzberg: There are 2 overriding issues to be addressed. First is the question of whether there is evidence of differential efficacy for major depression between single-action drugs and drugs that inhibit reuptake of both serotonin and norepinephrine. Second is the question of how to design a trial to evaluate whether one drug has enhanced or superior efficacy over another based on mechanism of action.

Dr. Keller: The evidence at this point is inconclusive regarding whether there are efficacy advantages either for one class of compounds over another or for any individual drug over another. Claims of class effects are exaggerations in the absence of compelling data. To settle this question, I would look at each compound separately. I would want to see a series of studies with a variety of single-acting and dual-acting agents, and then assess whether there is a statistically significant and clinically meaningful finding that one is better than the other.

Dr. Hirschfeld: I agree that there are not sufficient data to support a difference in efficacy with regard to single-action agents over dual-action agents. The pooled analysis by Thase and colleagues *[Thase ME, et al. Br J Psychiatry 2001;178:234–241]* and some other reports suggest that dual action may be advantageous in certain populations, but there are methodological problems in those studies and analyses that limit our ability to generalize.

Dr. Keller: Thase and colleagues' analysis, which shows positive data in favor of venlafaxine, compares venlafaxine with fluoxetine, fluvoxamine (which is not approved in the United States for depression), and paroxetine, but at lower doses of the selective serotonin reuptake inhibitors (SSRIs) than most people would acknowledge to be a reasonable comparison. If the Thase et al. study suggests any superiority of venlafaxine, it is in comparison with fluoxetine. The article cannot conclude anything about venlafaxine compared with escitalopram, citalopram, or sertraline.

Dr. Delgado: Intuitively, one would expect that dual-action compounds would have a more robust effect. If there is a difference in effect, it is worth knowing about; it is important to try to prove or disprove it. I think that there is enough evidence to warrant a carefully designed study, which has not been done.

Dr. Schatzberg: So, do we agree that there is a hint that some difference in effect may exist, but that to conclude this we would need prospective studies?

Dr. Burke: I do not disagree. There is a sense that in severely depressed inpatients and melancholic patients, dual-mechanism drugs may confer some advantage. The 2 prospective studies most supportive of this notion are the Danish University Antidepressant Group trials, in which patients did poorly with paroxetine *[J Affect Disord 1990;18:289–299]* and citalopram *[Psychopharmacology (Berl) 1986;90:131–138]* compared with clomipramine, but these studies are problematic because they were very brief and reported improvement only as measured using the Hamilton Rating Scale for Depression (HAM-D). Unfortunately, none of the trials we conduct now include the severely depressed inpatient and melancholic subsets of depression patients. We do not have melancholic patients or inpatients in our trials, so I am a little skeptical that we will be able to find or define the group of patients who may benefit most from a tricyclic or other multiple-mechanism drug. In mild-to-moderate depression, I think it may be difficult—regardless of the mechanism of action, and particularly if a placebo group is included—to show big differences between drugs. But again, nobody has done this prospectively.

Dr. Owens: I am surprised that there is only a hint of a difference in effect, not a raging fire, if a dual mechanism really is better. I thought that such a difference would have jumped out at us by now. I am also surprised that the selective norepinephrine reuptake inhibitor reboxetine has not been able to get approved for use in the United States.

Dr. Schatzberg: In Europe and South America, where the drug has been released, reboxetine has not been tremendously successful. There is a perception that it may not be as effective as other agents. Being a relatively pure norepinephrine drug may not be enough.

Dr. Delgado: A reasonable question to ask is if particular symptoms make a difference in terms of which people achieve remission. SSRIs are capable of achieving remission in a large number of patients, as are drugs with predominantly noradrenergic action. But are there certain symptoms that create issues for some patients, those who do not remit with a single-action drug? It is not clear who is in that subset, so a more symptom-oriented approach might be useful. I wonder if something might emerge that would help us understand the differences among patients who respond better to serotonergic drugs, patients who respond better to noradrenergic drugs, and patients who respond to both.

Dr. Schatzberg: What is meant by "better"? Better within an illness such as major depression, or better within other syndromes or disorders—for example, anxiety disorders or fibromyalgia—that might respond to different mechanisms of action?

Dr. Lucki: That also raises the issue of medical comorbidity. Medical conditions comorbid with depression might be affected differently by compounds with different mechanisms.

Dr. Delgado: There are relevant data about subgroups of depressed patients, as well as patients with other psychiatric or medical disorders, where there seem to be differences in efficacy. For example, there are venlafaxine and duloxetine data suggesting effects in painful conditions, both pain comorbid with depression and diabetic neuropathy, for which there is a positive trial with venlafaxine *[Kiayias JA, et al. Diabetes Care 2000;23:699]*. Conversely, for the anxiety disorders, mostly social anxiety and generalized anxiety, there is a suggestion of advantages with serotonergic drugs.

Dr. Schatzberg: Before we switch to anxiety, one of our basic scientists, Dr. Lucki, raised the point about medical comorbidity. In the venlafaxine study in diabetic neuropathy, venlafaxine separated from placebo only at the high doses, which suggests involvement of noradrenergic activity. In the context of depression trials, duloxetine seems to separate from placebo on measures of pain symptoms (such as back pain) on the visual analog scale. So there is some suggestion that, at least for peripheral pain, norepinephrine enhancement may have an effect that would be important for some patients.

Dr. Lucki: From a basic science perspective, one can make the case that serotonin and norepinephrine have both been shown to have analgesic effects, but probably act through different mechanisms. Compounds from either class of drugs would be decent candidates to try against comorbid conditions, and I think these are important questions to answer. We should move from studying just major depressive disorder to engaging multiple comparisons across multiple symptomatic categories. The different drug classes could compete for these new indications, and we would see whether a consistent predictive picture emerges.

Dr. Schatzberg: Chronic pain is common in depressed people, and it is worth remembering that even with $7 billion worth of SSRIs being sold every year, a lot of prescriptions are still being written for tricyclics, perhaps because that part of the market has not been as well served by the SSRIs. Patients with chronic pain may be a group that will do better on treatment with a dual-uptake blocker.

Dr. Keller: An abstract of the American College of Neuropsychopharmacology (2002) by Gendreau et al. reported unpublished data on milnacipran, a highly potent dual-uptake blocker, that suggested efficacy in the treatment of fibromyalgia. The results are impressive, although patients in this study did not have nearly as severe depression as I am sure would be found in patients in psychiatric practices. If we want to evaluate the effects of the SSRIs or the dual-uptake blockers on pain, we will need to conduct a study with one of the pain syndromes, such as irritable bowel syndrome. Functional somatic syndromes are very troublesome; they are hard to treat and cause terrible problems.

Dr. Schatzberg: Anxiety disorders, either comorbid or noncomorbid, represent another area where the issue of relative efficacy of single- versus dual-action drugs plays a large role.

Dr. Delgado: There are many positive studies in all of the anxiety disorders for all of the SSRIs. I recently conducted a review of norepinephrine and anxiety and was surprised that there were more data than I expected, especially for panic disorder. On the other hand, there are a number of negative studies with noradrenergic agents; there are negative studies in posttraumatic stress disorder, generalized anxiety disorder, and panic. So, something is not quite the same. However, if you look at depression studies, the bulk of what has been published suggests that if anxiety is comorbid with depression, both will respond to treatment, but none of those studies have been well designed. I would like to study a group of people with high anxiety levels and randomly assign them to venlafaxine, reboxetine, or escitalopram, then prospectively study the response of the high-anxiety group with depression. There are some unresolved questions.

Dr. Schatzberg: So, to summarize, we cannot say that the dual-uptake blockers are truly better. There are data, at least from the Thase et al. comparison of venlafaxine with fluoxetine, suggesting some advantage, but there are problems with those data. It is conceivable that venlafaxine could have better effect, and there are special patient populations in whom one could intuit some advantage for one group of compounds versus another.

Dr. Keller: The only way to take into consideration all the issues we are talking about is to conduct a well-designed trial of an SSRI against venlafaxine. In the absence of those data, convincing people that there is little or no additional benefit from dual action will be an uphill fight. My strong recommendation is that trials need to be done.

Dr. Schatzberg: I think we all agree that we need a more definitive, prospectively designed study to examine issues of adequate dosing and treatment duration and to measure outcomes including remission, quality of life, and social adjustment. Perhaps we should talk about the methodology questions in order to reach some consensus on some of the issues to address in a prospectively designed trial.

Dr. Leon: Let's consider the design of this clinical trial. We need to decide the patient population to study, the

sample size, what medications to test, whether to include a placebo, the length of the study, and the primary and secondary outcomes of the study. Can we agree that major depression should be the primary diagnosis for inclusion in the study?

Dr. Hirschfeld: Yes.

Dr. Owens: If this trial is to compare an SSRI with venlafaxine, it will be necessary to use a dose of venlafaxine high enough that no one questions whether the trial is a fair assessment of a dual-action agent. Perhaps the SSRI should be escitalopram since it is the most selective agent studied to date for the serotonin transporter.

Dr. Schatzberg: To evaluate efficacy, we should try to use the maximum allowed doses of both drugs. With venlafaxine, dosing might start at 37.5 mg/day for a few weeks.

Dr. Keller: But then patients will not reach a dose of 225 mg/day for a minimum of 3 or 4 weeks.

Dr. Schatzberg: If you push the dose, if you get to venlafaxine, 225 mg/day, in a week, the dropout rate will be higher. Even if we start at 37.5 mg/day for a week, or 75 mg/day, we may not get all of the patients' doses up to 225 mg/day. Additionally, the outcome measure should be remission, not simply response. For U.S. Food and Drug Administration (FDA) approval, response may be enough, but it is not the same as what is clinically important in practice.

Dr. Keller: We do not want to use the FDA criteria for approval of a drug to say one is any better than another, because we know they have all met the criteria. There is the question of remission versus sustained remission. It is not really meaningful to have patients reach a certain level for a week, or even 2 consecutive visits. I would favor a longer trial with a longer period of sustained remission if we are seeking to answer whether there is a difference between compounds.

Dr. Schatzberg: Sustained remission is important, although it is unsettled just how long that period is. The remission period must be more than a week; whether it is 2, 4, or 6 weeks or 3 months is the area of debate.

Dr. Leon: How long does a trial need to be if we are treating to remission?

Dr. Hirschfeld: At least 12 weeks. The curves for mean changes from baseline in HAM-D or Montgomery-Asberg Depression Rating Scale (MADRS) scores are still going down at the end of 6-week and 8-week trials. If we are looking for sustained remission, the trial will have to be longer, and we may also want to assess time to remission.

Dr. Leon: Do we include a placebo control in case the two active treatments do not separate?

Dr. Schatzberg: I probably would not. First, it is harder to recruit patients, and in a longer study, patients exposed to placebo will start dropping out. We are not interested in whether one drug is better than placebo; we are interested in the two drugs.

Dr. Leon: If the active compounds separate, then a placebo arm is not necessary. But that cannot be known until the trial is done. If the trial is big, with 200 or 300 subjects per treatment arm, and the treatment arms do not separate, there is no way to know if they would have separated from placebo. If they do not separate, one might want to know what kind of trial this was: one with a 50% placebo response rate or one with a 10% placebo response rate.

Dr. Keller: The null hypothesis would be that there is no difference in sustained remission between 2 compounds of different classes in a 12-week trial, where we define sustained remission as meeting criteria for 4 consecutive weeks.

Dr. Leon: Given the single null, the conclusion can only be "the agents are different" or "we do not know if they are different." To be able to conclude that either is efficacious (relative to placebo), a placebo arm would be required. If a placebo were included, we could consider randomizing half as many patients to the placebo cell as to the active cells.

Dr. Hirschfeld: We agree that the goal is to treat to remission. Are we interested in time to sustained remission?

Dr. Schatzberg: I would not use time to remission as a primary endpoint, because what is more important is degree of remission, or likelihood that remission will be achieved. You might instead use area under the curve analysis or some model that measures response over time, but time to remission is a separate issue. Speed and degree may be very different, depending on tolerability and half-life.

Dr. Hirschfeld: Multiple outcomes should be measured, including social functioning and quality of life.

Dr. Schatzberg: Measuring quality of life can be tricky because in shorter studies patients are less likely to show effects at work. These types of improvements take longer to appear. I would include quality of life, but not necessarily make it a primary outcome. Would you stratify and include people on the basis of comorbid pain?

Dr. Leon: Doing so would make the trial more generalizable if a high proportion of patients with major depression have comorbid pain. It could have a broader impact than other clinical trials. Can we operationalize remission in addition to the requirement that it is sustained for at least 4 weeks?

Dr. Hirschfeld: A HAM-D score of 7 or less is the usual standard for remission.

Dr. Keller: Or a MADRS score of 10 or less.

Dr. Leon: The last thing we need to consider is sample size, which can be calculated based on the degree of difference in remission rates that would be clinically important.

Dr. Schatzberg: We would need 1200 to 1500 patients.

Dr. Leon: To detect a 10% difference in remission rates between active compounds, a very large N is required.

Dr. Keller: Well, we want to do a blockbuster study.