The Mount Sinai Conference on the Pharmacotherapy of Schizophrenia

by Stephen R. Marder, Susan M. Essock, Alexander L. Miller, Robert W. Buchanan, John M. Davis, John M. Kane, Jeffrey Lieberman, and Nina R. Schooler

Abstract
This report summarizes the recommendations from a consensus meeting that focused on specific questions regarding the pharmacotherapy of schizophrenia. The issues were selected because there was evidence that experts had recently disagreed about the evidence supporting a particular practice or when there were substantial variations in a clinical practice indicating that there was disagreement among clinicians. The group of experts was able to reach a consensus regarding the evidence base pertaining to the following issues: First generation (FGAs) and second generation (SGAs) antipsychotics as first line agents; the duration of antipsychotic trials; the effectiveness of clozapine and other agents for treatment refractory schizophrenia; risk of tardive dyskinesia on FGAs and SGAs; differences among antipsychotics for different dimensions of psychopathology; and side effect monitoring for various antipsychotics.

Keywords: Schizophrenia, antipsychotics, tardive dyskinesia, evidence-based practice, clozapine.


There is broad agreement that pharmacotherapy in schizophrenia should be evidence based. With this goal in mind, a number of groups—including the Schizophrenia Patient Outcome Research Team (PORT) (Lehman et al. 1998), the Department of Veterans Affairs (VA) (Mental Health Strategic Health Care Group and The Psychosis Working Group 1997), the American Psychiatric Association (APA) (APA 1997), the New York State Office of Mental Health (OMH) (personal communication, Molly Finnerty, September 6, 2001), and the Texas Medication Algorithm Project (TMAP) (Miller et al. 1999)—have reviewed the literature and formulated recommendations for the prescribing of antipsychotic medications for the treatment of schizophrenia. The recommendations of these groups differ on important points. The differences exist for a number of understandable reasons including the evidence available at the time the review was carried out, the process of selecting evidence, the threshold for judging when the evidence is sufficient to support the creation of a treatment recommendation, and the viewpoint of the individuals who interpret the findings.

The Mount Sinai Conference was a gathering of individuals who had done the background research for and developed these various clinical guidelines. It was hoped that these individuals could reach a consensus about whether the evidence base concerning antipsychotic prescribing for the treatment of schizophrenia was clear enough to support establishing a particular clinical practice as a treatment standard. The identification of such evidence-based treatment standards could then be used by any groups creating treatment algorithms, performance standards, clinical prompts, quality-review mechanisms, or other tools to improve antipsychotic prescribing practices. The conference focused on treatment issues that arise frequently in routine practice where there is practitioner disagreement, as evidenced by broad variations in prescribing practices. Participants sought to pinpoint such areas and to identify what, if anything, the evidence would support as a best practice. Many important issues in pharmacotherapy were not discussed because they were not considered controversial. As a result, the conference did not produce a comprehensive approach to drug treatment for schizophrenia. Because the timing of the conference (September 6, 2001) corresponded to the updating of TMAP, the VA Guidelines, PORT, and the New York State OMH Guidelines, the products of the conference, reported here, may help minimize differences among these documents and their successors (e.g., the Robert Woods Johnson–Substance Abuse and Mental Health Services Administration Evidence-Based Practices Toolkit).

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A list of questions was developed by the meeting organizers—Susan Essock (Mount Sinai School of Medicine, New York), Stephen Marder (University of California at Los Angeles), and Alexander Miller (University of Texas Health Science Center at San Antonio)—and circulated to participants. Participants were asked to assist in further shaping the list. At least two panel members were assigned to each of the questions, and those individuals summarized the evidence base and led the discussion pertaining to the issue at hand.

Participants in the conference were selected based on their knowledge of and contributions to the literature in this area and their respective roles in groups charged with formulating evidence-based recommendations. In addition to the organizers, topic experts included John M. Davis (University of Illinois, Chicago), Jeffrey Lieberman (University of North Carolina), Robert Buchanan (University of Maryland), and Nina Schooler (Hillside Hospital–Long Island Jewish Medical Center). John M. Kane from Hillside–Long Island Jewish Medical Center provided written comments. Also in attendance representing various groups concerned with improving psychopharmacology in routine practice settings were Nancy Covell (Connecticut Department of Mental Health and Addiction Services), Molly Finnerty (New York State OMH), Thomas Mallman (Dartmouth Medical School), Mona J. Ritchie (VA Mental Health Quality Research Initiative), Scott Stroup (University of North Carolina), William Torrey (Dartmouth Medical School), and Ellen Weissman (Bronx VA Medical Center). The conference addressed a finite number of questions, and all of the questions involved pharmacotherapy for schizophrenia. The opinions of this group cannot be viewed as a summary of the state of evidence-based practice for the pharmacotherapy of schizophrenia because well-established issues were not addressed. Rather, the focus was on certain critical questions where prescribing practices or reports in the literature indicated that there was controversy as to whether the evidence base is or is not sufficient for formulating treatment recommendations.

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Below, we list the questions these attendees addressed—questions for which the evidence base was deemed adequate to reach a consensus as to what constituted an evidence-based best practice. For each question, we discuss the group’s consensus opinion about that best practice and offer a summary of the evidence base underlying the consensus. The level of evidence for each recommendation was graded using a modification of the rating scheme published in the U.S. Preventive Services Task Force Guide to Clinical Preventive Services, Second Edition (U.S. Preventive Services Task Force 1996). For this report, Level 1 evidence was supported by randomized clinical trials; Level 2 evidence was supported by nonrandomized studies such as mirror image studies or well-designed cohort comparisons; Level 3 was supported by expert opinion. The evidence level is documented with each Consensus Opinion.

Question 1. Should conventional agents still be considered first line agents?

Consensus Opinion. The term “first line” is imprecise because it can be interpreted differently for patients who have been treated with an antipsychotic medication and those who have not. We use the term “first line” to include agents that can be prescribed for a broad range of individuals with schizophrenia, including patients experiencing a first episode of schizophrenia (but see Question 2, below, for an exception with respect to the first line agent ziprasidone), patients who have a medication-responsive illness but whose obtainable drug history is inadequate, and patients who have responded to other antipsychotics but have been switched to new agents. A “second line agent,” as the term is used here, is an agent with demonstrated efficacy but with a risk or use profile that necessitates that it be prescribed when there is clinical evidence that first line agents are ineffective or poorly tolerated. By this definition, in the United States today, clozapine, mesoridazine, and thioridazine are second line antipsychotic agents.

First generation antipsychotics (FGAs) are those conventional antipsychotic medications that preceded clozapine’s entry into the antipsychotic armamentarium. Second generation antipsychotics (SGAs) include clozapine and those agents brought to market following clozapine: risperidone, olanzapine, quetiapine, and ziprasidone. Although the SGAs are discussed as a group, they are heterogeneous medications with different side effect profiles. (Question 7 addresses issues regarding the relative efficacy of SGAs.) But all SGAs are associated with fewer extrapyramidal side effects (EPS) than FGAs when prescribed at effective doses.

SGAs—other than clozapine and ziprasidone, as discussed below—should be selected before FGAs for patients experiencing a first episode of schizophrenia or for patients whose history of response to antipsychotics is not available. (Level 1)

FGAs may be appropriate for the following groups of patients: (1) patients who have responded well to conven-
tional antipsychotics without experiencing EPS, (2) patients who have responded better to FGAs than to SGAs, and (3) patients who have responded better to long-acting depot medications than to oral antipsychotics. (Level 3)

**Background.** The clearest advantage of SGAs involves safety. As will be discussed in Question 5, there was a consensus that SGAs are associated with a reduced risk of tardive dyskinesia (TD). There is also convincing evidence that SGAs are associated with reduced EPS compared to conventional drugs and that the effect sizes for these differences are medium to large (Leucht et al. 1999). Because EPS are one of the important factors in nonadherence to medication and one of the drivers of the subjective response to an antipsychotic, this potential adverse reaction should receive the close attention of antipsychotic prescribers. One of the important difficulties in managing EPS is that many patients will experience akathisia and other forms of EPS at the antipsychotic doses that are needed for managing their illness.

A meta-analysis by Geddes and coworkers (2000) took the position that there is insufficient evidence to conclude that SGAs offer a safety advantage. The authors agreed that there was an EPS advantage for SGAs, but they suggested that this should be weighed against the other side effects of these agents, such as weight gain. However, conference participants agreed that the high prevalence of EPS with conventional agents and the higher risk of TD outweighed the differences in liability for weight gain. Moreover, if patients demonstrate early evidence of weight gain, there are alternative medications such as ziprasidone that can be prescribed.

The evidence supporting superior efficacy and effectiveness of SGAs remains controversial. The previously cited meta-analysis by Geddes and colleagues found that efficacy advantages for SGAs over conventional drugs tended to occur when patients received relatively high doses of haloperidol as the comparison medication. The researchers found that when studies used doses of haloperidol below 12 milligrams daily, there were no advantages in efficacy for the newer agents. The meta-analyses by Leucht and colleagues (1999) found that when there were statistically significant advantages for newer drugs over older drugs, the effect sizes tended to be very small. These results differ from a recent meta-analysis (by J.M.D.) that compared SGAs and conventional antipsychotics in controlled trials. Effect sizes for the advantages in efficacy of clozapine, risperidone, and olanzapine over FGAs were 0.54, 0.22, and 0.21, respectively. The effect sizes were 0.00 for quetiapine and −0.08 for ziprasidone, suggesting that these agents demonstrated effectiveness similar to FGAs’. To provide a perspective on these effect sizes, Davis noted that the effect size for haloperidol versus placebo using similar methods was 0.54. There were fewer studies of quetiapine and ziprasidone, and these agents were studied at later dates than the other agents. As a result of being studied later, patients may have entered these trials after already failing to respond to other SGAs. If such individuals are less likely to respond to any medication, this would put these agents at a disadvantage and may explain, at least in part, the smaller effect sizes observed.

There is also evidence supporting advantages for SGAs for treating patients who are experiencing their first psychotic episode. A number of studies—usually industry sponsored—have randomly assigned first episode patients to newer or older drugs and found advantages for the newer agents. A large international study (Emsley 1999) randomized 183 patients to either risperidone or haloperidol and found that response rates were high on both drugs. Risperidone was better tolerated and led to fewer dropouts due to side effects. In a large multicenter study (Sanger et al. 1999) that compared olanzapine and haloperidol, a subgroup of 83 patients was recovering from a first episode. These recent-onset patients demonstrated a better response to olanzapine than haloperidol for both positive and negative symptoms. Moreover, patients taking olanzapine tended to demonstrate improvements in EPS while patients taking haloperidol worsened. Although we are unaware of controlled studies of quetiapine and ziprasidone for first episode patients, the medications’ side effect profiles indicate that they also may offer safety and tolerability advantages for these individuals (but see Question 2, below, for a caveat concerning ziprasidone).

**Question 2. Should ziprasidone be a first line agent?**

**Consensus Opinion.** The cardiac safety of ziprasidone will become clearer as greater numbers of patients are exposed to this agent. Until sufficient information is available on the rates of arrhythmias or sudden death on ziprasidone, this antipsychotic should be prescribed only when patients have received a trial with another SGA. This is consistent with ziprasidone’s package insert, which states that this drug’s tendency to prolong the QT interval would lead in many cases to the conclusion that “other agents should be tried first.” Note that this recommendation simply states that an agent other than ziprasidone should be selected as the first antipsychotic a person will ever receive. After that first antipsychotic, ziprasidone would be considered alongside the other first line antipsychotics (i.e., alongside all SGAs except clozapine). (Level 3)
Background. Ziprasidone is associated with prolongation of the QT interval of the electrocardiogram. This is a serious concern because excessive prolongation can lead to a potentially fatal ventricular arrhythmia known as torsades de pointes. A study mandated by the U.S. Food and Drug Administration (FDA) prior to ziprasidone’s approval found that the amount of prolongation was relatively brief and did not lead to patients reaching durations, such as 500 milliseconds, that have been associated with an increased risk of arrhythmia. However, the risk of arrhythmia associated with ziprasidone will become clear only after a large number of patients have been exposed to the drug. Postmarketing data for ziprasidone (as of 10/01) with more than 150,000 patient exposures have revealed no deaths that could be attributed to arrhythmias.

Question 3. What is an adequate trial? Is a 4-, 6-, 8-, or n-week trial sufficient? If these cutoff points were used, how many individuals would be discontinued from a medication that they would have responded to had the trial duration been longer? Are there individual characteristics that predict a slower or faster response? Are there reliable early predictors of eventual response? And are the answers to these questions different for different medications?

Consensus Opinion. Patients who have received an antipsychotic for 1 week at therapeutic doses for an acute exacerbation and have not demonstrated any evidence of improvement may be unlikely to respond robustly to that antipsychotic during that episode. However, it takes up to 4 weeks on full therapeutic doses to demonstrate convincingly that a patient should be considered a nonresponder to that regimen. If patients demonstrate a partial response, the trial should be extended to as long as 12 weeks in the face of a continuing partial response. (Level 2)

Background. In general, studies suggest that if a patient fails to demonstrate even minimal improvement after 4 weeks on an adequate dose of an antipsychotic, it is unlikely that the patient will respond to a longer trial. However, there is relatively little information from controlled clinical trials on the relationships among trial duration, antipsychotic dose, and treatment response that might help guide decision making about trial duration. In one of the few studies to address this issue, Janicak and colleagues (1997) examined patients’ responses to low, medium, and high antipsychotic doses. There were no differences in the rates of treatment response among the three groups. Patients who failed to respond to either low or high doses tended to have a better response when they were switched to medium doses. The results suggest that there is a subgroup of patients whose treatment response is dose dependent, whereas the responses of most patients—as long as doses are above some minimum level—are relatively independent of dose.

There is evidence indicating that patients who receive an antipsychotic that is effective for them will continue to improve over several months, although most of the improvement will occur during the first weeks of treatment. A study by Goldberg and coworkers (1967) followed the course of improvement of 250 schizophrenia patients who received antipsychotics. All symptoms changed between baseline and a 5-week rating; symptoms that would currently be classified as negative or disorganized did not demonstrate further improvement; and symptoms that included hallucinations, delusions, and hostility demonstrated further significant improvement between weeks 5 and 13 but not between weeks 13 and 26. Global ratings using the Clinical Global Impression found that patients continued to demonstrate improvement during the entire 6-month period. This slow trajectory of improvement in partial responders was confirmed in a study by Lieberman and colleagues (1993). Using stringent improvement criteria in first episode patients, the authors found that the mean time to remission was 35.7 weeks (standard deviation [SD] 7.8) and the median time was 11 weeks (SD 1.4).

Question 4. What is the relative effectiveness of clozapine and other second generation agents for treatment-refractory patients? How many failed trials, of what, should patients have before they receive clozapine?

Consensus Opinion. Clozapine appears to be the most effective antipsychotic for treatment-refractory patients. (Level 1) For this reason, patients should not be considered partial responders or nonresponders until they have had an adequate trial with clozapine. Clinicians should assess a patient’s response to at least one SGA before beginning clozapine. (Level 3)

Background. The evidence that clozapine is more effective than conventional agents for patients who have been treatment-refractory is substantial. A number of studies
have randomly assigned treatment-refractory patients to clozapine or a conventional agent and found substantially higher response rates on clozapine than the conventional agent (Essock et al. 2000; Kane et al. 2001).

The evidence is less clear when clozapine is compared to an SGA. A number of controlled studies have found that both risperidone (Bondolfi et al. 1998) and olanzapine did not differ significantly from (were equivalent to) clozapine in treatment-refractory populations. These studies have been criticized on grounds of inadequate sample size, exclusion of primarily treatment-refractory patients, and inadequate dosage of clozapine. A recent study comparing risperidone and clozapine found advantages for clozapine in treating a range of psychotic symptoms. A preliminary analysis of a 29-week trial comparing clozapine and risperidone in treatment-refractory patients (N.R.S.) found similar response rates on the two agents. However, significantly more patients were discontinued for lack of efficacy with risperidone than with clozapine.

A study by Conley and coworkers (1999) compared olanzapine and chlorpromazine in a group of severely ill treatment-refractory inpatients. Both groups did poorly, with very low response rates. However, when poor responders were later changed to clozapine, 41 percent met a priori response criteria. This suggests that, in the most severely ill patients, there is an advantage to clozapine over other SGAs.

Other evidence indicates that SGAs are more effective than FGAs for patients who are treatment-refractory. Studies with both risperidone (Wirshing et al. 1999) and olanzapine (Breier and Hamilton 1999) have found evidence of advantages for newer agents when they were compared to haloperidol. In both studies, the advantages of the SGA were relatively small when compared to the advantages of clozapine over an FGA. However, in both studies there was even stronger evidence indicating that risperidone and olanzapine were better tolerated than haloperidol. A limitation of these studies is that treatment refractoriness was usually defined by a poor response to a conventional agent as opposed to a different SGA. This definition may have given a substantial advantage to the SGA being evaluated. Nevertheless, these studies suggest that there may be individuals who will improve when they are changed from an FGA to an SGA. On balance, it appears that there is some evidence for efficacy of other SGAs over FGAs. The evidence is not as clear as the evidence for clozapine. However, given clozapine's side effect profile and the need for blood monitoring, it is reasonable to give patients a trial on a more easily administered SGA before moving to clozapine. The evidence that trials of more than one SGA prior to clozapine have a reasonable likelihood of success remains to be developed.

Question 5. Is there sufficient evidence to conclude that second generation antipsychotics have a lower TD risk?

Consensus Opinion. There is sufficient evidence to conclude that SGAs are less likely to cause TD than FGAs are. (Level 1)

Background. There is evidence that newer antipsychotics are associated with a reduced risk of causing TD. The best evidence is for clozapine (Kane et al. 1993). A study of olanzapine (Tollefson et al. 1997) and a study of risperidone in elderly patients (Jeste et al. 1999) both indicate that the SGA was associated with a reduced risk of TD. Although these studies are not conclusive, they suggest that the risk of TD will be reduced when patients are changed to a newer drug. Other preliminary reports with risperidone and quetiapine support the lower incidence on newer drugs. These findings also suggest—although they do not prove—that patients who have TD may demonstrate greater improvement in their movements if they are managed with an SGA.

Because the design of studies that would provide such proof raises ethical concerns, it is unlikely that evidence will emerge during the next several years proving or disproving that SGAs are associated with a reduced risk of TD. However, the evidence that SGAs are less likely to cause TD is substantial and should, therefore, guide antipsychotic drug selection.

Question 6. Are there characteristics of individuals that should influence drug prescribing?

Consensus Opinion. In terms of efficacy considerations, there is no evidence that personal or demographic characteristics should guide drug selection. For nonadherent patients, both depot medications and SGAs should be considered before FGAs. Side effect concerns should be central to medication selection. (Level 3)

Background. Aside from the previously discussed advantages for clozapine in severely ill refractory patients, there is no evidence that any one antipsychotic is particularly effective for any given population. On the other hand, the participants were unaware of controlled trials that addressed this issue.

There is evidence from double-blind controlled trials that patients who have a history of poor adherence to taking pills are likely to respond better to long-acting antipsychotics. Open-label studies found even larger differences favoring depot over oral treatment (Johnson
The difference probably results from the types of patients who enter these studies and the treatment conditions. Open-label studies usually take place in routine practice settings and include typical patients who may be unreliable pill takers. Double-blind studies usually include individuals who are selected in part because they are perceived as likely to be cooperative and to adhere to the prescribed medication regime. Also, these studies tend to have enriched staffs, and they may provide an unusually high quality of clinical care. As a likely result of these differences, double-blind studies are less conclusive. In a review of six studies, Davis and colleagues (Davis et al. 1993) found that the results favored depot in five. When the results were weighted for sample size, there was a significant difference favoring depot. In addition, the comparison that lasted the longest (2 years) (Hogarty et al. 1979) found an advantage for depot in the second year, but only for patients who did not relapse during the first year.

There are side effect differences that should guide the selection of antipsychotics. These can be related to gender (prolactin elevation), age (hypotension, TD), and physical condition (weight, diabetes, anticholinergic effects).

Question 7. Are there differences among antipsychotics—FGAs or SGAs—in their effectiveness for positive, negative, neurocognitive, aggressive, and mood symptoms?

Consensus Opinion. 1. For positive symptoms, there is no convincing evidence of differences among antipsychotics, with the exception of clozapine’s greater effectiveness in treatment-refractory patients.

2. Some SGAs produce greater improvement in negative symptoms than FGAs, but the evidence is not conclusive as to whether these changes are due to improvements in primary or secondary negative symptoms or to improvements in both.

3. SGAs may offer benefits for neurocognition, but the evidence is still preliminary and awaits randomized double-blind trials.

4. Clozapine may be more effective than conventional antipsychotic medications in reducing aggression. (Level 2) There is insufficient evidence to determine the ability of other SGAs to reduce aggression.

5. Some SGAs, including clozapine, are more effective than FGAs for relieving mood symptoms. (Level 1)

Background. As noted in Question 1, the relative effectiveness of FGAs and SGAs has generated controversy. The meta-analysis by Leucht and colleagues (1999) indicated that even where there were significant differences between older and newer drugs in positive symptoms, the effect sizes were small.

Double-blind comparisons of SGAs have been carried out by the pharmaceutical industry (Tran et al. 1997; Conley and Mahmoud 2001). Although these studies have found significant differences favoring one agent or another for positive or negative symptoms, these differences are inconsistent among studies and could have been accounted for by dosing that favored one of the agents. Comparisons between clozapine and other SGAs were discussed under Question 4. Some of these studies found slight advantages for clozapine or the comparator drug, but the effect sizes were overall rather small. Most studies found that patients treated with clozapine experienced more side effects, but the raw number of side effects experienced may be less important than patients’ discomfort with the particular side effects they experience.

The meta-analysis by Leucht and colleagues (1999) found that treatment with risperidone and olanzapine resulted in greater improvements in negative symptoms than treatment with haloperidol. However, the effect sizes were small. This is consistent with a multicenter short-term trial of clozapine (Kane et al. 1988) that found that clozapine-treated patients demonstrated greater improvements in the withdrawal-retardation cluster of the Brief Psychiatric Rating Scale than did patients treated with chlorpromazine. These advantages of SGAs for negative symptoms have paralleled improvements in positive symptoms, raising the possibility that the differences between drugs are generated by an advantage in secondary negative symptoms. The advantages of the SGAs could be secondary to their well-documented advantages in EPS. Moreover, long-term studies (Rosenheck et al. 1997; Buchanan et al. 1998) have not consistently found these advantages in negative symptoms, again suggesting that the differences may be secondary.

A meta-analysis by Keefe and colleagues (1999) found advantages for SGAs in important neurocognitive domains. However, the studies were limited in their methodology (as described by Harvey and Keefe [2001]), and the findings should be viewed as preliminary. Moreover, it is unclear whether the advantages of the newer agents are sufficient to affect a patient’s long-term functional outcome.

Other studies suggest that clozapine may decrease hostility and aggression. Citrone and coworkers (2001) randomly assigned 157 inpatients to olanzapine, risperidone, haloperidol, or clozapine. Clozapine resulted in greater reductions in the hostility item from the Positive and Negative Syndrome Scale than the other agents. A careful mirror-image study by Chengappa and colleagues (in press) compared the rates of seclusion and restraint in schizophrenia patients who received clozapine during the first 3 years after its introduction and prior to the advent of other SGAs.
Significant reduction in both measures was seen following the introduction of clozapine. This study is consistent with randomized trials, which have consistently found that patients treated with clozapine experience less hostility and fewer aggressive behaviors than patients on comparators (Kane et al. 1988, 2001; Essock et al. 2000). Thus, the conference participants concluded that the available data were sufficient to support a trial of clozapine in patients with chronic psychotic disorders and aggression.

Most studies of short-term treatment have found that patients treated with SGAs demonstrated greater improvements in mood symptoms. This effect was first identified in the multicenter clozapine trial and then confirmed in studies of risperidone (Chouinard 1993) and olanzapine. There is no conclusive and agreed-upon statistical method to determine whether the greater improvement in mood symptoms by some SGAs is primary or a consequence of fewer EPS. There is indirect statistical evidence suggesting that the greater improvement in mood associated with some SGAs is primary, but this evidence is correlational and model dependent. It is important to add the qualification that it is problematic to impute cause from correlation. While correlational models, such as path analysis, are one type of indirect evidence, much more is needed to support the attribution of primary cause.

There is also evidence indicating that patients who are treated with clozapine are less likely to attempt or complete suicide. Studies using large data bases have noted that mortality from suicide is reduced among individuals taking clozapine (Walker 1997; Reid 1998). However, this finding was not confirmed using a large VA data base (Sernyak 2001). One study (Meltzer 1995) followed patients who were changed to clozapine and found a reduction in the number of serious suicide attempts as well as in expressed depression and hopelessness. A multicenter, randomized comparison of clozapine with olanzapine in 980 patients with schizophrenia or schizoaffective disorder and a high risk of suicide found that clozapine was associated with significantly fewer suicide attempts (Meltzer 2001). Taken together, these studies suggest that a change to clozapine is an appropriate practice for some patients with schizophrenia who have a high risk for suicide.

**Question 8. What should a clinician monitor when prescribing olanzapine, ziprasidone, clozapine, and so forth, and how should the information obtained from such monitoring influence practice?**

**Consensus Opinion.** Table 1 summarizes, for FGAs as a group and for each SGA individually, the consensus recommendation concerning monitoring practices for specific adverse effects. (Level 3)

**Background**

**Tardive dyskinesia.** As noted in Question 5, there is evidence indicating that newer antipsychotics are associated with a reduced risk of TD. However, even though the risk is lower, it is likely that a finite risk exists for some of these agents, and it is recommended that patients on SGAs have at least yearly ratings for TD with an instrument such as the Abnormal Involuntary Movement Scale.

**EPS.** Studies of FGAs and SGAs indicate that nearly all of these agents—with the possible exceptions of clozapine and quetiapine—can be associated with EPS (tremor, parkinsonism, or akathisia) at effective clinical doses. In addition, the presence of EPS may increase the risk for TD. Moreover, the availability of agents with a reduced likelihood of causing EPS has made experiencing such discomforting side effects unnecessary for most patients. As a result, it is recommended that patients who are receiving agents other than clozapine and quetiapine should be evaluated for EPS at every visit until the patient is at a stable dose and then monitored every 3 to 12 months, depending on the agent, to assess changes in EPS and intervene accordingly.

**Blood pressure/pulse.** Lower potency FGAs and SGAs are more likely to produce clinically significant postural hypotension and tachycardia, but the effect is quite variable among patients, and frequency of monitoring is determined by the severity and persistence of the problem. The elderly are at greater risk for this side effect.

**Weight.** Individuals with schizophrenia are more likely to be overweight or obese than patients without schizophrenia. For many individuals, this obesity is severe enough to have profound effects on overall health and social adjustment. A meta-analysis by Allison and colleagues (1999) found that weight gain over a 10-week trial was 4.45 kilograms on clozapine, 4.15 kilograms on olanzapine, 2.10 kilograms on risperidone, and 0.04 kilograms on ziprasidone. There were insufficient data to estimate weight gain on quetiapine. Other studies have found similar weight gain associated with SGAs. Because weight gain begins during the first weeks of antipsychotic treatment, weighing patients frequently during the first weeks of treatment could lead to interventions such as starting weight reduction programs or changing to a different antipsychotic.

**Glucose.** A number of clinical reports suggest that some newer antipsychotics—particularly clozapine and olanzapine—may be associated with an increased risk of type II diabetes mellitus. Because these findings are based largely on case reports, there are insufficient data to calculate the relative risk associated with different antipsychotics.
Table 1. A summary of recommended monitoring frequency for particular safety concerns by type of antipsychotic medication

<table>
<thead>
<tr>
<th>TD</th>
<th>EPS</th>
<th>BP/pulse</th>
<th>Weight</th>
<th>Glucose¹</th>
<th>Cholesterol/triglyceride¹</th>
<th>Prolactin/sexual side effects</th>
<th>EKG</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGAs</td>
<td>B, q6M</td>
<td>B, every visit as long as a problem; then 1 yr</td>
<td>q1Y</td>
<td>B, 3M, q1Y</td>
<td>B, if weight gain &gt; 7% body weight, then q1Y</td>
<td>B, if weight gain &gt; 7% body weight, then q1Y</td>
<td>B, every visit first 3M until stable, q1Y</td>
</tr>
<tr>
<td>Clozapine²</td>
<td>B, q1Y</td>
<td>B, q1Y</td>
<td>Every visit until stable</td>
<td>Every visit for 6M; then q3M</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>B, q1Y</td>
<td>B, q1Y</td>
<td>Same as above</td>
<td>B, q1Y</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Risperidone</td>
<td>B, q1Y</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>B, q1Y</td>
<td>B, q1Y</td>
<td>Every visit until stable, then q1Y</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>B, q1Y</td>
<td>B, q1Y</td>
<td>Same as above</td>
<td>B, q1Y</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

Note.—B = baseline; BP = blood pressure; EKG = electrocardiogram; EPS = extrapyramidal side effects; FGA = first generation antipsychotic; M = months; NA = not applicable; q = repetition interval; TD = tardive dyskinesia; Y = year.

¹ If a fasting specimen was not collected and the value is abnormal, a fasting specimen should be obtained.

² Patients receiving clozapine should have their white blood count monitored. Current requirements mandate weekly white blood count monitoring for 6 months followed by monitoring every other week.

³ See text for discussion of EKG monitoring for ziprasidone.

Moreover, even before the introduction of SGAs, individuals with schizophrenia had a higher risk of developing diabetes.

Cholesterol/triglycerides/lipid levels. There are clinical reports (Osser et al. 1999; Henderson et al. 2000) suggesting that clozapine and olanzapine have the potential for increasing cholesterol and triglycerides. There is also a clinical report suggesting that changing patients to ziprasidone may lower lipid levels. These reports are insufficient to make an evidence-based recommendation about the relative risks in this area associated with different antipsychotics. However, monitoring of these health parameters is probably prudent for nearly every individual with schizophrenia because of the vulnerability of these individuals to weight gain and poor dietary habits.

Sexual side effects. Individuals with schizophrenia—particularly men—report decreases in libido and sexual thoughts when they are drug-free or treated with antipsychotic medication (Aizenberg et al. 1995). However, antipsychotic medications have the potential for causing disturbances in erectile or ejaculatory function. Sexual side effects in both men and women could be related to a number of factors, including dopamine blockade, prolactin elevation, decreased testosterone, or alpha adrenergic blockade (Rojansky et al. 1992). It is unclear if there are differences among FGAs and SGAs in their tendency to cause these side effects. Nevertheless, sexual side effects are an important cause of nonadherence with drug treatment and should be monitored. Lowering the dose of antipsychotic or changing drugs may be helpful, although empirical studies provide little guidance regarding which drugs are least likely to impair sexual functioning. A number of case reports have reported that sildenafil citrate (Viagra) can be effective for men facing these problems.
The introduction of ziprasidone focused attention on the association of QT prolongation with a number of antipsychotics. An unpublished study that was mandated by the FDA and carried out by Pfizer found that thioridazine was associated with sufficient QT prolongation to result in a recommendation that this agent—along with mesoridazine—be used only as a second line agent. Ziprasidone was associated with less QT prolongation, and it is unclear whether it will be associated with an increased risk of ventricular arrhythmia.

The package insert for ziprasidone does not contain recommendations for baseline or follow-up electrocardiograms (EKGs), but does warn the clinician to be alert to a number of conditions that can lead to prolongation of the QT interval. The simplest and most direct assessment is to measure the QT interval by EKG. At the time of this conference, given the cardiac safety issues raised by the package insert, there were insufficient post-marketing data for the participants to recommend other than a conservative approach to evaluating the potential cardiac conduction problems. The participants recognized that this recommendation would be subject to change if post-marketing data show that the cardiac safety concerns noted in the package insert are not evident in reports of serious adverse events.

The degree of QT prolongation with thioridizine and mesoridazine is substantially longer than with other antipsychotic agents. As a result, monitoring EKGs for the duration of the QT interval and the presence of abnormal rhythms should take place with these agents.

It is also worth noting that patients with schizophrenia are at increased risk for cardiovascular diseases and early mortality, so that an argument can be made for routine EKG examinations in the entire group of patients with this illness, regardless of type of medication treatment.

Discussion

The participants in the Mount Sinai Consensus Conference were able to reach a consensus on a number of important, controversial issues in the pharmacotherapy of schizophrenia. Whenever possible, the group’s conclusions were drawn from the review of randomized clinical trials and meta-analyses that have been published in peer-reviewed journals during recent years. There were issues (e.g., the risk of TD with SGAs, the duration of an adequate trial, and the appropriate monitoring for possible adverse effects) where the group was unable to use this standard. If it was unlikely that data would be developed in the near future that could resolve a particular question (e.g., where ethical considerations would preclude conducting definitive trials), this group was willing to make recommendations to clinicians based on available data. Other groups who review and analyze the clinical literature may opt not to use such a flexible rule as to when to make clinical recommendations. Clinicians, however, must make treatment decisions with or without expert recommendations. The group considered it preferable to provide as much clinical guidance as could be justified by current evidence.

There were important clinical questions where the group determined that there was insufficient evidence to form a recommendation. These issues included the combining of antipsychotics for purposes other than cross-titration during a change of medication, the relative effectiveness of SGAs for different dimensions of psychopathology, the upper limit on number of treatment trials prior to clozapine, and the use of SGA dosages above the recommended range for treatment-refractory patients. Some of these questions may be resolved by the National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and other research that is planned or ongoing. The lack of group data from clinical trials to address these areas of uncertainty emphasizes the need for clinicians to gather and use the data from each patient as support for their medication decisions. The use of quantitative measures can be of particular value in determining how outcomes have been affected by “nonstandard” treatment approaches.

It is important to emphasize again that the Mount Sinai Conference focused solely on questions where recent research may have resolved a controversial issue. Important issues in pharmacotherapy were not discussed when the group believed the issue had been previously resolved or when there was insufficient evidence to make a recommendation (APA 1997). As a result, the recommendations of the group should not be viewed as a comprehensive guide for treating schizophrenia.

Financial Disclosure

The following financial interests by coauthors include consultant fees, honoraria, and/or research funds.

Stephen R. Marder: Pfizer, Janssen, Novartis Abbott, Bristol-Myers Squibb, Lundbeck, Eli Lilly, Astra Zeneca, Solvay
Susan Essock: None
Robert W. Buchanan: Janssen Research Foundation, Novartis (Research support for both.)
John M. Davis: None
John M. Kane: Pfizer, Janssen, Novartis Abbott, Bristol-Myers Squibb, Eli Lilly, Astra Zeneca

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