Discussion

Scientific Expert Meeting

Dr. Keller: We have tried to single out the topics that had the greatest interest in each of the workshops and to have the expert panel discuss them. The question of dosing was raised in most of the groups. There were quite a number of expert clinicians who reported that, either individually or with groups they work with, they are actually prescribing mirtazapine in dosages between 60 and 90 mg/day, despite the fact that the recommended dose range is between 15 and 45 mg/day. Their clinical experience has shown that they get efficacy and even fewer adverse events with the higher dose than with the lower doses, and they usually start mirtazapine treatment at 30 mg/day.

Dr. Falkai: In our group, it was consistently reported that higher doses are not problematic. However, this strategy appears to be of no benefit in patients with treatment-refractory depression. Several group members recommended leaving the dose at 60 mg/day for a longer time (3 to 4 weeks). If there is no improvement, augmentation with either lithium or selective serotonin reuptake inhibitors (SSRIs) is preferred over further dose increase.

Dr. Keller: Weight gain is the one adverse event that probably led to the most discussion. Our colleagues who saw patients gaining weight while taking mirtazapine agree that gains are usually seen in women aged from their early 30s to mid 40s. However, most of our colleagues find that weight gain is manageable with education and dietary advice. Dr. Thase, please summarize different ideas about weight gain discussed during the workshops.

Dr. Thase: One issue that came up in at least 3 groups is that edema can be a minor or an occasional cause of weight gain. Interestingly, several different experienced clinicians have found that a dose increase can remedy edema. In other groups, it was suggested that diuretics like furosemide are also useful in the symptomatic treatment of edema. When confronted with weight gain, I would encourage trying to differentiate gaining fat weight from gaining water weight, since the interventions can be quite different. In reexamining experience with mirtazapine in randomized, controlled clinical trials, we have confirmed that the weight gain problem is principally apparent in women before menopause. We learned some useful guidelines. For example, if there is no weight gain by week 6 of treatment, it is unlikely that there will be problematic weight gain. Another useful guideline is that if a patient has gained 5 pounds, or 2.2 kg, by week 4 of treatment, there is a 50/50 chance of having a problem with weight gain during further treatment. In my opinion, the fear of potential weight gain should not stand in the way of choosing a medication or implementing a trial with a particular medication. Only knowing the patients' early experience and seeing whether they are gaining weight quickly and/or early can lead to a decision to intervene. In that case, the patients should be advised to reduce calorie intake, to increase exercise, and to not decrease the dose of mirtazapine. Decreasing the dose does not solve this problem and, paradoxically, may worsen it. Some clinicians believe increasing the dose can be helpful. Others see increases as neutral. Finally, there is some experience using histamine H_2 blockers (for example, ranitidine) as a symptomatic remedy for weight gain. My own approach would be to do this only if the patient is treatment resistant since salvaging the antidepressant medication is usually preferable to adding another medication. Switching antidepressants should then be considered for patients who continue gaining a problematic amount of weight despite other interventions.

Dr. Keller: Let's turn to the effects of antidepressants on rapid eye movement (REM) sleep.

Dr. Thase: About 60% to 80% of severely depressed patients enter REM sleep earlier than normal. This phenomenon has been called shortened REM latency or reduced REM latency in the literature. It is a state-independent, or trait-like, marker under some hereditary control. Most antidepressants prolong REM latency. For example, they move REM onset from 45 to 90 minutes or from 60 to 120 minutes. In the small study of depressed patients and mirtazapine, the 15-mg/day dose did not prolong REM latency, whereas the 30-mg/day dose did. This is interesting since it may suggest that the noradrenergic effects of the medication are more pronounced or more biologically apparent at 30 mg/day than at 15 mg/day. Another issue is that the drugs that prolong REM latency and thus push dream sleep into the last few hours of the night are often associated with patient complaints of increased dreaming. This is a paradox, because the patients spend less time in dream sleep, but are more likely to remember their dreams because the dreams are closer to waking or become more intense toward wakening. This is why REM-suppressing medications are frequently associated with complaints of increased dreaming.

Dr. Keller: There were several questions pertaining to the potentially faster onset of action of mirtazapine over SSRIs. In particular, what was the dosing of study medication?

Dr. Thompson: The key is that all these SSRI compounds (i.e., fluoxetine, citalopram, and paroxetine) as

well as mirtazapine were started at known therapeutic doses shown to have been superior to a placebo. Moreover, at all early timepoints where differences in favor of mirtazapine were seen, all drugs were used within recommended therapeutic dose ranges.

Dr. Keller: There was some discussion about the comparative clinical experience with mianserin and mirtazapine.

Dr. Thase: It came up several times in my group, and I will reflect the expert clinician experience rather than my own experience because we do not have mianserin in the United States. About half of our group had extensive clinical experience with both mianserin and mirtazapine. Without exception, the group members who spoke had replaced mianserin with mirtazapine or felt that mirtazapine was either more reliable or more potent in its antidepressant effects or better tolerated, especially with respect to somnolence, compared with mianserin.

Dr. Keller: What combinations of medications with mirtazapine might be recommended?

Dr. Nutt: Pharmacologically, it makes sense to use mirtazapine with SSRIs because the receptor-blocking properties of mirtazapine at the 5-HT_2 and the 5-HT_3 receptors will clearly offset many of the adverse effects of the SSRIs. However, I caution against mirtazapine in combination with very noradrenergic drugs. I have tried this combination a couple of times myself and generally found that the side effect profile is not ideal. While I am comfortable using mirtazapine with SSRIs, I would be reluctant to recommend using it with either monoamine oxidase inhibitors (MAOIs) or noradrenergic uptake blockers.

Dr. Pinder: There are some recent animal pharmacology data showing that combining mirtazapine with typical and some atypical antipsychotics may lead to effects that improve the ratio between developing extrapyramidal symptoms versus improving clinically.

Dr. Gorman: Some members of our group talked about their experience using mirtazapine with children. They reported very good efficacy and tolerability in doses as high as 60 mg/day. That is good news, and we look forward to randomized clinical trials to confirm this clinical observation.

Dr. Keller: Another issue that came out of Dr. Falkai's group was the positive experience with mirtazapine in patients who complain of excessive sweating.

Dr. Falkai: In my experience, mirtazapine, 15 mg/day, was effective in several persons who had excessive sweating as a problem in social situations. It might be that this dosage reduces the inner tension and anxiety to a degree that people can cope better with this unpleasant phenomenon.

Dr. Keller: Another topic of discussion was eating disorders.

Dr. Thompson: There were a couple members of our group who had experience with using mirtazapine to treat anorexia nervosa. There is a concern that with some anorexic patients, the drug might drive appetite and produce bingeing, potentially making the situation worse. However, those who have used mirtazapine in patients with eating disorders have been very pleased, particularly with the dysphoric, ego-dystonic, severely anorexic patients. It is an issue because anorexia nervosa is not a disorder of appetite per se, so we would not have as much concern about appetite issues. Even drugs like SSRIs that decrease appetite can in fact have a beneficial effect in anorexia nervosa for other reasons. It may be that the antiobsessional features of an antidepressant are responsible for the observed improvement.

Dr. Keller: Should we be concerned about a withdrawal phenomenon on abrupt discontinuation of mirtazapine?

Dr. Nutt: Two members of our group observed withdrawal syndrome from abrupt discontinuation of mirtazapine, characterized by marked nausea and sometimes vomiting and that lasted for about a week, which was interesting to me and the others in the group. Both patients had stopped taking the drug without the consent or knowledge of their physician. Obviously, it raises the fundamental issue about how to stop antidepressant treatment. I guess the best advice has to be the advice we give with all medications, which is to taper off slowly rather than just to stop abruptly. Of course, patients often do not understand that and stop taking their medications unilaterally.

Dr. Keller: Have there been any studies on mirtazapine's efficacy in recurrent brief depression?

Dr. Pinder: There are 2 recently published case reports by a group from the Psychiatric University Clinic in Vienna *[Stamenkovic M, et al. Int Clin Psychopharmacol 1998;13:39–40]*. It should be taken into account that recurrent brief depression is a difficult-to-treat illness; for example, SSRIs were found not to be more effective than placebo. In both patients, mirtazapine had a very favorable effect. However, further research is clearly needed.

Dr. Falkai: It is quite interesting that in patients who have been affected by this disorder for years, mirtazapine rapidly decreased the frequency and severity of the brief episodes within 1 to 2 months of treatment.

Dr. Keller: The rate of sexual dysfunction with mirtazapine in everyday clinical practice is not clinically significant. Dr. Hirschfeld, would you summarize the data about the lack of sexual dysfunction with mirtazapine?

Dr. Hirschfeld: The quality that distinguishes mirtazapine from the other antidepressants with almost no exceptions is the postsynaptic 5-HT_2 and 5-HT_3 blockade, at least one of which and probably both of which are helpful in preventing or treating sexual dysfunction. Mirtazapine may also be useful as an adjunctive agent when treating sexual dysfunction caused by other antidepressants, particularly the SSRIs. This is an issue that we want to explore with a randomized, double-blind clinical trial. In

general, in our group, most had very good success with mirtazapine and associated it with positive sexual functioning in patients.

Dr. Keller: We are incredibly appreciative of all of you in the workshop sessions who have shared your clinical experience and asked challenging and provocative questions. We tremendously enjoyed the interchange and found that participants were motivated both to ask the toughest questions they had and to give us the benefit of their experiences. We learned a lot from interaction with each other, and it is particularly helpful to have this opportunity because it gives a "reality check" of clinical practice to complement data from randomized clinical trials. We also appreciate feedback from the audience as to the helpfulness of the information presented. We are trying to communicate the knowledge that we have, either learned personally from our own research or from reviewing other studies, and your feedback has been extremely helpful. On behalf of the panel, I want to thank all of you for enthusiastic participation in the program.