The Texas Medication Algorithm Project Antipsychotic Algorithm for Schizophrenia: 2006 Update

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Background: A panel of academic psychiatrists and pharmacists, clinicians from the Texas public mental health system, advocates, and consumers met in June 2006 in Dallas, Tex., to review recent evidence in the pharmacologic treatment of schizophrenia. The goal of the consensus conference was to update and revise the Texas Medication Algorithm Project (TMAP) algorithm for schizophrenia used in the Texas Implementation of Medication Algorithms, a statewide quality assurance program for treatment of major psychiatric illness.

Method: Four questions were identified via premeeting teleconferences. (1) Should antipsychotic treatment of first-episode schizophrenia be different from that of multiepisode schizophrenia? (2) In which algorithm stages should first-generation antipsychotics (FGAs) be an option? (3) How many antipsychotic trials should precede a clozapine trial? (4) What is the status of augmentation strategies for clozapine? Subgroups reviewed the evidence in each area and presented their findings at the conference.

Results: The algorithm was updated to incorporate the following recommendations. (1) Persons with first-episode schizophrenia typically require lower antipsychotic doses and are more sensitive to side effects such as weight gain and extrapyramidal symptoms (group consensus). Second-generation antipsychotics (SGAs) are preferred for treatment of first-episode schizophrenia (majority opinion). (2) FGAs should be included in algorithm stages after first episode that include SGAs other than clozapine as options (group consensus). (3) The recommended number of trials of other antipsychotics that should precede a clozapine trial is 2, but earlier use of clozapine should be considered in the presence of persistent problems such as suicidality, comorbid violence, and substance abuse (group consensus). (4) Augmentation is reasonable for persons with inadequate response to clozapine, but published results on augmenting agents have not identified replicable positive results (group consensus).

Conclusions: These recommendations are meant to provide a framework for clinical decision making, not to replace clinical judgment. As with any algorithm, treatment practices will evolve beyond the recommendations of this consensus conference as new evidence and additional medications become available.

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This article summarizes the recommendations of a consensus process to update the Texas Medication Algorithm Project (TMAP) antipsychotic algorithm for schizophrenia. The update conference took place in June 2006 in Dallas, Tex.

First published in 1996, the schizophrenia algorithm of TMAP has been used in public mental health settings in at least 20 states, an estimate based on requests for training or technical assistance to 3 of the authors (M.L.C., A.L.M., and S.P.S.). The initiative to use TMAP algorithms in all public mental health facilities in Texas is the Texas Implementation of Medication Algorithms, a statewide quality assurance program for the treatment of major psychiatric illness. While it is difficult to evaluate exactly

what characteristics have contributed to this level of interest, 3 factors are typically cited by users and potential users of TMAP: (1) the algorithm and the user's manual were developed in a public mental health system, (2) the on-line availability of the user's manual with detailed recommendations and documentation forms, and (3) the currency of its recommendations.

If they are to continue to be useful for clinicians, the TMAP algorithms and user's manual must stay current, incorporating important new information in a timely fashion. "Important new information" means not only information about new drugs, but also newer information about drugs already in the algorithm, individually and as a group. There are no established rules to follow in deciding when and how to update guidelines and algorithms. Thus, it becomes a matter of expert consensus that an update is needed. The consensus view that an update is warranted is substantially influenced by accumulation of recent large randomized controlled trials (RCTs) that address clinically important questions. Prior updates of the TMAP schizophrenia algorithm have primarily been prompted by information about newer antipsychotics that need to be placed in the algorithm in light of what we know about them and their characteristics relative to other antipsychotics. Since the TMAP schizophrenia algorithm consensus conference in 2003, however, the most important new information regards effectiveness of drugs already in the algorithm. In particular, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[1] and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS)[2] trials have raised critical questions about the relative value of newer and older antipsychotics for treatment of chronic schizophrenia. Additionally, several large studies have addressed the issue of clozapine augmentation for persons with treatment-resistant schizophrenia.[3–7]

The TMAP initiative has been a collaboration among the Texas Department of State Health Services (formerly the Texas Department of Mental Health and Mental Retardation [TDMHMR]), the medical schools at The University of Texas Southwestern Medical Center at Dallas and The University of Texas Health Science Center at San Antonio, The University of Texas at Austin College of Pharmacy, public mental health providers, consumers, families, and mental health advocates in Texas.

The TMAP schizophrenia algorithm was originally developed in 1996. A consensus panel of academic experts, TDMHMR clinicians, administrators, consumers, family members, and mental health advocates convened to develop guidelines for the treatment of schizophrenia based on the Expert Consensus Guideline Series[8] and the Patient Outcomes Research Team project.[9] Using these previous efforts, TMAP investigators wanted to create a very specific and detailed treatment guideline that included quantitative outcome measures and clear directions on medication management.[10] To achieve this goal, clinical procedure manuals covering most aspects of antipsychotic medication management were also created for this project. The manuals have been updated along with the algorithms.

The TMAP medication algorithms are constructed in stages. Stage 1 is the medication or group of medications most highly recommended for the initial presentation of the illness with subsequent stages to be tried sequentially should response to the previous stage be unacceptable. Clinicians explicitly are given the option of skipping algorithm stages if clinical circumstances warrant.

In previous versions of the TMAP schizophrenia algorithm, stage 1 was labeled as "first episode or no prior treatment with second-generation antipsychotics (SGAs)." With the widespread use of SGAs, however, there are increasing numbers of persons who have never had a first-generation antipsychotic (FGA) trial, so, in this update of the guidelines, we define stage 1 strictly as first-episode cases.

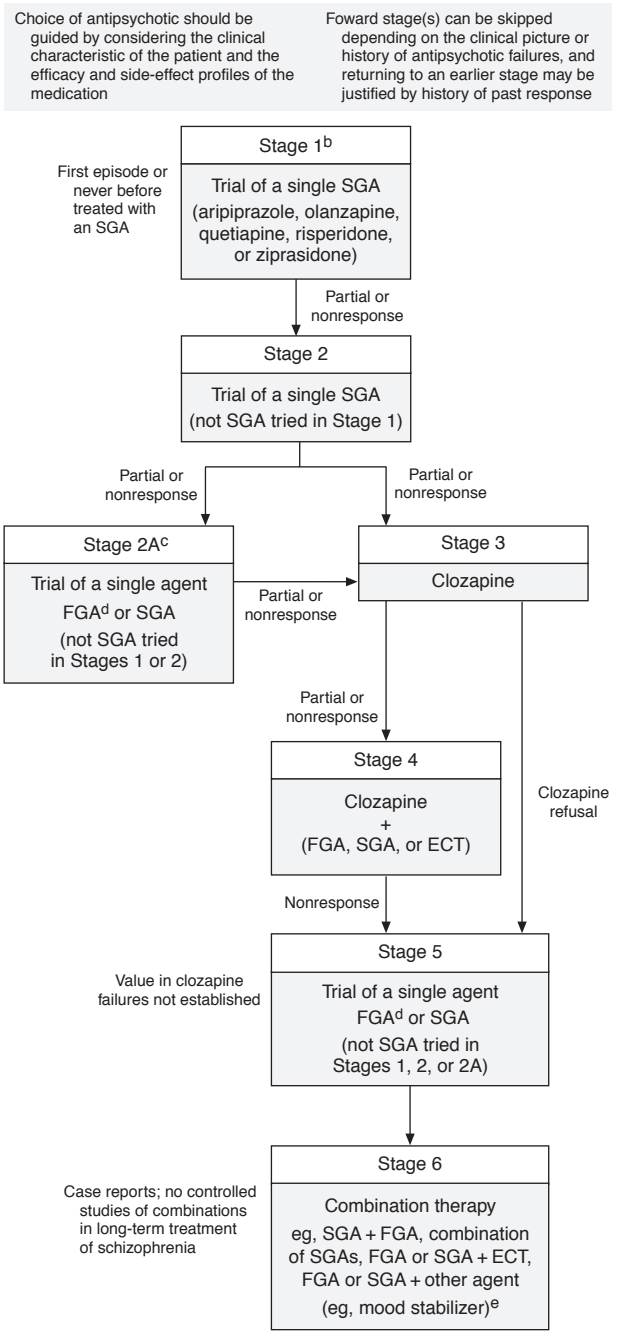
The previous update was published in 2004 (Figure 1).[11] At that time, ziprasidone and aripiprazole were added as treatment options in stage 1 of the antipsychotic algorithm. The FGAs were included with SGAs in stage 2A of the algorithm as an alternative for persons with symptoms unresponsive to 2 SGAs before progressing to clozapine treatment, although clozapine was the recommended option after 2 failed trials with SGAs.

The process of deciding on topics for the 2006 conference is described in the Method. The evidence for decisions on these topics and the subsequent recommendations are reviewed in the Results.

METHOD

In June 2006, the consensus panel, consisting of experts in the pharmacologic treatment of schizophrenia, experienced clinicians, consumers, and consumer advocates, convened in Dallas, Tex., to update the TMAP schizophrenia medication algorithm. In the months preceding the update conference, the expert panel had 3 teleconferences to review the old algorithm, discuss significant new evidence that could influence algorithm revisions, and select specific questions/topics for review at the conference. Four questions were identified. (1) Should antipsychotic treatment of persons with first-episode schizophrenia be different from that of persons with multiepisode schizophrenia? (2) In which algorithm stages should FGAs be an option? (3) How many antipsychotic trials should precede initiation of clozapine? (4) What is the status of augmentation strategies for clozapine? These topics were then assigned to work groups to review the literature prior to the conference, present their findings, and make preliminary recommendations to the full group at the meeting in Dallas. Whenever possible,

Figure 1. TMAP Antipsychotic Algorithm: 2003[a]



[a]Reprinted with permission from the Texas Department of State Health Services.
[b]If patient is inadequately adherent at any stage, the clinician should assess and consider a long-acting antipsychotic preparation, such as risperidone microspheres, haloperidol decanoate, or fluphenazine decanoate.
[c]Current expert opinion favors choice of clozapine.
[d]Assuming no history of failure on FGA.
[e]Whenever a second medication is added to an antipsychotic (other than clozapine) for the purpose of improving psychotic symptoms, the patient is considered to be in Stage 6.
Abbreviations: ECT = electroconvulsive therapy, FGA = first-generation antipsychotic, SGA = second-generation antipsychotic, TMAP = Texas Medication Algorithm Project.

the consensus panel members based their decisions on empirical evidence, but when inadequate evidence was available, panelists could draw on expert opinion and clinical judgment with the goal of reaching consensus. "Group consensus" on a recommendation means that the full panel agreed on a recommendation, and the evidence underlying this consensus view is presented. In the single instance in which group consensus was not reached, the recommendation endorsed by the majority is presented, and the evidence for both the majority and minority views is presented.

RESULTS

Should Antipsychotic Treatment of Persons With First-Episode Schizophrenia Be Different From That of Persons With Multiepisode Schizophrenia?

Recommendation 1. Recommended treatment of first-episode schizophrenia differs from that of multiepisode illness in that effective antipsychotic dose ranges are lower, individuals are more sensitive to metabolic and extrapyramidal side effects (EPS), and there is greater likelihood of achieving a symptom-free response (group consensus). The SGAs are preferred for treatment of first-episode schizophrenia (majority opinion).

Previous recommendation. Group consensus stated that first-episode schizophrenia should be treated with an SGA, and no stage-specific recommendations about dosing or side effects were made.

Current evidence review. Overall, the evidence available regarding antipsychotic treatment specific to first-episode schizophrenia, in comparison with that for multiepisode schizophrenia, is limited.

However, the available data suggest that persons with first-episode schizophrenia respond differently than persons with multiepisode schizophrenia to antipsychotic treatment. A number of studies have found that the average efficacious antipsychotic dose for the treatment of first-episode schizophrenia is often about half the average dose needed to treat chronic schizophrenia.[12–17] The single exception may be quetiapine.[18–20] It should be noted that dosing of aripiprazole and ziprasidone has not been systematically studied in first-episode schizophrenia. In addition, the short-term positive symptom response rates found in first-episode studies are high in comparison with those typically found in persons with multiepisode schizophrenia. The high response rates are notable given that first-episode studies often use more stringent response criteria than studies of multiepisode illness. However, first-episode persons also may be more sensitive to the adverse effects of antipsychotics. Persons with first-episode schizophrenia have been noted to be particularly sensitive to metabolic changes, weight gain, and EPS.[15–18]

Recent studies of FGAs and SGAs in persons with chronic schizophrenia, discussed in detail in the subse-

quent section, have failed to show overall advantages for SGAs compared with selected FGAs. Very few studies have compared multiple SGAs to FGAs. Moreover, all subjects in the CATIE study and most in CUtLASS were diagnosed with chronic schizophrenia, which precludes direct extrapolation of the results of these studies to the treatment of first-episode schizophrenia. Thus, the expert panel had limited empirical data on which to base any potential revision of this algorithm.

The expert panel was sharply divided on the extent of reliance on these studies in deciding whether FGAs should be a recommended option in stage 1 of the revised algorithm. A complicating factor is that the effects of the medications within each class, either FGA or SGA, vary. The limited number of antipsychotics studied in first-episode schizophrenia may not be representative of the range of effects of the medications within each class. The FGAs studied in first-episode schizophrenia have been mostly limited to high-potency agents (haloperidol and fluphenazine). The SGAs studied include clozapine, risperidone, olanzapine, and quetiapine. In persons with multiepisode schizophrenia, SGAs vary in the degree to which they produce metabolic side effects. The SGAs with lower metabolic side-effect risk in multiepisode schizophrenia (ziprasidone and aripiprazole) have not been studied yet in first-episode schizophrenia.

A majority of the panel favored recommending only SGAs, but a significant minority thought FGAs should be included. The arguments and data on either side of this question, arranged by clinical topic, are presented next.

Efficacy. Large sample size, randomized, controlled comparisons of SGAs with FGAs for first-episode schizophrenia have included trials of (1) clozapine versus chlorpromazine,[12] (2) olanzapine versus haloperidol,[15] and (3) risperidone versus haloperidol.[14,16] In these studies, rates of short-term response were higher than those typically found in chronic schizophrenia but did not differ significantly between SGAs and FGAs. Two studies directly comparing SGAs also found no differences in initial responses between agents.[17,18] Medication doses in first-episode trials have often been lower than those used in trials with multiepisode schizophrenia. The dosing for quetiapine may differ from this pattern. In the first-episode study, Comparison of Atypicals in First Episode (CAFE),[18] following double-blind dose adjustment, the mean modal daily dose for olanzapine (11.7 mg) and risperidone (2.4 mg) was low, but the dose used for quetiapine (506 mg) was quite similar to the quetiapine dose used in the CATIE study of chronic schizophrenia.[1]

Two studies sponsored by pharmaceutical companies have found potential advantages for SGAs over FGAs for maintenance treatment, although they did not find short-term efficacy differences. In a study of time to relapse of first-episode persons initially responding to risperidone or haloperidol, Schooler et al.[16] reported a longer mean time to relapse with risperidone compared with haloperidol (466 days vs. 205 days). In a secondary analysis, Green et al.[21] found a longer mean time to treatment discontinuation with olanzapine compared with haloperidol (322 days vs. 230 days). More information about FGAs and SGAs for first-episode schizophrenia will be available with the completion of a pragmatic trial of first-episode schizophrenia currently underway in Europe that compares olanzapine, amisulpride, ziprasidone, quetiapine, and low-dose haloperidol.[22]

Tardive dyskinesia (TD). Data specific to first-episode schizophrenia confirm that persons with schizophrenia can develop TD during the first years of treatment. Some first-episode studies suggest that persons with first-episode schizophrenia are at similar risk as multiepisode persons for developing TD. Chakos et al.[23] found a 6.3% incidence of TD at 1 year and an 11.5% incidence at 2 years using high daily doses of fluphenazine and haloperidol for treatment of first-episode schizophrenia. Oosthuizen and colleagues[24] found the 12-month incidence of probable or persistent TD according to the Schooler and Kane criteria was 12.3% among 57 subjects treated with low-dose haloperidol (mean dose of 1.68 mg/day).

The panel was divided regarding 3 key questions about TD relevant to treatment of first-episode schizophrenia. These questions can be summarized as follows. (1) Are there differences in TD incidence between FGAs and SGAs? (2) With careful monitoring, can most cases of TD be detected while still very mild and their progression stopped or even reversed by switching from the causative agent? (3) How do the risks of TD and its effect on quality of life balance against other side effects that are associated with use of some SGAs, such as the metabolic syndrome and its sequelae?

Data comparing TD incidence between FGAs and SGAs with first-episode patients are sparse. Schooler and colleagues[16] reported no differences in TD incidence between risperidone and low-dose haloperidol, but Green and colleagues[21] reported higher scores on the Abnormal Involuntary Movement Scale for low-dose haloperidol than olanzapine at weeks 24, 52, and 104. Given the few first-episode studies, the panel considered data on TD incidence with multiepisode patients. A recent meta-analysis of studies with multiepisode patients concluded that the risk of TD with SGAs is about 1% per year with SGAs and 5% with FGAs.[25] Some panel members questioned whether the latter figure, however, may be influenced by use of high doses of high-potency FGAs and if the difference in TD incidence might be lower in a comparison between SGAs and moderate doses of midpotency FGAs, such as perphenazine. In spite of agreement that there may be considerable variations within the SGA and FGA groups of drugs, the panel remained divided. A majority, however, concluded that available data support the

conclusion that clinically important differences in rates of TD exist between SGAs and FGAs. More definitive data are needed to resolve the relative risk among the non–high-potency FGAs and SGAs.

The fact that TD can be reversible is unquestionable. Less clear from existing data (available with multiepisode patients) is whether careful monitoring detects most cases before they become irreversible, allowing for timely switching to an agent putatively less likely to cause TD.[16,26–29] Many clinicians would be more sanguine about use of selected FGAs at low doses in first-episode schizophrenia if they were confident that early detection would be routine practice and that switching could reverse mild TD.

Tardive dyskinesia and metabolic side effects are sometimes juxtaposed as though clinician and consumer must choose between them in selecting an antipsychotic. In reality, risks differ across agents, and no agent inevitably causes TD or major metabolic side effects in all persons. Thus, the "lesser of 2 evils" argument in antipsychotic selection for first-episode schizophrenia does not take into account the very different side-effect profiles of each SGA or even the differences among the FGAs. However, there is a dearth of data on treatment of first-episode schizophrenia with ziprasidone or aripiprazole, the 2 SGAs least likely to cause metabolic side effects.

Acute EPS. Each of the first-episode SGA versus FGA studies cited in the efficacy section above found more EPS with the FGA comparator than with the SGA comparator. In the Schooler et al. study,[16] this EPS difference occurred even when comparing low-dose haloperidol (mean modal dose of 2.9 mg/day) with risperidone (mean modal dose of 3.3 mg/day). Extrapyramidal side effects occur in first-episode schizophrenia, even with the SGAs, at a clinically meaningful frequency. Lieberman et al.[15] reported a 26% rate of parkinsonism with olanzapine treatment, and Robinson and colleagues,[17] using a different definition of parkinsonism, found a rate of 9% with olanzapine and 16% with risperidone. The panel was divided about whether the EPS advantages for SGAs over FGAs generalize to treatment with a midpotency FGA such as perphenazine in low-to-moderate doses. In the CATIE study, the perphenazine group had more EPS discontinuations, although EPS ratings of this group did not differ from the SGA comparators.[1] Extrapyramidal side effects are potentially disturbing, and even mild levels of EPS are associated with medication nonadherence by persons with first-episode schizophrenia.[30]

Metabolic side effects. In 3 large first-episode FGA/SGA comparison studies that reported weight data, subjects gained less weight with FGAs. After 12 weeks of treatment, Lieberman and colleagues[15] found that 61% of their olanzapine-treated subjects gained more than 7% of baseline weight as compared with 23% of the haloperidol-treated subjects. In contrast, the FGA/SGA weight gain differences were considerably less in the clozapine versus chlorpromazine and risperidone versus haloperidol studies.[12,16] First-episode studies comparing SGAs have also reported substantial weight gain with SGA treatment.[17,18] Weight gain after 12 weeks of treatment in the CAFE trial by medication were olanzapine, 16 lb; quetiapine, 8 lb; and risperidone, 9 lb.[18] As noted above, first-episode data for aripiprazole and ziprasidone are lacking.

Discussion. The expert panel did not reach consensus on whether to include FGAs as a recommended option for first-episode schizophrenia. As noted above, the comparative studies generally used haloperidol, a high-potency FGA (albeit at low doses) and not midpotency FGAs. The majority thought that the data on TD, sensitivity to EPS, and possible longer-term effectiveness advantages warranted a preference for SGAs over FGAs for first-episode schizophrenia at this time. It should be noted that there was considerable concern expressed by consumer and some clinician members of the panel that inclusion of FGAs might be used as a basis for a policy that would require initial use of an FGA before any SGA solely because of lower drug costs. The expert panel concurred that choice of antipsychotic is a decision to be individualized on clinical grounds and that a policy favoring any single agent would not be justified by the evidence.

Given concerns about the long-term effects of early weight gain, one might argue that the SGAs least likely to produce weight gain should be used in preference to those with greater weight-gain potential. Against this approach, however, is (1) the lack of comparative first-episode data with aripiprazole and ziprasidone and (2) the need to individualize treatment. Thus, while the panel agreed that weight-gain potential is a very important consideration in antipsychotic selection for first-episode treatment, there may be instances in which this is not the preeminent issue. The panel considered that careful monitoring of all side effects and making indicated changes in dose or medication in a timely fashion were preferable to a blanket recommendation of some SGAs over others.

In Which Algorithm Stages Should FGAs Be an Option?

Recommendation 2. First-generation antipsychotics are an option in stage 2 of the antipsychotic algorithm after a trial of 1 SGA and in all subsequent stages that include SGAs as a group (group consensus).

Previous recommendation. Monotherapy with first-generation antipsychotics was an option in stage 2A, after trials of 2 SGAs, and in stage 5.

Current evidence review. Since the 2003 TMAP algorithm update, a number of meta-analyses and reviews of antipsychotic effectiveness have been published. In addition, several major RCTs have been completed.

The meta-analyses incorporate studies done almost exclusively prior to the last update and arrive at a range of

sometimes conflicting conclusions with regard to FGA/SGA differences: (1) efficacy is superior for some or all SGAs,[31–36] (2) efficacy is not superior for any SGAs except clozapine,[9,37–41] and (3) EPS occur less often with SGAs, but this depends somewhat on which FGAs were studied and at what doses.[31,33,36–41] By definition, these meta-analyses and reviews are limited to published comparison trials, which are dominated by registration trials intended to achieve regulatory approval for individual SGAs. Moreover, most of the trials used haloperidol as a comparator, often in doses that were high by today's standards. Selection of haloperidol as a comparator and choices of doses used are understandable in terms of community practices at the time the studies were designed, but the question of the advantages of the SGAs compared with more modest doses of FGAs, especially midpotency FGAs, has not been well addressed. Thus, the more recent RCTs noted below strongly influenced the panel's deliberations.

The CATIE phase 1 study found an advantage for olanzapine on the primary outcome, discontinuation of treatment for any cause, compared with quetiapine and risperidone but not compared with perphenazine or ziprasidone.[1] Olanzapine had fewer discontinuations due to lack of efficacy compared with perphenazine, risperidone, and quetiapine. Perphenazine, a moderate-potency FGA, was not statistically different from quetiapine, risperidone, and ziprasidone in all-cause discontinuation, efficacy, or tolerability discontinuations. Perphenazine was not significantly different from olanzapine in tolerability discontinuations. There were no differences between any of the antipsychotics on EPS or akathisia rating scales. Olanzapine had more discontinuations due to metabolic/weight side effects. Perphenazine had more EPS-related discontinuations compared with the SGAs. There were no differences in neurocognitive functioning between the drugs at the primary endpoint of 6 months.[42] Perphenazine was no less effective than any of the newer drugs on measures of quality of life.[43] Perphenazine was associated with lower costs than the newer drugs,[1] all of which were still under patent protection at the time of the study.

Phase 1 of CUtLASS, which was conducted in the United Kingdom, did not find SGAs as a group to be better than FGAs on quality of life (primary outcome) and other secondary scales.[2] Mean total costs were similar between the FGAs and SGAs, in spite of higher drug acquisition costs for the SGAs, because most of the costs in the study were associated with inpatient care. Forty-nine percent of the persons assigned to an FGA received sulpiride, an agent that is not available in the United States. As a result, the findings from this study are not fully applicable to psychiatric practice in the United States. It should also be noted that the CUtLASS study allowed clinician-determined antipsychotic switches, including between SGAs and FGAs, potentially blurring the comparison between classes.

A study conducted in the Veterans Administration that compared olanzapine and haloperidol (plus prophylactic benztropine) showed no difference in retention rates, symptom improvement, or quality of life between the 2 agents.[44] Persons taking olanzapine did have significantly less akathisia than those taking combined haloperidol and benztropine. Olanzapine did have a small advantage on some of the neuropsychiatric subscales used in the study.

A Finnish observational study by Tiihonen et al.[45] found that FGAs and SGAs varied in terms of effectiveness and adherence in community-based populations. Initial use of clozapine, olanzapine, and depot perphenazine was associated with lower rates of discontinuation for any reason versus oral haloperidol. Current use of clozapine, olanzapine, and depot perphenazine was associated with lower risk of rehospitalization.[45]

Discussion. The CATIE and CUtLASS trials particularly bring into question the superiority of the SGAs over FGAs in tolerability, side effects, and reduction of negative symptoms in treating persons with chronic schizophrenia. Each of these studies has been criticized on methodological grounds,[46–51] and there is considerable debate in the field as to how much they should influence clinical practice. While recognizing the merit of some criticisms of these studies, the panel concluded that the criticisms do not invalidate the results. It is therefore appropriate to incorporate the findings of these studies into recommendations about clinical practice.

Relative risks of long-term outcomes such as TD, sequelae of the metabolic syndrome, and risk of premature death remain to be adequately defined with the SGAs and FGAs. Providers need more and better comparative data on these long-term risks, as well as better information on which to base matching of consumer characteristics with antipsychotic properties.

The consumers and advocates stressed strongly the need for collaborative decision making between consumer and prescriber, with a focus on differential risks of TD and on the disfigurement and social stigma that can result from having TD. The panel emphasized the importance of avoiding use of FGAs at high doses and in persons at high risk for TD (e.g., elderly, persons with a history of EPS, persons with traumatic brain injuries). Additionally, the panel expressed considerable clinical concern about "fail-first" policies in which trials of relatively inexpensive antipsychotics would be required before trials of more expensive agents.

The panel recognized that, given expectations of roughly comparable efficacy, the decision regarding which antipsychotic to select for an individual should be driven by differences in the side-effect profiles of the medications under consideration and by which antipsychotic is more or less tolerable for the person in question. The corollary of this approach to medication selection is the need for monitoring side effects after initiation of each

new medication, preferably using validated scales and measures.

How Many Antipsychotic Trials Should Precede Initiation of Clozapine?

Recommendation 3. Two clear antipsychotic trial failures warrant initiation of clozapine, and long delays in clozapine treatment should be avoided. Moreover, persistent symptoms of suicidality or violence or a comorbid substance abuse disorder should prompt earlier institution of clozapine treatment (group consensus).

Previous recommendation. Two to 3 antipsychotic trials should be tried before initiating clozapine.

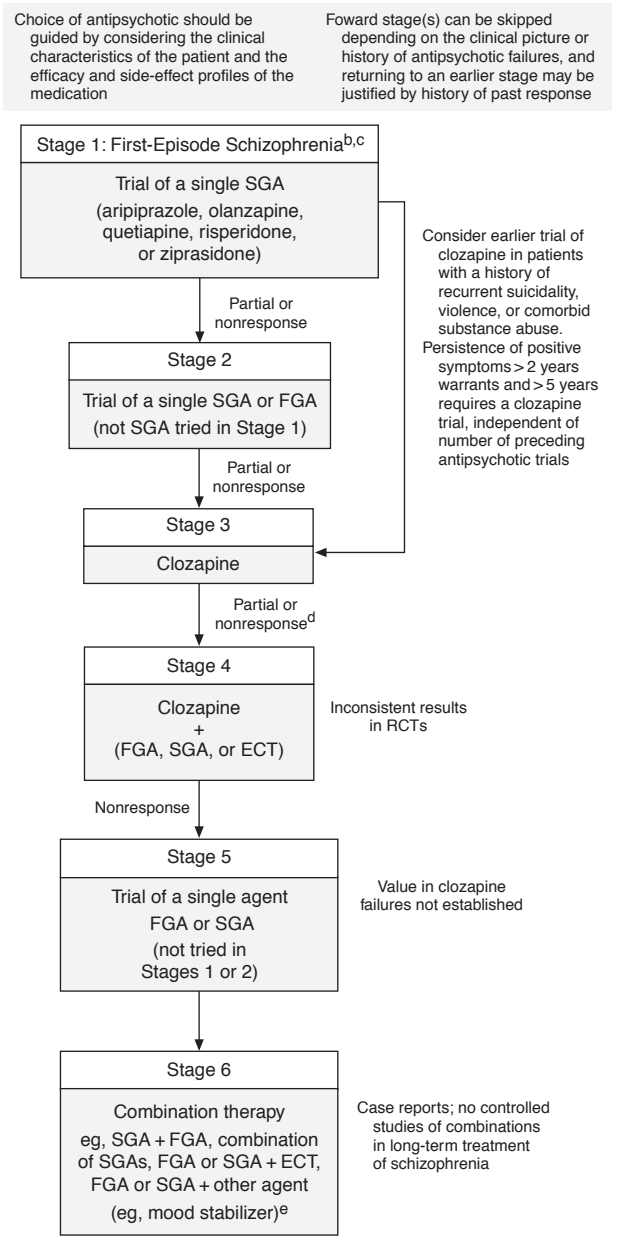
Current evidence review. Data obtained in 1999 from Novartis (manufacturer of clozapine) estimated that 160,000 persons with schizophrenia spectrum disorders had received a trial of clozapine in the United States. If an estimated 20% to 30% of the 2.6 million persons with schizophrenia in the United States at that time were treatment resistant (25%, N = 650,000), then only 25% of the persons with treatment-resistant schizophrenia had ever received clozapine, which is indicated in treatment-resistant schizophrenia.[52]

Since the 2003 schizophrenia update, there have been few new studies evaluating clozapine efficacy. The CATIE trial compared clozapine with other SGAs in phase 2. Persons experiencing efficacy failure while taking their initial study SGA had a longer median time to discontinuation of clozapine compared with quetiapine, risperidone, and olanzapine (10.5 months vs. 2.7–3.3 months).[53]

Clozapine has also shown benefits for persons with a history of suicidality,[54,55] violence,[56–58] or a comorbid substance abuse disorder.[59]

Discussion. The panel noted that dissemination of the TMAP algorithm does not seem to have increased clozapine use, even though progression to clozapine is explicitly encouraged in the procedures manual. This apparent reluctance to use clozapine is in accord with phase 2 results of CATIE, in which many participants did not enter the efficacy pathway (phase 2E) in favor of entering the tolerability pathway (phase 2T), perhaps to avoid being randomly assigned to clozapine treatment (clozapine was an option in phase 2E but not in phase 2T). In light of the evidence from CATIE confirming clozapine's unique effectiveness,[60–62] the panel agreed that the algorithm diagram should include a strong statement advocating clozapine use for individuals with treatment-refractory symptoms (Figure 2). The panel recognized that there are processes of coming to accept the diagnosis and the need for medication treatment that often must occur when a person is first diagnosed with schizophrenia and that these processes can take time and can interfere with undertaking consistent treatment. Apparent failure of medications during this period is often due to erratic adherence, and

Figure 2. TMAP Antipsychotic Algorithm: 2006[a]



[a]Reprinted with permission from the Texas Department of State Health Services.
[b]First-episode patients usually require lower antipsychotic dosing and should be closely monitored due to greater sensitivity to medication side effects. Lack of consensus on inclusion of FGAs as option for first episode.
[c]If patient is inadequately adherent at any stage, the clinician should assess contributing factors and consider a long-acting antipsychotic preparation, such as risperidone microspheres, haloperidol decanoate, or fluphenazine decanoate.
[d]A treatment-refractory evaluation should be performed to reexamine diagnosis, substance abuse, medication adherence, and psychosocial stressors. Cognitive-behavioral therapy and other psychosocial augmentations should be considered.
[e]Whenever a second medication is added to an antipsychotic (other than clozapine) for the purpose of improving psychotic symptoms, the patient is considered to be in Stage 6.
Abbreviations: ECT = electroconvulsive therapy, FGA = first-generation antipsychotic, SGA = second-generation antipsychotic, TMAP = Texas Medication Algorithm Project.

clinicians may want to consider use of a long-acting injectable antipsychotic. The panel noted that most persons are started on clozapine after many years of illness and concluded that clinicians should strongly consider clozapine use earlier in the course of illness. A consensus was reached on the recommendations that a person with persistent positive symptoms during 2 years of consistent medication treatment should be considered for clozapine therapy, and 5 years of inadequate response should mandate offering a trial of clozapine, independent of the number of previous antipsychotic trials.

The panel also noted that formation of clozapine clinics, while improving efficiency and logistics of clozapine treatment in the short run, may have had the unintended consequence of limiting the number of providers who are comfortable with and proficient at prescribing clozapine, thereby reducing training opportunities for residents. While noting that clozapine should not be reserved only for specialty practice or clinics (e.g., a referral for ECT), the panel also acknowledged that clinicians with limited exposure to clozapine do need to be provided with administrative and clinical support to gain expertise in clozapine therapy.

The choice of moving on to clozapine treatment is often complex. No universally accepted definition of treatment-resistant schizophrenia exists.[63] The classic clozapine study in treatment-resistant schizophrenia by Kane et al.[64] defined treatment resistance as failure with at least 2 FGAs from 2 different chemical classes, but this definition has not been systematically reassessed since the availability of multiple SGAs. For purposes of defining an adequate antipsychotic trial, at least 4 weeks of taking full therapeutic doses of the antipsychotic was recommended at the Mt. Sinai conference on use of antipsychotics in schizophrenia.[65]

What Is the Status of Augmentation Strategies for Clozapine?

Recommendation 4. Clozapine augmentation should be with an SGA, an FGA, or ECT at stage 4 preceded by a "treatment-refractory" evaluation (group consensus).

Previous recommendation. Augmentation of clozapine with an SGA, an FGA, or ECT at stage 4.

Current evidence review. Since the 2003 update, there have been a number of RCTs with risperidone, lamotrigine, or sulpiride augmentation of clozapine.

Four randomized, double-blind, placebo-controlled trials of risperidone augmentation of clozapine have been published.[3–6] In each of the 4 studies, all participants improved significantly over time, particularly during weeks 2 to 6 (regardless of treatment). Three of 4 trials found no advantage of risperidone versus placebo augmentation of clozapine in subjects with a history of partial or poor response to clozapine monotherapy. Thus, the evidence favoring risperidone augmentation is weak.

One published randomized, double-blind, placebo-controlled, 14-week, crossover trial of 34 inpatients examined lamotrigine augmentation of clozapine.[7] Clozapine plasma concentrations did not change significantly with the addition of either lamotrigine or placebo. Lamotrigine added to clozapine was superior to placebo added to clozapine for positive and general symptoms in persons with schizophrenia inadequately responsive to clozapine alone, but the mean changes in symptoms were fairly small.

In 2 as yet unpublished studies of antipsychotic augmentation with lamotrigine performed by GlaxoSmithKline, a total of 419 persons with schizophrenia and persistent residual symptoms were enrolled. Results can be viewed on the company's Web site.[66,67] Sixty-four subjects (15%) were taking clozapine in the 2 double-blind, placebo-controlled, 12-week trials. Participants were given 100 to 400 mg of lamotrigine gradually added to ongoing antipsychotic treatment. Changes from baseline in the Positive and Negative Symptom Scale (PANSS) total score were similar with added lamotrigine or placebo in both studies. No statistically significant improvement in positive, negative, or general subscales was observed for lamotrigine compared with placebo in either study for the entire study group.

A recent review of cognitive behavioral therapy (CBT) in schizophrenia by Turkington and colleagues[68] concludes that although more RCTs of CBT need to be performed in the area of schizophrenia, the evidence to date supports adjunctive use of CBT with antipsychotic medication for persistent psychotic symptoms. This is an available "augmenting" intervention for persons taking clozapine with persistent psychotic symptoms.

Use of adjunctive ECT with clozapine was reviewed at the last update.[11] Case series indicate positive effects, but no RCTs have been published.

Discussion. The evidence from randomized trials is mixed with regard to risperidone and lamotrigine augmentation of clozapine. On the other hand, there are no RCTs that have tested other agents for persons responding inadequately to clozapine, and a good deal of clinical experience suggests that persons not doing well on clozapine become worse when they discontinue the medication. Therefore, the panel elected to keep augmentation of clozapine as an option before trying another antipsychotic. Even though there are negative data for risperidone and lamotrigine as clozapine-augmenting agents, it could be quite incorrect to single them out as ineffective since results for agents other than sulpiride are not based on RCTs.

The panel did support the addition of a statement encouraging a "treatment-refractory evaluation" (including clozapine serum concentrations) before considering clozapine augmentation. "A treatment-refractory evaluation should be performed to re-examine diagnosis, substance abuse, medication adherence, and psychosocial stressors. Cognitive-behavioral therapy and/or other psy-

chosocial interventions should be considered." The expert panel emphasized that not all psychosocial interventions are equal and that any therapeutic intervention should be carefully chosen on the basis of best available evidence.

In addition, the mixed results of clozapine augmentation strategies serve to emphasize the need to optimize clozapine treatment. Attention to side effects and vigorous treatment of them when troublesome to the consumer or when medically problematic is critically important. Several studies have found that clozapine serum concentrations can be useful to help guide dosing.[69–72]

A fifth panel recommendation preceded the consensus conference and was arrived at in a series of teleconferences of the academic panel members in late 2005. The recommendation was reviewed and ratified at the 2006 conference. Because this recommendation has not been previously published, it is included here.

Recommendation 5. Long-acting injectable risperidone should be added to haloperidol decanoate and fluphenazine decanoate as options for treatment of persons with medication adherence problems (group consensus).

Previous recommendation. Long-acting injectable risperidone was not available at the time of the 2003 update.

Current evidence review. Studies varying in length from 12 weeks to 12 months have shown that long-acting injectable risperidone significantly reduces symptomatology in doses from 25 to 75 mg given once every 2 weeks.[73–75] Subgroup analyses examining open-label switching from oral risperidone to long-acting injectable and switching from FGA long-acting injectables to long-acting risperidone injectable showed further reduction in total PANSS scores.[76,77]

A double-blind, randomized trial evaluated time to relapse comparing 25- and 50-mg doses of long-acting injectable risperidone. The projected time to relapse was 161.8 weeks for the 25-mg dose and 259.0 weeks for the 50-mg dose. The 1-year incidence of relapse was 21.6% (N = 35) and 14.9% (N = 24) for the 25- and 50-mg doses, respectively.[78]

Discussion. Safety and efficacy data support long-acting injectable risperidone's addition to the algorithm, but a lack of studies comparing the drug with other oral antipsychotics and other long-acting injectables makes it difficult for providers to assess the utility of long-acting risperidone injectable relative to other options. The requirement for extended use of an oral antipsychotic while awaiting release of risperidone from microspheres presents challenges for brief inpatient stays and persons with problematic outpatient adherence to oral medications. Further studies of long-acting injectable risperidone are underway and should shed light on this preparation's role in the treatment armamentarium.

DISCUSSION

The revised TMAP recommendations represent the panel's assessment of the best available evidence on key clinical questions influencing antipsychotic prescribing for people with schizophrenia. Recent large-scale studies have added significantly to the evidence base, yet the number of recommendations that are based primarily on consensus rather than on randomized, blinded, placebo-controlled evidence is still distressingly high. In part, this is because many of the most critical questions in treatment of any chronic illness require studies that last for years. Such studies are expensive, very difficult to design and carry out, and provide few short-term rewards to sponsors or investigators and will only occur if there is a commitment to them on the basis of their national public importance.

Controlled trials of all the agents being used for first-episode schizophrenia are badly needed, as are longer-term studies of medication effects on long-term course of illness after onset. Further studies that build on CATIE and CUtLASS in addressing selection of antipsychotics on the basis of individual consumer characteristics and history could be extraordinarily helpful in identifying rational sequences of medications for individuals. The role of long-acting injectable antipsychotics in the current era needs much greater clarity. Clinicians still have no evidence-based choices for persons who do not respond adequately to clozapine. Moreover, given that clozapine showed no real advantages over chlorpromazine for first-episode psychosis,[45] greater understanding of when in the course of illness the unique characteristics of clozapine become essential for "treatment resistance" is badly needed.

On the basis of the limited data available and the lack of long-term data addressing FGAs versus SGAs, the group raised the following clinical questions that should be addressed by future research. Has the frequent use of relatively high doses of haloperidol as active comparator thrown us off the track in evaluating relative EPS/TD risks of newer antipsychotics? Is the FGA versus SGA distinction regarding EPS/TD less pronounced with low-to-moderate doses of midpotency FGAs? The group concurred that head-to-head trials incorporating FGAs other than haloperidol (using low-to-moderate dosing), trials examining consumer antipsychotic preferences and corresponding adherence differences, and more in-depth trials examining differences in negative symptoms would help clarify the utility of any FGA/SGA distinction.

The panel noted with dismay that clozapine use seems to be decreasing, even while the evidence base for it is growing. Since the most widely disseminated guidelines and algorithms, including TMAP, point clinicians to clozapine for treatment resistance, the explanation for this phenomenon is not that the field is in doubt about the

recommendation. Rather, the problem seems to lie with implementation at all levels—state, region, clinic, and practitioner. Research to identify and eliminate the barriers to clozapine use and to ameliorate clozapine's side effects, especially in the metabolic arena, should be a national health priority.

Lastly, the panel discussed some methodological issues that pertain to improving the evidence base that underlies treatment guidelines and algorithms. First, feasibility and ethical and ecological validity considerations each affect the degree to which important clinical treatment questions are amenable to being answered by results of RCTs. A greater effort is needed to achieve expert clinical consensus on defining the key questions and the alternate research strategies for addressing those questions not amenable to RCTs. Second, to the extent that results of studies have vital public policy implications, it becomes absolutely essential that the scientific justification for generalizing from the study population to the population with the disorder be as strong as possible. Historically, RCTs in schizophrenia have enrolled tightly defined populations using inclusion and exclusion criteria such as absence of substance abuse that clearly limit generalizability. Pragmatic studies such as CATIE have sought to enroll subjects who are representative of the entire treatment population, but persons who elect to participate in any studies may be different from those who do not and thus can result in some uncertainty about generalizability of results. Efforts to design and carry out large pragmatic trials that address key clinical questions are critically important and deserving of public support.

Clearly, this version of the algorithm is far from the last word on pharmacologic treatment for schizophrenia. Important questions currently under investigation include the role of augmenting strategies for treatment of negative symptoms, comparative studies of antipsychotic medications in first-episode schizophrenia, comparisons of risperidone microspheres to oral antipsychotic medications, and the role of ECT as an augmenting treatment for persons with schizophrenia refractory to clozapine treatment. Further, new antipsychotic medications are under development, some with novel mechanisms of action. Future updates will be developed as sufficient new data accumulate to warrant revisions.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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