Concluding Discussion

Dr. Jefferson: Dr. Settle, is there any evidence that sildenafil might be useful for treating antidepressant-induced sexual dysfunction?

Dr. Settle: The short answer to that question is that we don't know. There have been no studies done to determine this, and there are few anecdotal reports. I personally have prescribed sildenafil for 3 of my patients who were experiencing sexual difficulties, but it was not beneficial in any of them. Of course, the other issue is that the majority of sexual side effects induced by selective serotonin reuptake inhibitors (SSRIs) are related to orgasm difficulty, which is not really what sildenafil is targeted for.

Dr. Jefferson: Dr. Nelson, can you comment on the difficulties encountered in switching antidepressants? How do you deal with withdrawal effects from the first one, the overlapping of the drugs, and how each may change the blood concentration of the other? Do you wash out? Do you taper down?

Dr. Nelson: In terms of the switching issue, interestingly there is some information that withdrawal reactions are more common with the shorter-acting SSRIs than with fluoxetine because of its long half-life (one situation in which a long half-life may be an advantage). There is an interaction involved in switching that sometimes does produce difficulty. Switching from an SSRI to nefazodone can sometimes result in restlessness, particularly when switching from fluoxetine or paroxetine. The hypothesis is that the cytochrome P450 (CYP) 2D6–inhibiting aspects of these compounds raise blood *m*-CPP (*m*-chlorophenylpiperazine) levels and *m*-CPP is an agonist that causes anxiety, so that particular switch can be difficult. It is possible to switch from one SSRI to another quickly. You might be concerned about additive serotonergic side effects, but if the doses are not high, you can make a switch from one SSRI to another fairly quickly.

Dr. Jefferson: Dr. Nelson, when you use an SSRI/tricyclic combination, how do you dose the tricyclic?

Dr. Nelson: Normally you're starting a noradrenergic tricyclic, so you'd be adding desipramine or nortriptyline.

Dr. Jefferson: What is the dose that you start with?

Dr. Nelson: If the person is taking paroxetine or fluoxetine, start with one third the usual tricyclic dose. So for nortriptyline, the usual dose is 75 mg/day and one third is 25 mg/day. But you should check the plasma drug levels. If the person is taking sertraline or one of the newer agents, e.g., venlafaxine or citalopram, you probably don't need to worry about an SSRI/tricyclic interaction. Remember, though, if you are adding a tricyclic to one of the SSRIs that does not have an interactive effect, you have to be prepared to go up to an average dose of the tricyclic, which for desipramine is 200 to 300 mg/day.

Dr. Jefferson: Another related question is, Well, if this combination works, wouldn't switching from an SSRI to a tricyclic work just as well?

Dr. Nelson: The Peselow study *[Peselow ED, Filippi AM, Goodnick P, et al., Psychopharmacol Bull 1989;25: 272–276]* found a fairly high response rate to a tricyclic in an SSRI failure, but only 15 patients were in that study. This study suggests that if you've used combination treatment and the patient improves, then you should consider whether you can withdraw the first agent and if the patient will do fine on the second agent alone. This logic would apply if you added desipramine or nortriptyline or bupropion. At that point, you might taper the SSRI and see whether the patient does well on 1 agent.

Dr. Settle: I think a real question is, Do you really need both agents? Whenever I augment, I wonder if it is really the combination that's working or just the second agent. It's very difficult to determine.

Dr. Nelson: The largest series was one that Reynolds et al. reported in a group of elderly patients *[Reynolds CF III, Frank E, Perel JM, et al. Am J Psychiatry 1996;153: 1418–1422]*. They were trying to get patients ready for a maintenance trial, so they added perphenazine or lithium to nortriptyline. About a third of the patients received augmentation. When the augmenting agent was stopped, half these patients failed and/or relapsed. But the other half of those individuals that improved with augmentation didn't need to continue with it.

Dr. Jefferson: But they stopped the augmenting agent. What would have happened if they had stopped the initial agent?

Dr. Nelson: I think it depends on the augmenting agent. If you're augmenting with lithium and you're doubtful about the antidepressant value of lithium used alone, I would be hesitant to stop the original drug. If the combination is 2 antidepressants and you think the overall efficacy rates are just as high for the second as for the first, but the person had failed on treatment with the first, you might be tempted then to switch to the second.

Dr. Jefferson: If pindolol is mainly used to speed response, when should we add it to the treatment combination? Another interesting question is, of course, How would you decide when you are going to use pindolol and in which patient?

Dr. Nelson: If you have a patient who is just starting treatment, you would usually not start with a combination treatment. On the other hand, if you have someone in the hospital and you're trying to treat him or her quickly, then

you would think about all of the things that might act more rapidly. The usual pindolol dose is 2.5 mg t.i.d., and you would add it at the beginning of treatment.

Dr. Jefferson: What doses of methylphenidate are used for augmentation in depression?

Dr. Nelson: The usual methylphenidate dose is 10 mg 3 times a day. When it's being given in conjunction with the monoamine oxidase inhibitors (MAOIs), a lower methylphenidate dose is usually used. You can give the first dose in your office and then check the patient's blood pressure to make sure there is not a problem.

Dr. Jefferson: There is a fascinating question submitted by an audience member today. He has a 64-year-old female patient who has been very stable and doing well on treatment with amitriptyline, 250 mg, for 20 years. And the question was, Since we know that there is some danger with tricyclics of ischemic heart disease, and as patients get older they're more likely to have some form of silent ischemic heart disease, should that patient be switched?

Dr. Settle: What I like about that question is that I cannot answer it. It illustrates that no algorithm in the world can capture this kind of information, and this is my objection to treatment algorithms. You see them in the textbooks and they flow so beautifully down the page, but treating depressed patients is a dynamic process and there are simply more variables than any algorithm can capture. There may be some patients you would switch in this group, but there are a lot of patients you would not. Realistically, I probably would not switch that patient unless there was evidence of ischemia. Then I would discuss it with her and go through the odds and let her make that decision along with me. What is important is that lots of questions in clinical medicine and clinical psychiatry can not be captured in an algorithm.

Dr. Jefferson: What are the teratogenic effects of lithium in pregnancy?

Dr. Clayton: With female patients, you must discuss the dangers and problems of taking or not taking the drug they are receiving, either before they decide to become pregnant or when they discover they are already pregnant. I would recommend that this drug be avoided, if possible, during pregnancy, especially during the early part of pregnancy. But there are some patients who really don't want to end treatment with either their lithium or their antidepressant. With lithium, the most common teratogenic effect is Ebstein's anomaly, which consists of tricuspid valve malformation and atrial septal defects. Apparently, it is possible to monitor the heart of the baby at 16 to 18 weeks if that seems to be a concern. Certainly the majority of women who are left on lithium treatment during pregnancy do not have abnormalities, so that risk is low especially if compared with that of other mood stabilizers. I've had several patients who decided to stay on lithium treatment. I had one patient who ended lithium treatment immediately upon learning of the pregnancy and had a very healthy baby. So it's an individual decision that must be discussed with your patient and her family.

Dr. Jefferson: We had a case report presented to our information center about a woman who became pregnant while on lithium treatment. The drug was discontinued, and she had a very rapid and abrupt onset of a psychotic episode during which she murdered her 3-year-old child. So the concept of discontinuing lithium when a patient becomes pregnant has to be weighed against the growing evidence that there is a rebound effect that occurs in many patients if lithium is abruptly discontinued. This can put patients at risk particularly for manic episodes shortly after ending treatment with the drug. At least some experts are recommending that the lithium dose be lowered gradually as pregnancy approaches rather than discontinued abruptly.

Dr. Greist, there are a number of questions here about the availability of computer programs. How do we know that these patients in your study were not having a Hawthorne effect; that is, were they working on behalf of the success of this novel treatment?

Dr. Greist: Many of these patients had extensive treatments in the past that were not beneficial. A Hawthorne effect is possible, but one wonders why it didn't appear or work with previous treatments. We don't have the answers to that question.

Dr. Jefferson: What if patients had a choice of a human therapist versus the computer?

Dr. Greist: Again, 44% had previous psychotherapy for depression. They may have elected to participate because of disappointment with past psychotherapy experiences or for other unrelated reasons. We don't know. One of the advantages we will have in doing these psychotherapy studies is that we can truly dismantle the computer therapies. For example, we can take out the pleasant activities module and see if that makes a difference. It's hard for us to take out part of our repertoire and our way of relating with patients. We feel halfhearted in our efforts to help them if we do. So we don't have all the answers, but this methodology permits us to understand psychotherapy in ways that have been impossible in the past.

Dr. Jefferson: Dr. Greist, have you looked into a comparison between antidepressant medication and COPE, or the combination of the two?

Dr. Greist: Yes, this wasn't a randomized controlled trial, but we made an indirect comparison of COPE with the National Institute of Mental Health (NIMH) collaborative study on the treatment of depression, which compared cognitive behavior therapy, interpersonal therapy, imipramine, and placebo. There was no difference in the outcomes for the mild-to-moderate depression across any of those 4 comparisons or with COPE. I personally would be very reluctant to assign people to any psychotherapy alone if their Hamilton Rating Scale for Depression score is very

much over 20. Adding COPE as an adjunct to pharmacotherapy would be very appealing.

Dr. Jefferson: If a patient is already taking quinidine, a very potent inhibitor of CYP2D6, does it really make a difference what antidepressant you treat the person with?

Well, CYP2D6 should be fully inhibited by quinidine. If you put someone on treatment with fluoxetine or paroxetine, you are not going to magnify that inhibitory effect. At the same time, if you have inhibited CYP2D6 with quinidine, you are likely to get a much higher blood level of a tricyclic in the presence of quinidine. If you knew that CYP2D6 had been inhibited with quinidine, you would start the person on a considerably lower dose. Paroxetine is metabolized by CYP2D6, and perhaps fluoxetine is to a certain degree. You would end up with higher blood levels of those drugs, although they are so safe, it probably doesn't make a big difference.

There are also questions about drug interactions involving nefazodone and buspirone. Buspirone is metabolized by CYP3A4 and nefazodone inhibits CYP3A4. Whether nefazodone inhibits CYP3A4 enough to increase blood buspirone levels significantly requires further study. There has been a study showing marked increases in buspirone levels caused by itraconazole and erythromycin, two more potent inhibitors of CYP3A4 *[BuSpar (package insert). Princeton, NJ: Bristol-Myers Squibb Company; 1998]*. Buspirone side effects appeared as a result. Therefore, by combining buspirone and nefazodone, you may well end up with a higher blood level of buspirone.

Another questioner has noted the apathy/indifference syndrome in a significant fraction (20%–25%) of patients treated with SSRIs and venlafaxine. What dopaminergic agent do you use to counter this apathy/indifference from these serotonergic drugs?

Dr. Settle: I would, as a disclaimer, say that there's no right answer to this question. What I personally use is bupropion, and I've had good results with it. I have a colleague who uses desipramine and has had pretty good results with that. Dr. Nelson, in his discussion on combination treatment, indicated that adding bupropion was potentially safer than adding a tricyclic. In my own experience, bupropion has proved to be safe in countering the apathy/indifference found with serotonergic drugs.

Dr. Jefferson: How do you distinguish major depression from anxiety symptoms and major depression from generalized anxiety disorder (GAD)?

Dr. Clayton: Actually, what I was talking about is a combination of major depression and GAD. Essentially, DSM-IV states that you should not diagnose GAD when it occurs exclusively during major depression. So the authors of DSM-IV think of them as different or mutually exclusive disorders. I would say that GAD is a minor depression (not an anxiety disorder), and when those symptoms continue during a major depressive episode, they predict a more severe, harder-to-treat illness.

Dr. Jefferson: Does seasonal affective disorder (SAD) occur less frequently near the equator?

Dr. Clayton: Yes. The preponderance of evidence indicates that the prevalence of SAD increases with distance from the equator.

Dr. Jefferson: Do you recommend light therapy in postpartum depression?

Dr. Clayton: It was my own suggestion from reading the literature. If the depressive episode is the mild depression that occurs in the fall, then I would certainly try it. Light therapy is a fairly benign treatment, and the results occur quickly. Also, you can give additional treatment if light therapy does not work, or it can be used as an adjunct form of therapy.

Dr. Jefferson: What about using computer measures or computer therapies as an adjunct?

Dr. Greist: I think that's an excellent use of computer-administered assessments and guides to self-help therapies. We should use computer tools to complement, supplement, and reinforce the things that clinicians do. There are many things we want our patients to have and do but don't have the time or money to provide them without using computer aids.

Dr. Jefferson: The last question to me was related to eating asparagus and forming a malodorous urine. It makes a point that perhaps it is not whether or not people put out a malodorous urine when they eat asparagus, but perhaps there is a genetic polymorphism that allows some people to smell the odor and other people to not smell the odor.

Actually there may be 2 asparagus genetic polymorphisms. One that produces or does not produce the odorous urine and the other that allows or does not allow the odor to be recognized.

On another subject, treatment resistance may be in part due to subtherapeutic dosing, yet elderly patients are often started on and remain on low doses. At the same time, elderly patients are more sensitive to antidepressant side effects. How do you balance this?

Dr. Nelson: That's an excellent question and a tough one. Most neurotransmitter systems are declining in the elderly and, as a result, older patients are more sensitive to drugs that block neurotransmitters, for example, anticholinergic drugs. Alternatively, the therapeutic value of antidepressants in the elderly is accomplished by enhancing neurotransmission. This presents a dilemma. You need to "start low" and "go slow" in order to determine if the person can tolerate the drug, but we ought to add something like "keep going." You do not stop with a low dose. You keep going with gradual dose increases until you reach a full dose in order to be sure you achieve an adequate response.