Conclusions

Side Effects of Antipsychotic Medications: Physician's Choice of Medication and Patient Compliance

Dr. Meltzer: We brought up the issue of the patient perspective on side effects. If you were a patient, given what you heard today about the side effects of the typical and atypical antipsychotics, would you want to take a typical neuroleptic first? Would side effects determine your choice?

From a societal perspective, we have raised ethical issues and cost issues. Are there ethical issues that society should be concerned about? The cost-effectiveness issue is an important one. How does one weigh, on one hand, the costs of noncompliance, relapse, and rehospitalization against the increased costs of atypical antipsychotics on the other? Should the cost issue be considered? We must also consider whether a side effect—namely, agranulocytosis in schizophrenic patients taking clozapine—has been exaggerated beyond its real significance and whether doctors are avoiding its use out of an exaggerated sense of the frequency and poor outcome of agranulocytosis.

Probably the most important perspective here is that of the clinician. Should doctors make decisions about what drug to use in these various indications—whether in the adult schizophrenic patient, the elderly schizophrenic patient, the patient with dementia, or the patient with a mood disorder—on the basis of side effects?

Dr. Garver: If I were a schizophrenic patient, I would want my next psychotic episode to be treated with an atypical antipsychotic.

Dr. Miller: I used to point out that my patients with schizophrenia never thanked me for care. That changed with the use of clozapine. Today, it is very common for young people I have treated with atypical antipsychotics to come back and say, "I'm feeling better. Thank you." It is not hard to know what a patient would want to do. I have patients who are clearly pleased with their treatment, considering the terrible illness they have to deal with. They still have problems. The outcome fails to be perfect, but a substantial number of my patients are pleased with their lives, which was hardly true 15 years ago. On the other hand, dramatic recoveries in patients taking clozapine were accompanied by tremendous weight gain. Patients had the choice of continuing to take the drug or becoming intractably psychotic again, which is still a terrible choice. Almost all of these patients have chosen to continue to take clozapine.

Dr. Blackburn: In quality of life, what higher outcome could one have than patients sending a card saying, "Thank you," which means that they are functional and independent and their families are relieved of their pain. This is a new definition of outcome, and it is very difficult to know what costs to associate with this outcome.

Dr. Arana: I agree. If we say nothing else today, we should emphasize that cost should not be a factor in determining treatment for psychotic patients. The new medicines have their toxicities, but they are safer than the old ones.

Dr. Masand: What cost do you assign to quality of life? What is the cost of being able to interact with your child, go out to a movie, or have less akinesia and tardive dyskinesia?

Dr. Meltzer: A previous roundtable of this kind dealt, in fact, with cost-effectiveness issues. When most people consider cost, they think about cost minimization. All they are looking for is a drug or new treatment that will reduce the total cost of the illness. But cost-utility deals with quality of life. Cost-effectiveness deals with criteria like a change in the Brief Psychiatric Rating Scale score or a patient's return to work. With these criteria, these new treatments are very cost-effective. And most important, a cost-utility model can show that the cost of obtaining these advantages for patients with schizophrenia are well within the range of what society is willing to pay for cost advantages in medical illnesses. The cost issue should never preclude the use of atypical antipsychotics. The direct costs of schizophrenia are $17 to $20 billion a year; the indirect costs are $20 billion a year. If every patient in the United States were taking one of these medications, the bill would be $4 to $6 billion a year. There would be offsets in terms of decreased hospitalization and a significant return to work, particularly in line with some enlightened policies about Social Security. We must communicate this message to payers.

It is unethical, certainly, to deny patients access to atypical antipsychotics because of cost. We hope all rational people would agree. Ethical issues have been raised around simply exposing patients to the risk of tardive dyskinesia with the use of conventional antipsychotics. In a 60-year-old patient, there is a 50% risk of tardive dyskinesia in 3 years, and there is a 25% risk in a 20-year-old. How important is tardive dyskinesia to this group as a reason for not exposing patients to typical neuroleptics?

Dr. Masand: The risk of tardive dyskinesia is probably the most important reason not to expose patients to con-

ventional neuroleptics. Clinicians who prescribe conventional antipsychotics seldom discuss the relative risks of conventional neuroleptics and alternative treatments available with a lower risk of tardive dyskinesia in the patient. Patients are seldom allowed to choose their treatment or provide informed consent, an opportunity they have in virtually every other field.

Dr. Meltzer: When psychiatrists explain treatment options to patients, they should have to tell them that there are risks of tardive dyskinesia with the use of typical neuroleptics that are much reduced with the use of atypical antipsychotics, which might represent an increased risk for sexual dysfunction or weight gain. If that practice became a standard in the field, pharmacy benefits managers who impede the free use of atypical antipsychotics might be liable to legal action if they failed to require informed consent.

Dr. Conley: Tardive dyskinesia is an unfamiliar term for a side effect. When patients at our center are making the decision about which medication to begin, we show them a video of someone who has moderate tardive dyskinesia and say, "This is what tardive dyskinesia is." It is difficult for the patient alone to recognize in the early stages.

Dr. Zarate: Patients might call tardive dyskinesia tics, shakes, or something else.

Dr. Masand: If a heart, lung, or cancer medication had a side effect as devastating as tardive dyskinesia, doctors would be obliged to tell patients about it before they chose a treatment, but somehow we presume that psychiatric patients lack the privilege of choosing their own treatment and that we as clinicians have the right to choose for them. Patients, when shown a video, are able to make a decision for themselves: It is a fairly simple choice of the side effects of one drug versus those of another.

Dr. Miller: We obviously should bring up the issue of weight gain with our patients.

Dr. Conley: We also do that at our center, but patients do not have to watch a video to understand weight gain. Weight gain has much greater medical consequences than tardive dyskinesia does.

Dr. Masand: I agree. Weight gain should be taken into consideration when looking at long-term morbidity and mortality. Tardive dyskinesia is more distressing to the patient than the morbidity and mortality of weight gain.

Dr. Meltzer: The difference is that clinician and patient have very little control over whether tardive dyskinesia emerges. Weight gain, unlike tardive dyskinesia, is a potentially treatable or preventable side effect. We must be attentive to weight gain from the day the patient begins treatment.

Weight gain is a challenge, also, to the pharmaceutical industry. There is a massive effort being made right now to understand satiety and weight gain. We hope for a breakthrough.

Dr. Masand: We need to raise awareness of medical illnesses in schizophrenic patients. A basic physical exam is important at baseline and on a 1-year or 2-year basis in psychiatric patients. Weight and waist circumference should be measured at baseline and periodically thereafter, because there is evidence that both are associated with morbidity. We see psychiatric patients with medical comorbidity that has proceeded beyond the point at which interventions can be fairly simple, because symptoms were neglected or ignored by the physicians and patient. Medical evaluations are an important part of psychiatric treatment.

Dr. Meltzer: Someone comes into an outpatient clinic who has been noncompliant but is not so ill that hospitalization is needed. One must decide on a medication for that patient. How do side effects affect your choice?

Dr. Arana: The first-line treatment for first-episode major psychotic illness in a drug-naive patient should be the atypical antipsychotics. Atypical antipsychotics are the treatment of choice for psychosis. Conventional antipsychotics are very effective but extremely toxic. If a patient has been taking haloperidol and doing well for 10 years with no dyskinetic movements, the decision to switch to atypical antipsychotics is less straightforward, but I would think about moving that patient—especially one over 50 years old—to an atypical antipsychotic.

Dr. Meltzer: Which atypical antipsychotic would you use?

Dr. Arana: I would start the patient taking risperidone first and then ziprasidone, but if that drug fails to win approval, my second choice would be olanzapine.

Dr. Garver: The choice is determined largely by the patient's previous history. If the patient is particularly sensitive to extrapyramidal side effects (EPS), olanzapine or quetiapine induce the least amount of EPS of the atypical antipsychotics. If the patient has a weight problem, avoid olanzapine or clozapine. If the patient has been refractory to previous medications, then use clozapine. In the patient who has a first psychotic episode without a known history of response to medications, the point is debatable.

Dr. Masand: When conventional antipsychotics are used, a fairly high percentage of patients have EPS. And then the question arises—how does one define a significant problem for the patient? Does everybody who had parkinsonian side effects or akathisia and complained have a significant problem? A related issue is whether patients were given too high a dose of the conventional antipsychotics. If those patients are then given an adequate dose of an atypical antipsychotic—4 to 6 mg/day of risperidone, 10 to 15 mg/day of olanzapine, or 300 to 450 mg/day of quetiapine—do any data show that the rates of EPS are substantially higher with one of these atypical antipsychotics than another, even though risperidone undoubtedly causes more dose-dependent EPS than olanzapine or quetiapine do? Do any data suggest that somebody who had EPS when taking haloperidol is more likely to be noncompliant taking 4 to 5 mg/day of risperidone than

taking 10 to 15 mg/day of olanzapine or 400 mg/day of quetiapine?

Dr. Meltzer: If one wants to use risperidone in a patient who is very sensitive to EPS, one would try very hard for a response to a low dose. If one wants to use olanzapine in a patient who had a weight gain problem, one would monitor weight closely and be ready to change medications quickly if weight gain became a problem. My colleagues and I have focused intensely on side effects, but side effects are seldom the only basis upon which a good clinician will make a decision. Still, side effects are important enough that—along with efficacy—they contribute to the view that we should be using atypical antipsychotics in virtually all circumstances. Until we have a long-acting atypical antipsychotic, though, we will need to use a long-acting typical neuroleptic for a number of patients. For some acute emergency-room situations, for example, until we have a fast-acting, fairly sedating atypical antipsychotic, we will use something like haloperidol. But for most circumstances, we can confidently recommend atypical antipsychotics as the drug of choice for treating schizophrenia.

Dr. Conley: We need more data addressing when weight gain occurs. It looks as though weight gain appears early in the course of drug treatment, but we cannot rule out a delayed weight gain. In my colleagues' and my adolescent study [*Kelly DL, et al. J Child Adolesc Psychopharmacol 1998;8:151–159*], weight gain usually occurred within the first 6 weeks. Whether this pattern is typical remains to be seen.

Dr. Meltzer: The data we have about the proportion of people who gain weight come from many studies done for different reasons. They do not necessarily reflect community practice, which regularly includes polypharmacy. We know that weight gain is a problem in many patients, but we lack data to tell us how many.

Dr. Masand: We know that a 5-lb weight gain identifies somebody at high risk for weight gain and that at this point some intervention—dietary, nutritional, exercise—should be attempted.

Dr. Blackburn: The Nurses Health Study [*Colditz GA, et al. Int J Sports Med 1997;18(suppl 3):S162–S170*] showed that it takes four 5-lb increments for the patient to be at relative risk for mortality. A simple lipid profile is part of the U.S. Preventive Services Task Force guidelines [*Whelton PK. J Gen Intern Med 1990;5(suppl 5):S17–S19*] for risk assessment. An adult baseline lipid factor measurement at baseline allows one to compare later readings and assess whether a patient is comorbidly weight sensitive.

Dr. Zarate: But what has clinical experience indicated about a patient's ability to lose excess weight once gained?

Dr. Masand: And at what point of time, if the patient has failed to lose the weight, is it reasonable for the clinician to say, "This antipsychotic is not the right one for this patient; let's switch to another"?

Dr. Blackburn: That question can be answered easily. Take each one of your units, go back a year, and consecutively take the entry—either outpatient or inpatient—of a consecutive series of patients. Have them analyzed independently, and then characterize the change of weight over that year—20 patients, 5 units, 100 subjects.

Dr. Arana: Weight gain is an issue in drugs other than the atypical antipsychotics. If one had to choose between tardive dyskinesia in typical neuroleptics and weight gain in atypical antipsychotics, one would be faced with a conundrum. Weight gain occurs in patients taking conventional neuroleptics as well as atypical neuroleptics. Its onset probably fails to be as fast as with the atypical antipsychotics, but it will appear.

Dr. Blackburn: A consecutive series of entries from 5 sites will yield a demographic characterization of how big or little the problem is.

Dr. Meltzer: The clozapine U.S. multicenter trial was performed out of concern about tardive dyskinesia rather than looking for increased efficacy in treatment-resistant patients. A television news program had reported on tardive dyskinesia, and a public outcry ensued. Two colleagues and I went to the U.S. Food and Drug Administration to propose clozapine as a solution. There was so much concern about agranulocytosis that we were only allowed to perform a study in treatment-resistant patients. Perhaps we have reached that point of awareness with weight gain now, and it will become the specific focus of clinical research. Studies will answer our questions. We lack knowledge of what interventions will work, what we can do, and what can be reversed.

Dr. Masand: Certain side effects are overestimated in terms of their problems by clinicians—agranulocytosis and prolactin elevation in the absence of amenorrhea, for example. Clinicians fail to use certain drugs because of concerns about side effects that are not supported by the data.

Dr. Miller: People in the general population who are overweight and try to lose weight find it very difficult and have little success. Why would this be different among patients with schizophrenia, where much more sophisticated methods have been tried?