Introduction: Methods, Commentary, and Summary

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ABSTRACT

Objectives. **A growing number of atypical antipsychotics are available for clinicians to choose from in the treatment of psychotic disorders. However, a number of important questions concerning medication selection, dosing and dose equivalence, and the management of inadequate response, compliance problems, and relapse have not been adequately addressed by clinical trials. To aid clinical decision-making, a consensus survey of expert opinion on the pharmacologic treatment of psychotic disorders was undertaken to address questions not definitively answered in the research literature.**

Method. **Based on a literature review, a written survey was developed with 60 questions and 994 options. Approximately half of the options were scored using a modified version of the RAND 9-point scale for rating the appropriateness of medical decisions. For the other options, the experts were asked to write in answers (e.g., average doses) or check a box to indicate their preferred answer. The survey was sent to 50 national experts on the pharmacologic treatment of psychotic disorders, 47 (94%) of whom completed it. In analyzing the responses to items rated on the 9-point scale, consensus on each option was defined as a nonrandom distribution of scores by chi-square "goodness-of-fit" test. We assigned a categorical rank (first line/preferred choice, second line/alternate choice, third line/usually inappropriate) to each option based on the 95% confidence interval around the mean rating. Guideline tables indicating preferred treatment strategies were then developed for key clinical situations.**

Results. **The expert panel reached consensus on 88% of the options rated on the 9-point scale. The experts overwhelmingly endorsed the atypical antipsychotics for the treatment of psychotic disorders. Risperidone was the top choice for first-episode and multi-episode patients, with the other newer atypicals rated first line or high second line depending on the clinical situation. Clozapine and a long-acting injectable atypical (when available) were other high second line options for multi-episode patients. The experts' dosing recommendations agreed closely with the package inserts for the drugs, and their estimates of dose equivalence among the antipsychotics followed a linear pattern.**

The experts considered 3–6 weeks an adequate antipsychotic trial, but would wait a little longer (4–10 weeks) before making a major change in treatment regimen if there is a partial response. The experts recommended trying to improve response by increasing the dose of atypical and depot antipsychotics before switching to a different agent; there was less agreement about increasing the dose of conventional antipsychotics before switching, probably because of concern about side effects at higher doses. If it is decided to switch because of inadequate response, risperidone was the experts' first choice to switch to, no matter what drug was initially tried. Although there was some disparity in the experts' recommendations concerning how many agents to try before switching to clozapine, the experts' responses suggest that switching to clozapine should be considered after failure to respond to two atypical antipsychotics. Clozapine was also the antipsychotic of choice for patients with suicidal behavior. When switching oral antipsychotics, the experts considered cross-titration the preferred strategy. When switching to an injectable antipsychotic, the experts stressed the importance of continuing the oral antipsychotic until therapeutic levels of the injectable agent are achieved.

The experts considered psychosocial interventions the first choice strategy for partially compliant patients, with pharmacologic interventions the first choice for patients with clear evidence of noncompliance. However, because it can be difficult to distinguish partially compliant from noncompliant patients, the editors recommended combining psychosocial and pharmacologic interventions to improve compliance whenever possible. When patients relapse because of compliance problems or if there is any doubt about compliance, the experts recommended the use of a long-acting injectable antipsychotic and would select an injectable atypical when this option becomes available. The experts would also consider using an injectable atypical antipsychotic (when available) in many clinical situations that do not involve compliance problems.

The experts stressed the importance of monitoring for health problems—especially obesity, diabetes, cardiovascular problems, HIV risk behaviors, medical complications of substance abuse, heavy smoking and its effects, hypertension, and amenorrhea—in patients being treated with antipsychotics.

Although many patients are prescribed adjunctive treatments, multiple antipsychotics, and combinations of different classes of drugs (e.g., antipsychotics plus mood stabilizers or antidepressants) in an effort to enhance response, the experts gave little support to any of these strategies, with the exception of antidepressants for patients with dysphoria/depression, antidepressants or ECT for patients with suicidal behavior, and mood stabilizers for patients with aggression/violence.

When asked about indicators of remission and recovery, the experts considered acute improvement in psychotic symptoms the most important indicator of remission, whereas they considered more sustained improvement in multiple outcome domains (e.g., occupational/educational functioning, peer relationships, independent living) important in assessing recovery.

Conclusions. **The experts reached a high level of consensus on many of the key treatment questions in the survey. Within the limits of expert opinion and with the expectation that future research data will take precedence, these guidelines provide direction for addressing common clinical dilemmas that arise in the pharmacologic treatment of psychotic disorders. They can be used to inform clinicians and educate patients regarding the relative merits of a variety of interventions. Clinicians should keep in mind that no guidelines can address the complexities involved in the care of each individual patient and that sound clinical judgment based on clinical experience should be used in applying these recommendations.**

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WHY ARE NEW GUIDELINES ON THE USE OF ANTIPSYCHOTICS NEEDED?

Now that the new generation of antipsychotics has been in widespread use for several years, it is important to provide guidelines reflecting this experience. In addition, despite considerable activity in clinical trials, clinicians continue to struggle with a number of very important practical issues concerning the treatment of psychotic disorders that are not adequately addressed by clinical trial data. We were interested in determining how the atypical antipsychotics are perceived by experts in the field with regard to questions such as drug choice, use in different clinical situations, dose equivalencies, duration of adequate trials, and preferences for switching. We were also very interested in the best strategies for managing poor or partial response to treatment. We therefore asked the experts about the number of trials of different types of agents that they would recommend before going to clozapine and the role of adjunctive pharmacologic treatment strategies in enhancing response in a number of different domains. Since the first long-acting formulation of a newer atypical antipsychotic is expected to be marketed in the near future, we wanted to determine what role the experts believe this new formulation will play in the treatment of patients with psychotic disorders. We also asked what role psychosocial interventions play in improving compliance and promoting better functional outcomes. Finally, given increasing expectations for treatment outcomes, we were particularly interested in how experts in the field conceptualize and evaluate remission and recovery in their patients.

METHOD OF DEVELOPING EXPERT CONSENSUS GUIDELINES

The contribution of expert consensus to practice guideline development continues to evolve throughout medicine, alongside the "gold standard" of meta-analysis of clinical trials and other experimental data. The sheer number of possible combinations and sequences of available treatments for many diseases makes it difficult to provide comparative recommendations based entirely on clinical trial data.[1,2] A method for describing expert opinion in a quantitative, reliable manner to help fill some of the gaps in evidence-based guidelines has been developed. This method has been applied to a variety of psychiatric disorders.[3–14]

Creating the Surveys

We first created a skeleton algorithm based on a literature review. We sought to identify key decision points in the use of antipsychotics to treat psychotic disorders as well as a list of feasible options for intervention. We highlighted important clinical questions that had not yet been adequately addressed or definitively answered in the literature.[15] A written questionnaire was developed with 60 questions and 994 options. We asked about medication selection, dosing, and dose equivalence, compliance issues, the most appropriate way to use long-acting atypical antipsychotics when they become available, and how best to define the concepts of remission and recovery in schizophrenia.

The Rating Scale

For approximately half the options in the survey, we asked raters to evaluate appropriateness using a 9-point scale slightly modified from a format developed by the RAND Corporation for ascertaining expert consensus.[16] For the other questions, we asked respondents to write in answers (e.g., target dose of a drug). We asked the experts to draw on their knowledge of the research literature (we did not provide a literature review) and their best clinical judgment in making their ratings, but not to consider financial cost. We presented the rating scale to the experts with the anchors shown in figure 1. Figure 2 shows an excerpt from Survey Question 26 as an example of our question format.

Figure 1. The Rating Scale

Extremely Inappropriate ← 1 2 3 4 5 6 7 8 9 → Extremely Appropriate

- 9 = Extremely appropriate: this is your treatment of choice
- 7–8 = Usually appropriate: a first line treatment you would often use
- 4–6 = Equivocal: a second line treatment you would sometimes use (e.g., patient/family preference or if first line treatment is ineffective, unavailable, or unsuitable)
- 2–3 = Usually inappropriate: a treatment you would rarely use
- 1 = Extremely inappropriate: a treatment you would never use

Composition of the Expert Panel

We identified 50 leading American experts in the treatment of schizophrenia. The experts were identified from several sources: recent research publications and funded grants, the DSM-IV advisors for psychotic disorders, the Task Force for the American Psychiatric Association's *Practice Guideline for the Treatment of Patients With Schizophrenia*,[17] those who worked on the Patient Outcomes Research Team (PORT guidelines),[18] and participants in previous Expert Consensus surveys on psychotic disorders.[4,7] We provided a $500 honorarium. Panelists reported taking 2 or more hours to complete the survey. This project was supported by an unrestricted grant from Janssen Pharmaceutica, L.P. However, the experts were kept blind to the sponsorship for this project while they completed the survey to reduce the chance of possible bias.

We received responses from 47 of the 50 experts (94%) to whom the survey was sent. All of the respondents held an MD degree and 1 also held an MPH and 1 a PharmD degree. Of the respondents, 6 (13%) were female and 41 (87%) male. Their mean age was 52 years, with a mean of 24 years in practice or research; 40% reported spending at least half their work time and 43% about a quarter of their work time seeing patients. The majority of the experts worked in an academic clinical or

Figure 2. Sample Survey Question

26. Rate the appropriateness of each of the following types of antipsychotic medications for a patient with suicidal behavior. Give your highest ratings to the medications you consider most appropriate for this problem.

Oral formulations			
1) Aripiprazole	1 2 3	4 5 6	7 8 9
2) Clozapine	1 2 3	4 5 6	7 8 9
3) Olanzapine	1 2 3	4 5 6	7 8 9
4) Quetiapine	1 2 3	4 5 6	7 8 9
5) Risperidone	1 2 3	4 5 6	7 8 9
6) Ziprasidone	1 2 3	4 5 6	7 8 9
7) High-potency conventional	1 2 3	4 5 6	7 8 9
8) Mid-potency conventional	1 2 3	4 5 6	7 8 9
9) Low-potency conventional	1 2 3	4 5 6	7 8 9
Injectable formulations			
10)Long-acting injectable atypical	1 2 3	4 5 6	7 8 9
11)Long-acting depot conventional	1 2 3	4 5 6	7 8 9

research setting, while 19% were in private practice and 17% in the public sector. Of the 47 respondents, 98% had participated in a research project involving antipsychotics during the past 5 years, 87% had held a federal (NIMH or NIH) research grant as a principal investigator, and 96% had been principal investigator for an industry-sponsored grant. Respondents had received grants, speaking fees, and funding for studies from a wide variety of sources. The pharmaceutical companies from whom at least 30% of respondents reported receiving support included Eli Lilly (83% of respondents), Janssen (77%), Pfizer (72%), Bristol-Myers Squibb (57%), AstraZeneca (57%), Abbott (30%), and Novartis (32%).

Data Analysis for Options Scored on the Rating Scale

For each option, we first defined the presence or absence of consensus as a distribution unlikely to occur by chance by performing a χ^2 test ($p < 0.05$) of the distribution of scores across the 3 ranges of appropriateness (1–3, 4–6, 7–9). Next we calculated the mean and 95% confidence interval (C.I.). A categorical rating of first, second, or third line was designated based on the lowest category in which the C.I. fell, with boundaries of 6.5 or greater for first line, and 3.5 up to 6.5 for second line. Within first line, we designated an item as "treatment of choice" if at least 50% of the experts rated it as 9.

Data Analysis for Write-In Options

For many questions concerning dosing, we asked respondents to write in their answers. This kind of question typically produces a number of extreme outlier responses. In analyzing the results of this type of question in this survey, we subjected these write-in responses to a Winsorizing(1) process,[19] which involved replacing the highest and lowest responses to a given question with the next highest and next lowest responses, respectively. Practically speaking, Winsorizing has an impact on a distribution only if there is a single extreme outlier in either direction from the mean; in such situations, that extreme value is replaced with the next most extreme value. Our rationale for using this process was that a single extreme outlier might have interpreted the question differently than his or her peers—but that two extreme outliers would be less likely to have done so. Using the Winsorized data, means and standard deviations were calculated for each dosing question. The aggregate dosing values given in the guidelines are based on those means and standard deviations adjusted based on available pill strengths to the nearest available dosage for each drug.

Displaying the Survey Results

The results of the section of Question 26 asking about choice of antipsychotics for a patient with suicidal behavior (figure 2) are presented graphically in figure 3. The C.I.s for each treatment option are shown as horizontal bars and the numerical values are given in the table on the right.

The Ratings

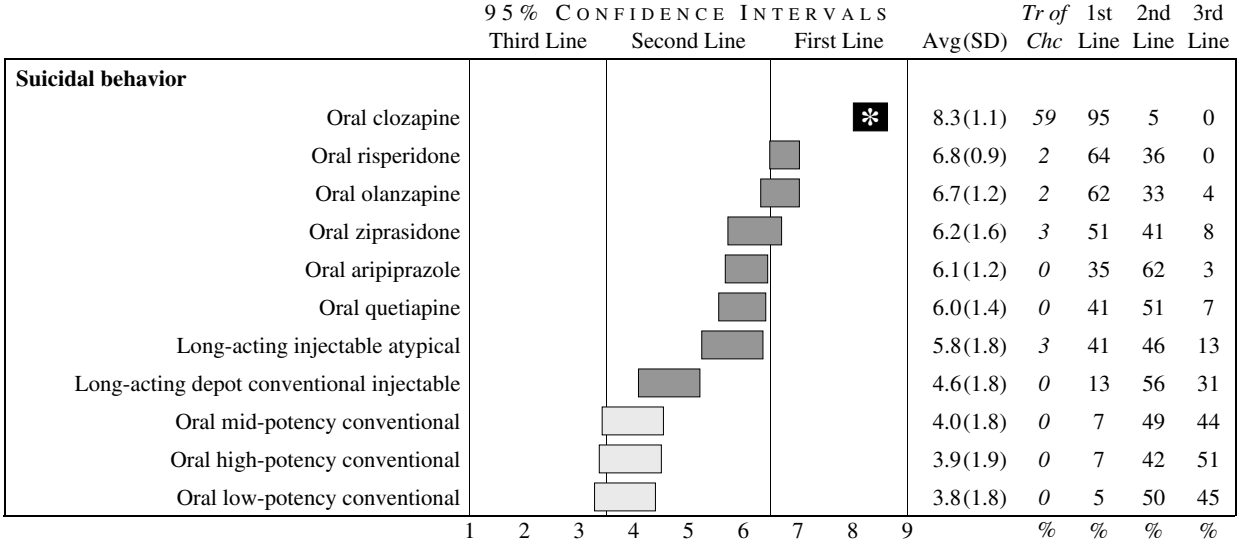
- ✻ Treatment of choice
- First line
- Second line
- Third line
- No consensus

First line treatments are those strategies that came out on top when the experts' responses to the survey were statistically aggregated. These are options that the panel feels are usually appropriate as initial treatment for a given situation. Treatment of choice, when it appears, is an especially strong first line recommendation (having been rated as "9" by at least half the experts). In choosing between several first line recommendations, or deciding whether to use a first line treatment at all, clinicians should consider the overall clinical situation, including the patient's prior response to treatment, side effects, general medical problems, and patient preferences.

Second line treatments are reasonable choices for patients who cannot tolerate or do not respond to the first line choices. A second line choice might also be used for initial treatment if the first line options are deemed unsuitable for a particular patient (e.g., because of poor previous response, inconvenient dosing regimen, particularly annoying side effects, general medical contraindication, potential drug interaction, or if the experts do not agree on a first line treatment). For some questions, second line ratings dominated, especially when the experts did not reach any consensus on first line options. In such cases, to differentiate among the alternatives, we label those items whose C.I.s overlap with the first line category as "high second line."

Figure 3. Graphic Results of Survey Question 26 (Section on Suicidal Behavior)

26 Complicating problems. Rate the appropriateness of each of the following types of antipsychotic medications for a patient with a psychotic disorder who has suicidal behavior. Give your highest ratings to the medications you consider most appropriate.



Third line treatments are usually inappropriate or used only when preferred alternatives have not been effective.

No consensus. For each item in the survey, we used a χ^2 test to determine whether the experts' responses were randomly distributed across the 3 categories, which suggests a lack of consensus. These items are indicated by an unshaded bar in the survey results.

Statistical differences between treatments. While we did not perform tests of significance for most treatments, the reader can readily see whether C.I.s overlap (roughly indicating no significant difference between options by *t*-test). The wider the gap between C.I.s, the smaller the *P* value would be (i.e., the more significant the difference). In some questions there are striking and important differences within levels, which we occasionally point out. Often, however, differences within levels are not significant from a statistical perspective. Also, there are sometimes no statistical differences between choices at the bottom of first line and those at the top of second line.

From Survey Results to Guidelines

After the survey results were analyzed and ratings assigned, the next step was to turn these recommendations into user-friendly guidelines. We generally present three levels of recommendations: first line, high second line (options for which the confidence interval bar crosses or touches the boundary with first line), and other second line. For some guidelines, we present just preferred (first line) options and also consider (second line) options. Whenever the guideline lists more than one option in a rating level, we list the options in the order of their mean scores. As an example, the full results of the question presented above are shown on pages 75–76 and are used in Guideline 10A. For a patient with suicidal behavior, clozapine was rated the treatment of choice. High second line options were oral risperidone, olanzapine, and ziprasidone.

Degree of Consensus

Of the 474 options rated on the 9-point scale, consensus was reached on 418 options (88%) as defined by the χ^2 test. When there was no first line recommendation, we chose the highest-rated second line option as the "preferred" treatment and indicated this in the guideline.

RESULTS AND COMMENTARY

In the following sections, we summarize the key recommendations from the guidelines and consider how the experts' recommendations relate to the available research literature. The complete set of data from the survey is presented on pages 52–94. The guidelines derived from the data are presented on pages 21–51.

Initial Medication Selection

An increasingly wide range of medications is available for the treatment of schizophrenia. While the growing number of options increases the chances of a positive treatment outcome for patients, clinicians are faced with ever more complex choices in trying to select the best medication for each specific patient. Recommendations in current textbooks state that, with the exception of clozapine, all available antipsychotics have similar efficacy when given at optimum doses.[20] However, at least con-

cerning the traditional conventional antipsychotics, this statement may have been biased by the use of small studies without enough power to detect modest to moderate differences in treatment effects. Furthermore, there are important differences in side-effect profiles that may influence treatment choices.[21,22]

We asked the experts to rate the appropriateness of all of the currently available antipsychotic medications for first-episode patients and for patients who had had multiple previous episodes of psychosis, depending on their predominant symptomatology. Note that in this survey we asked only about oral and long-acting injectable formulations of antipsychotics. In the discussion of the results that follows, unless otherwise specified, all medications mentioned refer to the oral formulations.

For a ***first-episode patient with predominantly positive symptoms***, the experts considered risperidone to be the treatment of choice. Other recommended medications for this clinical situation were aripiprazole, olanzapine, ziprasidone, and quetiapine (although the first two were rated first line and the second two high second line, these four options clustered together and all were rated first line by approximately two thirds of the experts).

For a ***first-episode patient with predominantly negative symptoms***, the experts recommended one of the newer oral atypical antipsychotics. Risperidone and aripiprazole received first line ratings, and the other three were rated high second line; however, all of the options clustered together with only small differences in their confidence intervals.

For a ***first-episode patient with both prominent positive and negative symptoms***, the experts preferred risperidone. Other recommended medications for this clinical situation are aripiprazole, ziprasidone, olanzapine, and quetiapine (again these four options clustered together with only small differences in their confidence intervals).

At the time of the survey, a long-acting injectable atypical antipsychotic was not available in the United States, although it was available in several other countries. We therefore asked the experts to tell us how they would use such a formulation if it were available. As a group, the experts varied in their ratings of using a long-acting injectable atypical antipsychotic for a first-episode patient to such an extent that there was no consensus on this item (with approximately a quarter of the experts rating it first line and approximately a third of the experts giving it third line ratings). The experts did not recommend the use of either oral or depot conventional antipsychotics for a first-episode patient (conventional antipsychotics received third line ratings in every case).

For a ***multi-episode patient with predominantly positive symptoms***, the experts considered risperidone treatment of choice. Other recommended first line medications for this clinical situation were aripiprazole, ziprasidone, olanzapine, and quetiapine and a long-acting atypical antipsychotic. Clozapine was rated high second line. Other lower rated second line options were a long-acting conventional antipsychotic (depot) and an oral high-potency conventional.

For a ***multi-episode patient with predominantly negative symptoms***, risperidone, aripiprazole, and ziprasidone were rated first line; high second line choices were olanzapine, quetiapine, a long-acting atypical antipsychotic, and clozapine. All these options tended to cluster together, with only small differences in their confidence intervals. A long-acting depot conventional antipsychotic was a lower rated second line option.

For a ***multi-episode patient with both prominent positive and negative symptoms***, the experts preferred risperidone, followed by aripiprazole. Other first line options were ziprasidone and olanzapine. High second line choices were a long-acting atypical antipsychotic, quetiapine, and clozapine. Again, ratings for most of these options tended to cluster together with only small differences in their confidence intervals. Other lower rated second line options were a long-acting depot conventional antipsychotic and an oral high-potency conventional.

The experts were clearly more willing to consider using clozapine or a long-acting injectable antipsychotic in a patient with a history of previous psychotic episodes. The experts did not recommend the use of mid- or low-potency conventional antipsychotics and gave only very limited support to the use of oral high-potency conventionals.

Adequate Dose of Antipsychotics

The experts' dosing recommendations generally agree closely with recommended doses given in the package labeling. For olanzapine and quetiapine, their recommendations for highest acute dose were somewhat higher than the highest doses for which safety data from clinical trials are available (20 mg of olanzapine and 800 mg of quetiapine). The panel would generally use higher doses for a patient who had had multiple episodes of psychosis than for a first-episode patient. The recommended dose ranges for maintenance treatment were also slightly lower than for acute treatment.

Use of Therapeutic Drug Monitoring

We asked the experts for which antipsychotics plasma level assays were available to them and whether and how they used such levels to adjust dosing. Over 50% of the experts reported that plasma levels were available to them only for clozapine, haloperidol, and haloperidol decanoate. Clozapine was the agent for which the experts considered plasma levels most clinically useful. Over half of the experts use plasma levels of clozapine and haloperidol to monitor compliance; 88% use clozapine levels to adjust dose, primarily if there has been an inadequate response or side effects are a problem; 50% of the experts use plasma levels of oral haloperidol and haloperidol decanoate to adjust dose levels if the patient has an inadequate response or problematic side effects.

Dose Equivalence

Dose equivalences of different antipsychotics are an important but tricky issue. For the conventional antipsychotics, certain estimates can be derived from their different affinities for dopamine receptors.[23] For the newer atypical antipsychotics, the issue is more complicated, because their effectiveness seems to be related not only to dopamine but also to other receptors, especially serotonin receptors. We therefore asked the experts to

write in doses of conventional and atypical antipsychotics that they would consider equivalent to a range of haloperidol doses. The goal was to obtain a better sense of the equivalency between the older conventional antipsychotics and the new generation of atypical antipsychotics. We also asked the experts to write in doses of conventional and atypical antipsychotics that they would consider equivalent to a range of risperidone doses. The goal here was to obtain a better sense of the equivalency of doses among the new generation of atypical antipsychotics. In general, the experts' responses followed a very linear pattern, indicating that it would probably be possible to use linear formulas to calculate dose equivalency. It is interesting to note that, in every case, the dose the experts considered equivalent to 30 mg of haloperidol is higher than the highest acute dose the experts indicated they would usually use (see Guideline 2). In addition, the doses the experts considered equivalent to 10 mg of risperidone were closest to those they considered equivalent to 20 mg of haloperidol (as would be expected since they indicated that they considered 10.5 mg of risperidone to be equivalent to 20 mg of haloperidol).

Dose Adjustment

Data indicate that there is a relationship between certain patient characteristics and necessary dose adjustments. For example, smoking can reduce the plasma levels of some antipsychotic drugs[24] and there is a constantly increasing literature on the effects of genetic polymorphisms involving cytochrome P450 enzymes and the metabolism of psychotropic drugs.[25] It has also been shown that elderly patients are more sensitive to the side effects of antipsychotic drugs.[26] However, the clinical relevance of individual factors is not always clear. We therefore asked the experts which factors they would consider in adjusting the acute antipsychotic dose. The experts considered the use of concomitant medications, the patient's age, and the presence of hepatic disease the most important factors to consider in adjusting the acute antipsychotic dose. The priority given to the use of concomitant medications reflects our expanding knowledge of drug-drug interactions and their potential consequences. Other important factors to consider are the presence of cardiovascular or renal disease, whether or not the patient smokes, and the patient's weight. There was no consensus about the importance of the patient's sex, with 30% of the experts saying they would nearly always consider the patient's sex in dose adjustment and 23% saying they would rarely or never consider it. It is surprising that many of the experts (45%) would only sometimes consider the patient's weight in adjusting the dose. This may reflect the fact that clinicians tend not to pay adequate attention to the weight of patients with schizophrenia and what impact it may have on blood levels of psychotropic drugs following specific doses.

Dose Selection for Special Populations

Dose selection for children and adolescents. A majority of the experts would not generally use the following medications in children with a psychotic disorder who are 12 years of age or younger: aripiprazole, clozapine, chlorpromazine, fluphenazine, perphenazine, thioridazine, thiothixene, trifluoperazine, fluphenazine decanoate, and haloperidol decanoate. A majority of the experts would not generally use the following medications in an adolescent (13–18 years old) with a psychotic disorder: chlorpromazine, perphenazine, thioridazine, thiothixene, trifluoperazine. The doses recommended for pediatric patients were generally much lower than those given for adult patients (see Guideline 2), while the doses recommended for adolescents were only somewhat lower than those recommended for adults. These results underscore the need for more data on optimum dosing for children and adolescents.

Dose selection for elderly patients. The experts generally recommended using lower doses in elderly patients than in younger adults. This probably reflects previous recommendations and concerns about slower metabolism and greater sensitivity to adverse effects in older patients.[26] Older patients are also more likely to have comorbid medical conditions and to be taking multiple medications, increasing the risk for adverse effects and drug-drug interactions. The experts generally recommended using much lower doses in elderly patients with dementia than in those with a psychotic disorder. The majority of the experts would not generally use the following medications in an elderly patient with a psychotic disorder or with dementia: chlorpromazine, thioridazine, thiothixene, trifluoperazine; 70% would also avoid haloperidol or fluphenazine decanoate in elderly patients with dementia.

Inadequate Response to Treatment

Adequate treatment trial. The time-course of the antipsychotic effect is poorly understood.[27] It has recently been shown that, in general, antipsychotic drugs do not have a delayed onset of action, but rather that their clinical effects begin to appear in the first week of treatment.[28] Patients then continue to improve over longer periods of time. We asked the experts about the appropriate duration of an antipsychotic trial. If a patient is having little or no response to the initial or to the second antipsychotic that was prescribed, the experts recommended waiting a minimum of 3 weeks and a maximum of 6 weeks before making a major change in treatment regimen. By a major change in treatment regimen, we mean either a significant dose increase or switching to a different agent. If the patient is showing a partial response to treatment, the experts would extend the duration of the trial somewhat to 4–10 weeks for the initial antipsychotic and 5–11 weeks for the second antipsychotic prescribed. Note that the experts would wait longer if the patient is having a partial response, especially in the second trial. Although the differences in the recommendations were not dramatic, they are interesting, particularly given the lack of data from controlled trials addressing these issues. It should also be noted that the results are similar to the recommendations given in the 1996 *Expert Consensus Guidelines on the Treatment of Schizophrenia*,[4] which recommended waiting 3–8 weeks if there is no response and 5–12 weeks if there is a partial response before switching to another pharmacologic strategy.

When to switch antipsychotics. For each antipsychotic, we asked the experts whether they would increase the dose or switch to another agent if a multi-episode patient was having an inadequate response to the average target dose of the medication (see Guideline 2 for recommended target doses). Over 90% of the experts would first increase the dose of clozapine and olanzapine before switching, going as high as 850 mg/day of clozapine and 40 mg of olanzapine. Over 80% would increase the dose of quetiapine and risperidone before switching, going as high as 950 mg/day of quetiapine and 10 mg/day of risperidone. Approximately 60% or more of the experts would also increase the dose of aripiprazole, ziprasidone, and the decanoate formulations of fluphenazine and haloperidol. The experts were divided fairly evenly as to whether increasing the dose or switching is the best strategy if a patient is having an inadequate response to the recommended target dose of one of the conventional oral antipsychotics, except for thioridazine, where 67% would switch to another agent. The experts may be less willing to increase the dose of the conventional oral medications because of concern about side effects, especially extrapyramidal side effects (EPS) and tardive dyskinesia (TD), at higher doses.

Switching antipsychotics: selecting the next agent and dose. We asked the experts to indicate the first and second antipsychotics they would try if there was an inadequate response to the initial medication. Guideline 7B lists those agents that were written in by 10% or more of the experts in response to Question 15. It should be noted that, after trials of two atypical antipsychotics, 30% or more of the experts would switch to clozapine; this was recommended as a first line strategy in this situation by 70% of the experts in Question 18. The discrepancy between the responses given in Questions 15 and 18 probably reflects differences in the way the question was posed as well as the lack of certainty in the field as to the most appropriate place for clozapine in the treatment algorithm. The editors note that they would endorse the response given in question 18, where approximately three quarters of the experts recommended switching to clozapine after inadequate response to two atypical antipsychotics. For patients who had started with a conventional antipsychotic, the experts were more likely to try two other atypical antipsychotics before moving to clozapine.

The recommended target doses for the second and third antipsychotics the experts would try were mostly consistent with the acute target doses shown in Guideline 2, although there was a tendency to consider using doses at the higher end of the range, especially for the third medication tried.

Switching strategies. Some recent studies compared different strategies for switching from one antipsychotic drug to another.[29,30] These studies did not usually show dramatic differences in outcomes between different strategies. However, only a small number of antipsychotics have been examined and there might be pragmatic reasons to prefer one strategy over another. We therefore asked the experts what strategy they would use in switching to each of the oral atypical antipsychotics, assuming the first antipsychotic does not require tapering before discontinuation. In switching to any of the oral atypicals except clozapine, the experts recommended using cross-titration (gradually tapering the dose of the first antipsychotic while gradually increasing the dose of the second) or overlap and taper (continuing the same dose of the first antipsychotic while gradually increasing the second to a therapeutic level and then tapering the first). Of the two strategies, cross-titration was rated first line by a higher percentage of the experts. In switching to clozapine, the experts' preferred strategy is cross-titration, probably reflecting the need for relatively slow titration of clozapine. They would also consider using overlap and taper in switching to clozapine (high second line).

Even fewer evidence-based data are available to determine the optimum method for switching to a long-acting injectable antipsychotic; we therefore asked the experts about strategies for this situation. In switching to a depot conventional antipsychotic, the experts recommended either continuing the oral antipsychotic at the same dose until therapeutic drug levels of the injectable antipsychotic are achieved and then gradually tapering the oral antipsychotic or else beginning to taper the oral antipsychotic gradually after giving the first injection, with a larger percentage of the experts favoring the first strategy. Some experts would consider discontinuing the oral antipsychotic immediately once therapeutic levels of the injectable antipsychotic are achieved. The experts' recommendations for switching to a long-acting atypical antipsychotic were similar, except that there was stronger support for continuing the oral antipsychotic at the same dose until therapeutic drug levels of the injectable antipsychotic are achieved and then gradually tapering the oral antipsychotic compared with the other options. It should be noted the experts definitely did not recommend stopping the oral antipsychotic when the first long-acting injection is given, since this would leave the patient without adequate antipsychotic coverage during the switchover and potentially increase the risk of relapse.

Strategies for enhancing a partial response. We asked the experts about the appropriateness of a number of strategies to try to improve response in a patient who is having a partial but still inadequate response (e.g., a patient with some persisting positive symptoms). The experts gave only limited support to any of the options and rated many of them third line. This probably reflects the lack of strong empirical data in the literature. For example, although mood stabilizers are frequently used in combination with antipsychotic drugs,[31] a recent meta-analysis found no benefits of carbamazepine augmentation in patients with schizophrenia.[32] Most of the trials in this field are underpowered. A noteworthy exception is a recent trial of valproate augmentation that clearly showed a more rapid onset of action; however, the superiority vanished over time.[33]

The experts considered adding a second oral atypical a low second line treatment for those patients who failed to respond adequately to an oral conventional or atypical antipsychotic. This is striking given the widespread use of combined antipsychotics in the field. This practice, which continues despite a lack of supportive data from clinical trials or guidance from expert opinion,

adds to the cost of treatment. It also increases the potential side-effect burden for patients, since studies suggest that those patients who are taking multiple antipsychotics are generally receiving a higher dose equivalence than patients receiving only one drug.[34]

Use of clozapine. Clozapine is indicated for treatment-refractory schizophrenia.[35] However, clinicians vary in how they define treatment-refractory illness and there are no universally accepted criteria for treatment-refractoriness in schizophrenia. We therefore asked the experts in what clinical situations they would be most likely to consider a switch to clozapine. The experts considered a trial of clozapine a strategy of choice for a patient who has failed to respond to adequate trials of one or more conventional antipsychotics and two atypical antipsychotics. They would also consider it a strategy of choice for a patient who had failed to respond to trials of one or more conventionals and all of the atypicals. However, 13% of the experts rated this option third line, probably reflecting the feeling that there would be no advantage in conducting trials of all of the other five atypicals before considering clozapine. The experts also considered a trial of clozapine a first line option for patients who have failed to respond to trials of two or three atypicals or trials of one or more conventionals and one atypical. Although some experts would consider clozapine for patients who have not responded to two conventionals or one atypical, there was much less support for these options. When it is appropriate to switch to clozapine remains an area of controversy and there are few data to inform clinical practice. We may in fact be doing our patients a disservice by trying multiple drugs before going to clozapine (see discussion on switching antipsychotics above).

Managing Relapse

Unfortunately, drug research often stops after determining whether an antipsychotic is efficacious in reducing positive symptoms. Hardly any data are available concerning sequential treatment steps, including strategies for managing relapse. Thus, expert opinions are relevant here.

Relapse when taking an oral antipsychotic. When relapse occurs in a patient whom the clinician believes to be compliant with medication based on all available evidence (e.g., family report, plasma levels), the experts recommended (high second line ratings) either switching to a different oral antipsychotic or increasing the dose of the current medication. The only study the editors are aware of is an inconclusive small pilot trial that did not find a difference between increasing the dose of fluphenazine and maintaining the same dose in 32 relapsed patients.[36] Another second line option the experts would consider is switching to a long-acting injectable antipsychotic. This probably reflects concerns that the patient may not actually be compliant, since studies have found that clinicians are often incorrect in their assessment of patients' compliance.[37]

When the clinician is unsure of the level of compliance or there is clear evidence of noncompliance, the experts' first line recommendation was to switch to a long-acting injectable atypical if available. They would also consider a long-acting conventional antipsychotic (high second line). If the clinician is unsure of the level of compliance, the experts would also consider adding a long-acting atypical to the oral antipsychotic.

Relapse on a long-acting injectable antipsychotic. If a patient relapses when receiving a long-acting conventional antipsychotic, the experts' first line recommendation was to switch to a long-acting injectable atypical antipsychotic. They would also consider increasing the dose or the frequency of injections of the long-acting conventional (high second line options).

If a patient relapses when receiving a long-acting injectable atypical antipsychotic, the experts' first line recommendation was to increase the dose of the injectable antipsychotic. They would also strongly consider adding the oral form of the injectable antipsychotic to try to boost response (very high second line). The experts did not recommend switching to a conventional depot antipsychotic (third line rating).

Dose Adjustment in Stable Patients

If the patient is being treated with an atypical antipsychotic or with fluphenazine or haloperidol decanoate, the majority of the experts would continue maintenance treatment with the same dose that was effective acutely, although over 40% would lower the dose of olanzapine or risperidone. A majority of the experts said they would lower the dose of an oral conventional antipsychotic for maintenance treatment; however, the percentages were very close, with 40% or more of the experts recommending continuing the acute dose of the conventional antipsychotic. The uncertainties shown in this area are consistent with a lack of information concerning optimum doses for maintenance treatment with both conventional and atypical antipsychotics.

Managing Complicating Problems

Choosing antipsychotics for patients with complicating problems. There has been increasing interest in the efficacy of the different atypical antipsychotics for symptoms and problems that are frequently associated with schizophrenia (e.g., cognitive dysfunction, depression, substance abuse) and often lead to significant functional impairment. For the most part, the experts' recommendations reflect findings in the literature. The experts considered clozapine the treatment of choice for patients who present with suicidal behavior. Clozapine was also the top choice for aggression and violence. Other highly rated options for aggression and violence were risperidone (rated first line), olanzapine, and a long-acting injectable atypical (both rated high second line). These recommendations reflect studies that have found clozapine to be more effective than other available antipsychotics in reducing rates of suicide[38] and moderating aggressive behavior.[39] There is a new indication for clozapine for "reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder."[40]

There were no first line recommendations for the other problems we asked about—dysphoria/depression, cognitive problems,

and substance abuse—for which all of the oral atypical antipsychotics as well as a long-acting injectable atypical received second line ratings. The experts would also consider a long-acting depot conventional for a patient with substance abuse problems. The lack of first line consensus on these items probably reflects the fact that, although an increasing number of studies have looked at the effects of the atypical antipsychotics on mood,[41,42] cognition,[43] and substance use,[44] there are few empirical data definitive enough to guide clinical practice. A good example are the studies on cognition by Kern et al.[45] and Green et al.[46] In an initial trial using high haloperidol doses (15 mg/day in the fixed dose phase), these researchers found that risperidone was superior on several domains of cognition,[45] but they could not confirm this in a subsequent trial using relatively low haloperidol doses (mean 5 mg/day).[46] It is interesting that the experts would not recommend oral conventional antipsychotics for patients with any of the problems we asked about, except aggression/violence, for which conventional orals were second line options.

It is possible that these complicating problems may be caused or exacerbated by noncompliance. Therefore, it is not surprising that a long-acting atypical antipsychotic was a prominent alternative, especially for aggression/violence and substance-abuse problems.

Selecting adjunctive treatments for patients with complicating problems. When we asked about a number of adjunctive medications that are commonly used in clinical practice to treat a variety of complicating problems in patients with schizophrenia, the experts as a group had few strong recommendations, probably reflecting the lack of decisive empirical data in this area. The only first line recommendation was a selective serotonin reuptake inhibitor (SSRI) for dysphoria/depression. The first line ratings given to the SSRIs probably reflect a concern to choose an antidepressant associated with few side effects. Venlafaxine was a very high second line for dysphoria/depression. The support given to the use of antidepressants probably reflects studies suggesting that antidepressants may be helpful for patients with comorbid depression, although the literature is conflicting in this area. For aggression and violence, valproate and lithium received high second line ratings. For suicidal behavior, the same two antidepressants recommended for dysphoria/depression received high second line ratings, with ECT another high second line option. The question of how to treat persisting negative symptoms has long been a difficult issue in the field. Although there was no consensus on any of the adjunctive treatments that were rated second line for negative symptoms, it should be noted that approximately a quarter of the experts or more rated the following options first line: a glutaminergic agent, an SSRI, another antipsychotic, or venlafaxine.

Obesity. There is increasing concern about long-term medical problems in patients with schizophrenia, especially obesity and its complications. It has been reported that over one-third of the adults in the United States are obese.[47] Obesity is a threat to health and longevity and has been associated with a number of diseases such as hypertension, type II diabetes, coronary heart disease, and stroke. Moreover, obesity is a common concomitant of schizophrenia,[48] and individuals with schizophrenia appear to be at increased risk for certain obesity-related conditions such as type II diabetes and cardiovascular disease.[49] Many psychotropic medications can contribute to weight gain[21] and clinicians face difficult clinical dilemmas when a patient with clinically significant obesity (BMI $\geq$ 30) responds well to a medication that is likely to be contributing to the patient's weight problem. If a patient with clinically significant obesity has responded to an antipsychotic other than clozapine, the experts recommended a trial of a different antipsychotic with less weight gain liability combined with nutritional and exercise counseling if possible. They would also consider (high second line) continuing the same antipsychotic and providing nutritional and exercise counseling to try to help the patient lose weight. However, reflecting the fact that most patients receiving clozapine have already failed to respond to other agents, the experts would continue clozapine in this situation and try to address the weight problem with nutritional and exercise counseling. Although the experts gave a high second line rating to lowering the dose of clozapine in this situation, clinical studies have found that weight gain does not appear to be a dose-related effect. It is interesting that the experts gave second line ratings to the addition of topiramate. Although there have been case reports of weight loss with this agent in schizophrenia, there are no controlled studies supporting this practice. The experts did not recommend the use of weight loss medications (orlistat, sibutramine) or surgical treatment of obesity in this population.

Monitoring for comorbid conditions and risk factors. Many patients with schizophrenia rely on their psychiatric care provider for general medical care. With the improving outcomes being achieved with the newer atypical antipsychotics, more attention is being focused on short- and long-term health and wellness in this population. We asked the experts which conditions and risk factors they felt it was most important to monitor. We also asked which ones it was feasible to monitor in a psychiatric treatment setting. The experts strongly felt that it was important to monitor for all the conditions we asked about, with obesity and diabetes considered the most important (rated 9 by 60% and 56% of the experts, respectively). Amenorrhea was included among these conditions, because many antipsychotics can lead to an increase in prolactin levels and associated problems.[50] The experts' ratings of feasibility reflect the relative difficulty of the assessments involved (e.g., it is relatively simple to monitor weight, blood pressure, and amenorrhea, but much harder to evaluate osteoporosis).

Although we did not ask about obtaining lipid profiles, the editors note that clinicians should obtain lipid levels on a regular basis, because some antipsychotics are associated with hyperlipidemia. At the Mount Sinai Conference on the Health Monitoring of Patients with Schizophrenia, held in 2002, a group of psychiatric and medical experts met to evaluate the existing literature and develop recommendations for improving the medical monitoring of patients with schizophrenia who are managed

in outpatient settings. A publication outlining the recommendations generated at this conference is in preparation.[51] The conference concluded that, as part of routine care, a lipid panel should be obtained if a recent panel is not available. Given that individuals with schizophrenia, as a group, are considered to be at high risk for coronary heart disease, lipid screening should be carried out at least once every 5 years and more often when there is evidence of lipid levels that approach those that would lead to treatment.[51] The conference also recommended that clinicians should be aware of, and monitor regularly for, symptoms of increased prolactin. If clinically indicated, prolactin should be measured, and, if elevated, a work-up for the cause of the elevation should be initiated. Consideration should also be given to switching to a prolactin-sparing medication—if the symptoms disappear and prolactin levels fall to normal, an endocrine work-up can then be avoided.[51] Recommendations on other complicating conditions, such as cardiac problems (QTc prolongation and myocarditis), cataracts, and EPS will also be included in the Mount Sinai guideline when it is published.

Compliance (Adherence)

Noncompliance is a frequent phenomenon in psychiatric disorders.[52] Studies have shown that continuous antipsychotic medication provides significantly better protection from psychotic relapse than no antipsychotic maintenance therapy[53] or so-called intermittent treatment.[54] Although it is clear that, below a certain degree of compliance, patients are at risk to relapse, thresholds have not been established. This is partly because the impact of partial compliance is difficult to study: schizophrenic relapses usually do not occur immediately after stopping medication but rather after a delay of several weeks to months (or even years).[55]

Levels of compliance. We provided the experts with the following definitions of compliance to use as benchmarks in answering a series of questions about the assessment and management of compliance problems:

- Compliant: misses < 20% of medication
- Partially compliant: misses 20%–80% of medication
- Noncompliant: misses > 80% of medications

We also asked the experts to tell us how they would define levels of compliance. On average, the expert panel would set a higher threshold for compliance, as shown below, and would consider a patient who missed more than 65% of his or her medication noncompliant:

- Compliant: misses < 25% of medication
- Partially compliant: misses 25%–65% of medication
- Noncompliant: misses > 65% of medications

Not surprisingly, the experts reported that their patients show higher levels of compliance than are generally reported in the literature.

Assessing compliance. The experts considered asking the caregiver or patient first line strategies for assessing compliance; they would also consider pill counts, obtaining blood levels, and using self-rating scales. They did not consider routine use of urine tests appropriate.

When to intervene for compliance problems. The experts would usually intervene if a patient is missing approximately 50% of prescribed medication (91% would usually intervene) and were unanimous about the need to intervene if a patient is missing more than 80% of medication. The majority of the experts (52%) would usually intervene when a patient is missing approximately 20% of medication. There was less agreement about whether to intervene if a patient is only missing occasional doses (13% would usually intervene, 39% would sometimes intervene, and 48% would generally not intervene).

Strategies for addressing compliance problems. We asked the experts about the appropriateness of three different types of strategies that have been used to address compliance problems:

- Pharmacologic interventions (e.g., switching to a long-acting medication)
- Psychosocial interventions (e.g., patient education, compliance therapy [focused cognitive-behavioral therapy targeting compliance issues])
- Programmatic interventions (e.g., intensive case management, assertive community treatment)

The experts gave first line ratings to all three types of interventions. The editors note that clinicians should generally employ a combination of strategies tailored to the specific needs of the patient. The experts gave the highest ratings to psychosocial interventions for patients who are partially compliant, probably reflecting findings that such interventions can improve compliance levels. Psychopharmacologic interventions received the highest ratings for noncompliant patients, probably reflecting the fact that patients who are not taking their medication are at the highest risk for relapse and it is especially important to try to get the patient back on medication as quickly as possible.

Psychosocial interventions to improve compliance. Among psychosocial interventions for improving compliance, the experts gave the highest ratings to patient/family education, medication monitoring, and compliance therapy. Their ratings agree with research findings concerning the efficacy of these strategies in improving compliance. Cochrane reviews[56,57] and other meta-analyses[58] have found a reduction in relapse rates associated with family interventions and psychoeducation. Compliance therapy is a new strategy for promoting medication compliance that has shown positive effects in one trial.[59] Findings concerning the efficacy of group and individual psychotherapy in improving compliance are equivocal, as shown by the lower ratings given to these options.

Programmatic interventions to improve compliance. Among programmatic interventions, the experts recommended assertive community treatment (ACT), ensuring continuity of treatment

provider across treatment settings, and intensive case management services. Studies have shown that the kind of assistance provided by ACT programs can significantly improve compliance levels.[60] Lack of continuity in care providers can lead to serious compliance problems, since patients may be continued on an ineffective or difficult-to-tolerate treatment regimen or may not receive continuing medication coverage after discharge. Although case management is considered to be effective by the experts, the scientific data are conflicting. A Cochrane review showed that, with this intervention, more people remain in contact with psychiatric services, but readmission rates increased.[61] The experts also considered supervised residential services, partial hospitalization, rehabilitation services, and involuntary outpatient commitment useful options for improving compliance.

Pharmacologic strategies for addressing compliance problems. The experts strongly agreed that the first line pharmacologic strategy for addressing compliance problems is to switch the patient to a long-acting injectable atypical antipsychotic once this option is available (first line for partially compliant patients and treatment of choice for noncompliant patients). High second line options were to switch to a long-acting depot conventional or add a long-acting injectable atypical. Although the advantages of long-acting injectable medication—assured compliance and immediate awareness of noncompliance—are obvious, they are difficult to prove in randomized, double-blind trials. This is partly because patients who are willing to participate in such trials may *per se* be compliant.[62] Despite this, meta-analyses that included only long-terms trials in outpatients showed superiority of long-acting agents; however, the database involved is old and small.[63, 64] Large pragmatic trials in which patients are randomized to depot or oral medication and then followed in an open fashion are needed to further examine this issue. Another high second line option for a patient who is partially compliant was to continue the same pharmacotherapy and intensify psychosocial interventions to improve compliance. However, the experts did not recommend this strategy for a patient who is noncompliant.

Use of Long-Acting Injectable Antipsychotics

Benefits. The experts considered the greatest benefit of long-acting injectable antipsychotics to be assured medication delivery. Other important advantages are the ability to know immediately when a patient misses medication and the fact that the patient continues to have some medication in his or her system even after a missed dose. Additional advantages are the reduced risk of relapse associated with continuous medication and the ability to know that relapse, if it occurs, is not the result of compliance problems.

Potential disadvantages. The experts considered lack of patient acceptance the most important potential disadvantage of long-acting injectable antipsychotics. To some extent, this response probably reflects an assumption that patients will not accept the idea of continuing injections. However, once they try a long-acting medication, many patients are surprised to find how easy it is to tolerate receiving medication in this way. Although lack of patient autonomy is another potential concern that is sometimes mentioned, patient surveys do not support this as being a major factor.[65] Although the experts said that they considered inability to stop medication immediately should side effects become a problem somewhat important as a potential disadvantage, the editors were hard pressed to find examples of situations in which immediate discontinuation of a long-acting antipsychotic was a medical necessity. Even in neuroleptic malignant syndrome, there is no evidence that mortality rates are higher among patients receiving a long-acting injectable antipsychotic than in those receiving an oral medication (assuming the condition is identified and appropriately treated).[66]

Factors favoring the use of long-acting injectables. In deciding whether to use a long-acting injectable antipsychotic, 96% of the experts considered the availability of an atypical antipsychotic in such a formulation very important. This doubtless reflects concerns about the side effects associated with the conventional depot antipsychotics. Other factors that the experts considered very important in deciding to use a long-acting injectable are good patient acceptance of the injection, evidence that the rate of relapses and side effects will be lower than with oral equivalents, better quality of life for patients, and ease of administration.

Indications for switching to a long-acting injectable atypical antipsychotic. We asked the experts about the appropriateness of using a long-acting injectable atypical antipsychotic, when available, in a variety of clinical situations. The experts considered a long-acting atypical antipsychotic the treatment of choice for a patient who is taking an oral atypical and requests the long-acting formulation, for a patient who relapses because of noncompliance with an oral atypical antipsychotic, and for a patient who is experiencing EPS on a depot conventional antipsychotic. The experts considered a long-acting injectable atypical first line for a patient in involuntary outpatient commitment, for a patient who is chronically relapsing on an oral conventional, for a patient with lack of insight or denial of illness, for a patient taking an oral atypical antipsychotic who is relapsing for reasons that are unclear, and for a patient with a history of aggressive or violent behavior. It is interesting that the experts perceived a role for the use of long-acting injectable atypicals that goes well beyond treatment of patients with compliance problems (see the many other second line indications listed in Guideline 18). Of all the situations we asked about, the only ones in which the experts would not generally consider a long-acting injectable atypical are a patient taking an oral atypical or conventional who is stable and not experiencing EPS or a patient who has been newly diagnosed with schizophrenia and has had no previous antipsychotic treatment.

We then asked the experts how concern about the potential for TD would affect their decision to switch to an injectable atypical antipsychotic. The majority of the experts would definitely switch if there is concern about TD in a patient who is experiencing EPS on a depot or oral conventional antipsychotic (96%

and 73% first line, respectively). Even if the patient is not experiencing EPS, many of the experts would consider switching from a depot or oral conventional if there is concern about TD (49% and 38% first line, respectively). The editors were unsure on what basis a clinician would decide that there was in fact no or minimal risk of TD.

Beginning injections while hospitalized. We asked the experts about the appropriateness of beginning treatment with a long-acting injectable atypical while the patient is hospitalized, given shorter lengths of hospital stays. This strategy was rated high second line by the expert panel, in order to ensure continuing medication coverage when the patient is discharged and to facilitate acceptance of an injectable medication in outpatient treatment. The experts also noted that this strategy may be helpful because patients are most vulnerable to relapse soon after discharge.

Motivating patients to return for repeat injections. The experts consider the influence of family/caregivers and physician/treatment team to be most important in motivating patients to return for repeat injections.

Defining Remission and Recovery

With improving outcomes, research studies are now trying to evaluate the effectiveness of different antipsychotics not only in producing remission of symptoms but in promoting long-term recovery in patients with schizophrenia. However, as yet there is no general consensus on how best to define these terms. We therefore asked the experts to rate the appropriateness of a number of factors as indicators of remission and recovery. There was strong agreement that the level of positive symptoms is the single most important indicator of remission. High second line indicators were levels of cognitive/disorganized, negative, and depressive symptoms, reflecting studies showing that these associated symptoms contribute in a substantial way to the functional disability associated with schizophrenia.[67–73] In defining recovery, however, the experts gave almost equal weight to all of the indicators we asked about, indicating that recovery is a concept involving improvement in multiple domains.

Rank ordering of symptomatic indicators. When the experts were asked to rank four key indicators of remission and recovery, their responses agreed very closely with the responses described above: 89% considered level of positive symptoms the most important indicator of remission, followed by cognitive/disorganized, negative, and depressive symptoms, all three of which were ranked similarly. However, there was less agreement on the most important indicator of recovery, with 41% considering level of positive symptoms most important, 33% giving the highest ranking to level of cognitive/disorganized symptoms, and 28% ranking level of negative symptoms as most important.

Rank ordering of functional outcomes. When asked to rank three functional outcomes as indicators of remission, the experts were divided, with 45% considering independent living, 32% occupational/education functioning, and 20% peer relationships the most important functional indicator of remission. This division among the panel may reflect the fact that one is unlikely to see major changes in any of these areas in the shorter time frame usually used to measure remission (see Guideline 21). However, when asked about the same functional outcomes as indicators of recovery, the majority (64%) felt that occupational/educational functioning was the most important functional outcome in recovery, followed by peer relationships (rated most important by 20%) and independent living (rated most important by 18%). When asked about the most appropriate way of defining functional improvement in their patients, 86% of the experts considered relative rather than absolute change in the patient the most appropriate indicator.

Severity and duration of symptoms as indicators of remission and recovery. We asked the experts what levels of symptom severity were most appropriate to use in defining remission and recovery. Their ratings are summarized in the bar charts in Guideline 21. The majority of the experts would consider a patient in remission who had mild levels of positive, cognitive/disorganized, negative, and depressive symptoms (62%, 69%, 62%, and 73% of the experts, respectively). However, a third of the experts felt that no positive symptoms should be present for a patient to be considered in remission.

When asked about indicators for recovery, the experts said that they would look for greater reduction in positive symptoms, with a majority (62%) saying that there should be no positive symptoms present for a patient to be considered in recovery. In terms of negative symptoms, 62% of the panel would consider a patient in recovery who had mild negative symptoms while 33% would look for no negative symptoms. The panel was more evenly split as to whether a patient could have mild cognitive or depressive symptoms and still be considered in recovery.

In terms of duration of symptoms, the experts said that the improvement in symptomatic indicators should be maintained for at least 3 months for a patient to be considered in remission and for a year or more for a patient to be considered in recovery. The experts said that improvement in functional indicators (occupational/vocational functioning, independent living, peer relationships) needs to be maintained for somewhat longer, 15–17 months, for the patient to be considered in recovery.

SUMMARY OF KEY RECOMMENDATIONS

The experts overwhelmingly endorsed the atypical antipsychotics for the treatment of psychotic disorders. Risperidone was their top choice for first-episode and multi-episode patients, with the other newer atypicals rated first line or high second line depending on the clinical situation. Clozapine and a long-acting injectable atypical (when available) were other high second line options for multi-episode patients. The experts' dosing recommendations agreed closely with the package inserts for the drugs. The experts recommended using much lower doses for pediatric patients and somewhat lower doses for adolescent and elderly

patients. They also stressed the importance of considering concomitant medications and the presence of comorbid medical conditions (hepatic, renal, or cardiovascular disease) in selecting the most appropriate dose. The experts' estimates of dose equivalence among the different antipsychotics followed a linear pattern, suggesting that linear formulas could be used to calculate dose equivalency.

The experts considered 3–6 weeks an adequate antipsychotic trial, but would wait a little longer (4–10 weeks) before making a major change in treatment regimen if there is a partial response. The experts recommended trying to improve response by increasing the dose of atypical and depot antipsychotics before switching to a different agent; there was less agreement about increasing the dose of conventional antipsychotics before switching, probably because of concern about side effects at higher doses. If it is decided to switch because of inadequate response, risperidone was the experts' first choice to switch to, no matter what drug was initially tried. Although there was some disparity in the experts' recommendations concerning how many agents to try before switching to clozapine, the experts' responses suggest that switching to clozapine should be considered after failure to respond to two atypical antipsychotics. Clozapine was also the antipsychotic of choice for patients with suicidal behavior. When switching oral antipsychotics, the experts considered cross titration the preferred strategy. When switching to an injectable antipsychotic, the experts stressed the importance of continuing the oral antipsychotic until therapeutic levels of the injectable agent are achieved.

The experts considered psychosocial interventions the first choice strategy for partially compliant patients, with pharmacologic interventions the first choice for patients with clear evidence of noncompliance. However, because it can be difficult to distinguish partially compliant from noncompliant patients, the editors recommended combining psychosocial and pharmacologic interventions to improve compliance whenever possible. When patients relapse because of compliance problems or if there is any doubt about compliance, the experts recommended the use of a long-acting injectable antipsychotic and would select an injectable atypical when this option becomes available. The experts would also consider using an injectable atypical antipsychotic (when available) in many clinical situations that do not involve compliance problems.

The experts stressed the importance of monitoring for health problems—especially obesity, diabetes, cardiovascular problems, HIV risk behaviors, medical complications of substance abuse, heavy smoking and its effects, hypertension, and amenorrhea—in patients being treated with antipsychotics.

Although many patients are prescribed adjunctive treatments, multiple antipsychotics, and combinations of different classes of drugs (e.g., antipsychotics plus mood stabilizers or antidepressants) in an effort to enhance response, the experts gave little support to any of these strategies, with the exception of antidepressants for patients with dysphoria/depression, antidepressants or ECT for patients with suicidal behavior, and mood stabilizers for patients with aggression/violence.

When asked about indicators of remission and recovery, the experts considered acute improvement in psychotic symptoms the most important indicator of remission, whereas they considered more sustained improvement in multiple outcome domains (e.g., occupational/educational functioning, peer relationships, independent living) important in assessing recovery.

LIMITATIONS AND ADVANTAGES OF EXPERT CONSENSUS GUIDELINES

These guidelines can be viewed as an expert consultation, to be weighed in conjunction with other information and in the context of each individual patient-physician relationship. The recommendations do not replace clinical judgment, which must be tailored to the particular needs of each patient and clinical situation. We describe groups of patients and make suggestions intended to apply to the average patient in each group. However, individual patients will differ greatly in their treatment preferences and capacities, history of response to previous treatments, family history of treatment response, and tolerance for different side effects. Therefore, the experts' first line recommendations certainly will not be appropriate in all circumstances.

We remind readers of several other limitations of these guidelines:

1. The guidelines are based on a synthesis of the opinions of a large group of experts. From question to question, some of the individual experts would differ with the consensus view.
2. We have relied on expert opinion precisely because we are asking crucial questions that are not yet well answered by the literature. One thing that the history of medicine teaches us is that expert opinion at any given time can be very wrong. Accumulating research will ultimately reveal better and clearer answers. For example, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a multisite investigation sponsored by the National Institute of Mental Health, is currently underway to determine the long-term effects and usefulness of a number of antipsychotic medications.[74] The study will enroll 1600 patients with schizophrenia for whom a medication change may be indicated for reasons of limited efficacy or tolerability. It will evaluate the atypical antipsychotics clozapine, olanzapine, quetiapine, risperidone, and ziprasidone and the conventional antipsychotics perphenazine and fluphenazine decanoate for up to 18 months of treatment. It is estimated that the study will be completed in the fall of 2004. We hope to revise the guidelines periodically based on new research information and on reassessment of expert opinion to keep them up-to-date.
3. The guidelines are financially sponsored by the pharmaceutical industry, which could possibly introduce biases. Because of this, we have made every step in guideline development transparent, reported all results, and taken little or no editorial liberty.
4. These guidelines are comprehensive but not exhaustive; because of the nature of our method, we omit some interesting topics on which we did not query the expert panel.

Despite the limitations, these guidelines represent a significant advance because of their specificity, ease of use, and the credibility that comes from achieving a very high response rate from a large sample of the leading experts in the field.

FINAL WORD

Advances in public health do not always require technological breakthroughs or long periods of waiting for new data. Immediate gains can be made by increasing the speed with which best practices are implemented. Guidelines offer a rapid means for communicating a distillate of expert opinion. When reaching a clinical decision point, practitioners and patients can use guidelines to generate a menu of reasonable choices and then select the option that is judged best for each individual. This process drives the next round of expert opinion and the next round of empirical studies.

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Guideline Organization and Key Terms

Guideline Organization

I. Medication Selection, Dosing, and Dose Equivalence
II. Compliance
III. Long-Acting Injectable Antipsychotics
IV. Defining Remission and Recovery

Terminology Used in the Ratings

First line is used to designate treatment strategies that came out on top when the experts' responses to the survey were statistically aggregated. These are options that the panel feels are usually appropriate as initial treatments for a given situation. ***Treatment of choice*** indicates an especially strong first line recommendation: an option that received the highest rating of "9" (extremely appropriate) from at least 50% of the experts.

Second line is used to indicate treatments that are reasonable choices for patients who cannot tolerate or do not respond to the first line choices. "High second line" refers to options for which the confidence intervals overlap with the first line category.

Third line is used to indicate options that are usually inappropriate or used only when preferred alternatives have not been effective.

Definitions of Terms Used in the Survey

Psychotic disorders. The term "psychotic disorder" in the survey refers to one of the disorders that appears in the DSM-IV-TR section on "Schizophrenia and Other Psychotic Disorders": schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, and brief psychotic disorder.

Phases of treatment

- Acute treatment: goal is to resolve the symptoms and signs of a current psychotic episode
- Maintenance treatment: goal is to prevent development of a new psychotic episode (a recurrence).

Levels of compliance (adherence)

We asked about the following levels of treatment compliance:

- Compliant: only misses occasional doses (e.g., < 20% of prescribed medication)
- Partially compliant: misses more than occasional doses (e.g., misses 20%–80% of medication)
- Noncompliant: misses > 80% of medication

Antipsychotics

We presented antipsychotics alphabetically within questions and told respondents to opt out of answering questions about any medication with which they were unfamiliar by drawing a line through that single line item. We asked about the following specific antipsychotics in this survey.

- Conventional Antipsychotics:
  - High potency (e.g., haloperidol [Haldol], fluphenazine [Prolixin])
  - Medium potency (e.g., thiothixene [Navane], perphenazine [Trilafon], trifluoperazine [Stelazine])
  - Low potency (e.g., chlorpromazine [Thorazine], thioridazine [Mellaril])
- Atypical Antipsychotics: aripiprazole (Abilify), clozapine (Clozaril), olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel), ziprasidone (Geodon)