The Texas Medication Algorithm Project Antipsychotic Algorithm for Schizophrenia: 2003 Update

Alexander L. Miller, M.D.; Catherine S. Hall, Pharm.D.; Robert W. Buchanan, M.D.; Peter F. Buckley, M.D.; John A. Chiles, M.D.; Robert R. Conley, M.D.; M. Lynn Crismon, Pharm.D.; Larry Ereshefsky, Pharm.D.; Susan M. Essock, Ph.D.; Molly Finnerty, M.D.; Stephen R. Marder, M.D.; Del D. Miller, M.D., Pharm.D.; Joseph P. McEvoy, M.D.; A. John Rush, M.D.; Sy A. Saeed, M.D.; Nina R. Schooler, Ph.D.; Steven P. Shon, M.D.; Scott Stroup, M.D.; and Bernardo Tarin-Godoy, M.D.

Background: The Texas Medication Algorithm Project (TMAP) has been a public-academic collaboration in which guidelines for medication treatment of schizophrenia, bipolar disorder, and major depressive disorder were used in selected public outpatient clinics in Texas. Subsequently, these algorithms were implemented throughout Texas and are being used in other states. Guidelines require updating when significant new evidence emerges; the antipsychotic algorithm for schizophrenia was last updated in 1999. This article reports the recommendations developed in 2002 and 2003 by a group of experts, clinicians, and administrators.

Method: A conference in January 2002 began the update process. Before the conference, experts in the pharmacologic treatment of schizophrenia, clinicians, and administrators reviewed literature topics and prepared presentations. Topics included ziprasidone's inclusion in the algorithm, the number of antipsychotics tried before clozapine, and the role of first generation antipsychotics. Data were rated according to Agency for Healthcare Research and Quality criteria. After discussing the presentations, conference attendees arrived at consensus recommendations. Consideration of aripiprazole's inclusion was subsequently handled by electronic communications.

Results: The antipsychotic algorithm for schizophrenia was updated to include ziprasidone and aripiprazole among the first-line agents. Relative to the prior algorithm, the number of stages before clozapine was reduced. First generation antipsychotics were included but not as first-line choices. For patients refusing or not responding to clozapine and clozapine augmentation, preference was given to trying monotherapy with another antipsychotic before resorting to antipsychotic combinations.

Conclusion: Consensus on algorithm revisions was achieved, but only further well-controlled research will answer many key questions about sequence and type of medication treatments of schizophrenia.

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Received July 15, 2003; accepted Jan. 21, 2004. *From the Department of Psychiatry, The University of Texas Health Science Center at San Antonio, San Antonio (Drs. A. L. Miller, Hall, and Ereshefsky); San Antonio State Hospital, San Antonio, Tex. (Drs. A. L. Miller and Ereshefsky); Maryland Psychiatric Research Center, Baltimore (Drs. Buchanan and Conley); Department of Psychiatry, Medical College of Georgia, Augusta (Dr. Buckley); Department of Psychiatry, University of Washington School of Medicine, Seattle (Dr. Chiles); College of Pharmacy, The University of Texas at Austin, Austin (Drs. Crismon and Ereshefsky); Texas Department of Mental Health and Mental Retardation, Austin (Drs. Crismon and Shon); Mount Sinai School of Medicine, New York, N.Y. and Mental Illness Research, Education, and Clinical Center, Veterans Administration, Bronx, N.Y. (Dr. Essock); New York Office of State Mental Health, Albany (Dr. Finnerty); West Los Angeles VA Health Care Center, Los Angeles, Calif. (Dr. Marder); Department of Psychiatry, University of Iowa College of Medicine, Iowa City (Dr. D. Miller); Department of Psychiatry and Behavioral Sciences, Duke University, Durham, N.C. (Dr. McEvoy); Department of Psychiatry, The University of Texas Southwestern Medical Center at Dallas, Dallas (Dr. Rush); Department of Psychiatry and Behavioral Medicine, The University of Illinois College of Medicine, Peoria (Dr. Saeed); Hillside Hospital-Long Island Jewish Medical Center, Long Island, N.Y. (Dr. Schooler); Department of Psychiatry, University of North Carolina, Chapel Hill (Dr. Stroup); and El Paso Community Mental Health and Mental Retardation Center, El Paso, Tex. (Dr. Tarin-Godoy).*

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Corresponding author and reprints: Alexander L. Miller, M.D., Department of Psychiatry, University of Texas Health Science Center at San Antonio, MC 7792, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900 (e-mail: millera@uthscsa.edu).

This article reports the recommendations of a consensus process to update the antipsychotic algorithm for schizophrenia of the Texas Medication Algorithm Project (TMAP). An update conference took place in San Antonio, Texas, in January 2002.

TMAP has been a collaboration among the Texas Department of Mental Health and Mental Retardation (TDMHMR) in Austin, 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 psychiatrists, consumers, families, and mental health advocates in Texas. The first phase of TMAP consisted of drafting medication algorithms for the 3 most prevalent psychiatric disorders in the state mental health system: schizophrenic, bipolar,

and major depressive disorders.[1–4] The second phase of TMAP evaluated the feasibility of implementing the algorithms in the public mental health sector,[5–8] while the third phase was a research study comparing the clinical and economic outcomes of patients receiving algorithm-guided treatment with outcomes of patients receiving treatment-as-usual.[9–11] Currently, the antipsychotic algorithm for schizophrenia is being used throughout the Texas public mental health system. In addition, clinicians in 14 other states and the District of Columbia have been trained on its use.

The original antipsychotic algorithm for schizophrenia was developed in 1996. At that time, a consensus panel of academic experts, TDMHMR clinicians, administrators, patients, family members, and mental health advocates convened to develop guidelines for the treatment of schizophrenia based on the Expert Consensus Guidelines Series[12] and the Patient Outcomes Research Team (PORT) project.[13] While the TMAP Antipsychotic Algorithm for Schizophrenia was based on these prior efforts, the TMAP investigators wanted to create a very specific and detailed treatment guideline that included quantitative outcome measures and clear directions on medication management.[6] Thus, in addition to the medication algorithm for each illness, clinical procedures manuals covering most aspects of medication management were also created for the project and updated along with the algorithms. The current procedures manual for schizophrenia can be found at the following URL: http://www.mhmr.state.tx.us/CentralOffice/MedicalDirector/timasczman.pdf.

The 1996 version was revised in 1999 to incorporate olanzapine and quetiapine, respectively. (Figure 1 shows the algorithm as it appeared after the 1999 revisions; this was the version in use at the time of the update conference in January 2002.) These compounds were approved by the U.S. Food and Drug Administration (FDA) during the TMAP project, and the algorithm had to be modified without convening a consensus panel because of the time constraints imposed by concurrently doing the project.

METHOD

In January 2002, experts in the pharmacologic treatment of schizophrenia, experienced clinicians, and administrators met in San Antonio, Texas, to update the TMAP Antipsychotic Algorithm for Schizophrenia. Prior to the conference, the meeting organizers assigned topics to each expert for literature review and presentation at the update conference. The materials presented were discussed by the group, which then arrived at consensus recommendations.

The presenting experts were asked to grade recommendations according to the system developed by the Agency for Healthcare Research and Quality (AHRQ) (formerly the Agency for Health Care Policy and Research [AHCPR]) to develop depression guidelines. Under this rating system, level A recommendations are based on randomized, blinded, and placebo-controlled trials; level B recommendations are based on open controlled trials and/or large case series; and level C recommendations are based on smaller case series and case reports.[14] Whenever possible, the consensus panel members based their decisions on empirical evidence, but when inadequate data were available, decisions were based on clinical and expert consensus. The strength of the group consensus on these recommendations has been characterized as weak, moderate, or strong, and the reasons for the strength of the rating are discussed in the text.

RESULTS

The format adopted in this article is to first pose the question facing the update conference attendees. Each question is followed by the consensus recommendation, the level of evidence upon which the recommendation is based, and supporting background information. For further discussion of the development of previous versions of the TMAP Antipsychotic Algorithm, see Miller et al.[6] and Chiles et al.[3]

One of the topics discussed at the update conference was how to monitor for antipsychotic side effects, both short- and long-term. After some discussion, the experts decided that this topic merited its own conference, and final recommendations were deferred. The results of the Mt. Sinai Medication Monitoring Conference of October 2002 are being reported separately by Marder et al. and, once available, will be incorporated into the revised algorithm implementation manual.

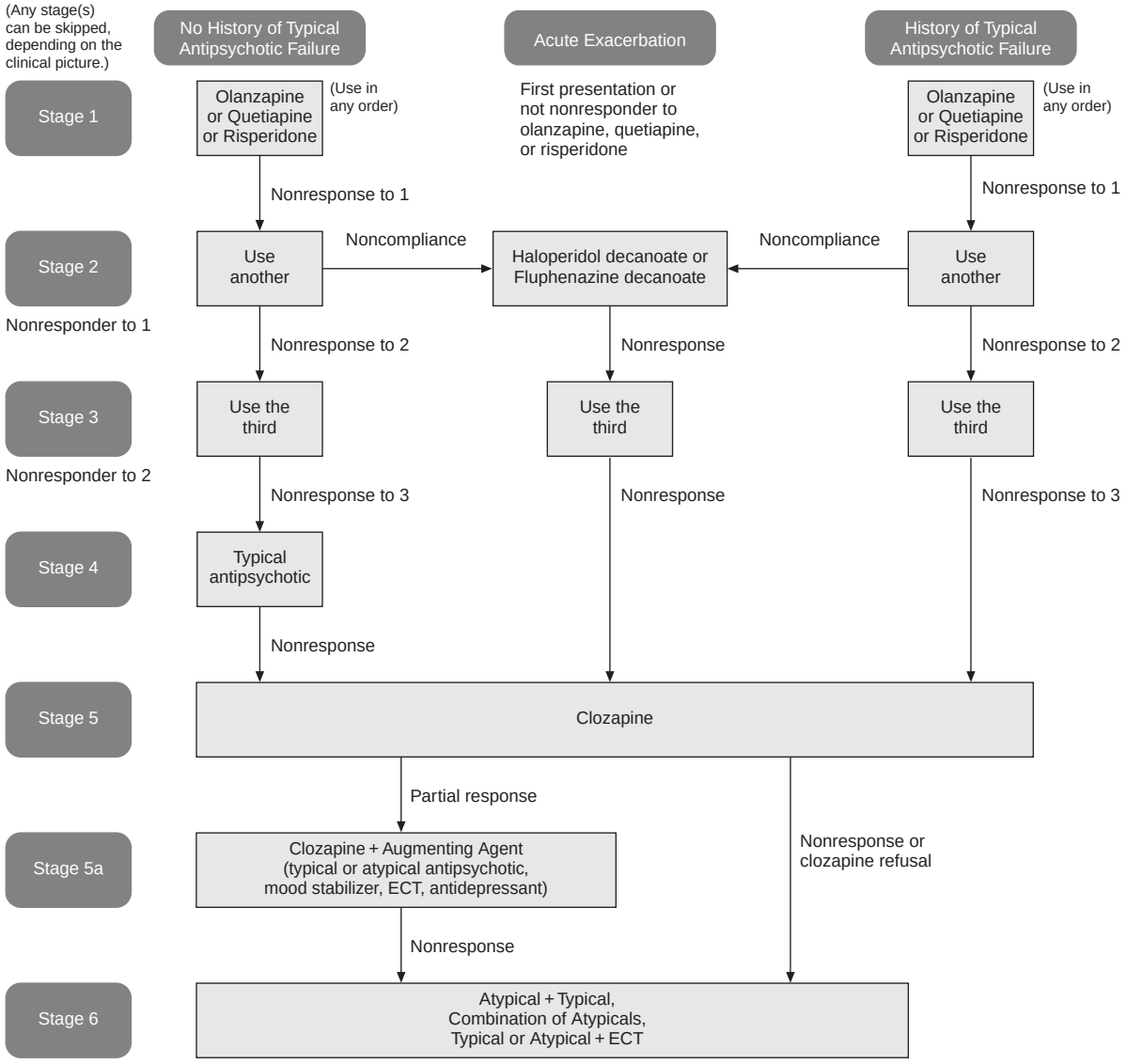
The TMAP Schizophrenia Module consists of multiple distinct algorithms: one for antipsychotics, several for side effects, and several for coexisting symptoms. The conference addressed only the updating of the antipsychotic algorithm.

Question 1. Should Ziprasidone Be a First-Line Antipsychotic in the Revised Antipsychotic Algorithm?

Consensus recommendation (Level A). Because of its apparent weight-neutrality, slight effects on glucose and lipids, and the evidence to suggest that, when used as indicated, ziprasidone's risk of cardiac events and sudden death is no greater than that of other first-line agents, the conference attendees decided to add ziprasidone to the other medications that comprise Stage 1 of the Antipsychotic Algorithm (Figure 2) (See Contraindications, Warnings sections of package insert for detailed prescribing information for ziprasidone.[15]).

Background information. Ziprasidone was initially submitted to the FDA in 1997, but concern over the

Figure 1. TMAP Antipsychotic Algorithm: 1999[a]



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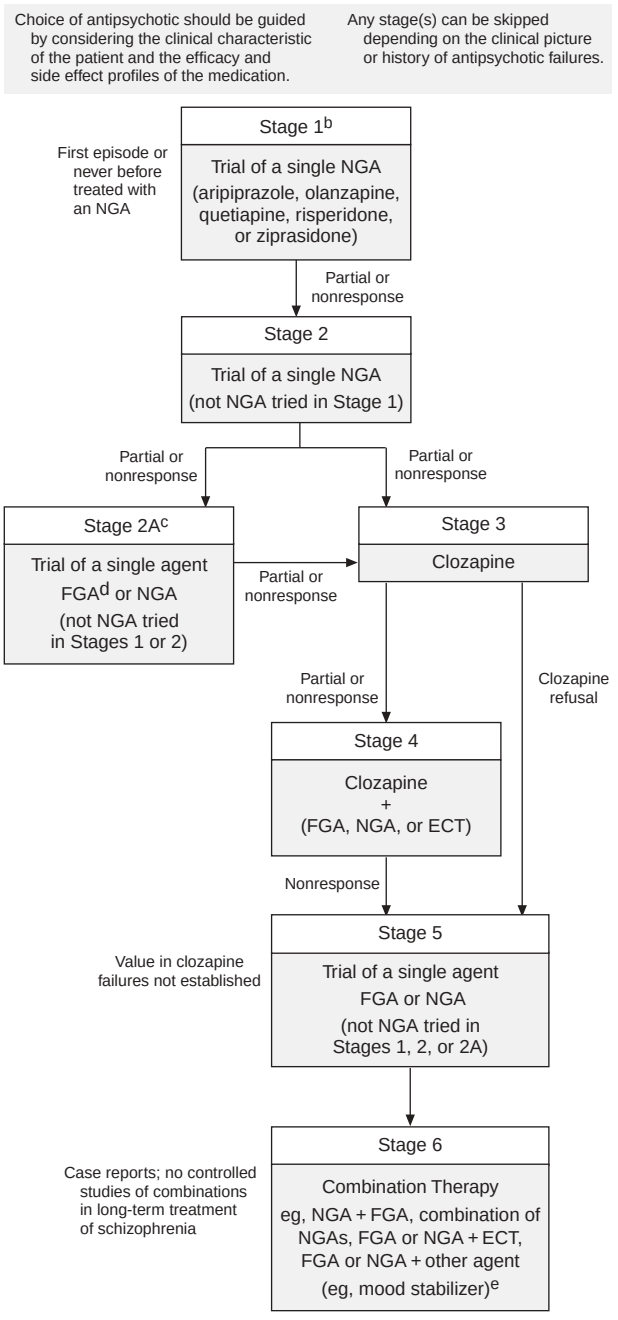
Abbreviations: ECT = electroconvulsive therapy, TMAP = Texas Medication Algorithm Project.

medication's propensity to prolong the QTc interval delayed its approval until February 2001. After denying ziprasidone's approval in 1997, the FDA requested that Pfizer conduct a study to characterize the electrocardiographic (ECG) effects of ziprasidone.[16] The principal results of that study, which also evaluated the QTc effects of risperidone, olanzapine, quetiapine, thioridazine, and haloperidol, are as follows: Ziprasidone appeared to prolong the QTc interval more than haloperidol, olanzapine, quetiapine, and risperidone, but these differences were not statistically significant. Thioridazine was the only antipsychotic whose QTc prolongation was statistically greater than that of the other antipsychotics studied, and metabolic inhibition did not result in further QTc prolongation for any antipsychotic. The QTc prolongation associated with ziprasidone did not appear to be dose-related.[17,18]

Data from premarketing trials of ziprasidone have also been evaluated in an effort to elucidate the effect of ziprasidone on the QTc interval. These analyses revealed that 0.07% (2/2988) of patients taking oral ziprasidone had a QTc of > 500 ms compared with 0.23% (1/440) of patients taking placebo.[15] At the time of the update conference, about 150,000 patients had received ziprasidone since its approval by the FDA, and there had been no documented cases of sudden death attributable to torsades

Figure 2. TMAP Antipsychotic Algorithm: 2003[a]



[a]This material is in the public domain and can be copied and distributed without permission but with appropriate citation.
[b]If patient is nonadherent to medication, the clinician may use haloperidol decanoate or fluphenazine decanoate at any stage but should carefully assess for unrecognized side effects and consider a different oral antipsychotic if side effects could be contributing to nonadherence.
[c]See text for discussion. Current expert opinion favors bypassing Stage 2A and going directly to Stage 3.
[d]Assuming no history of nonresponse to an 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, NGA = newer generation antipsychotic, TMAP = Texas Medication Algorithm Project.

de pointes.[18] Thus, postmarketing experience has not yielded a signal of increased sudden death.

Clinical trials show that therapeutic doses of ziprasidone are equal in efficacy to therapeutic doses of haloperidol[19] and olanzapine.[20] In a "switch" study, patients who either did not respond adequately to or could not tolerate risperidone, olanzapine, or first generation antipsychotics (FGAs)[21] appeared to improve after a 6-week trial of ziprasidone. Some conference attendees were concerned that the data supporting ziprasidone's efficacy are less robust than the data supporting the efficacy of previously released newer generation antipsychotics (NGAs). Others thought that ziprasidone's study population was different than that of the earlier NGAs because many patients who participated in the ziprasidone registration trials may have failed trials of other NGAs, while patients in the earlier registration trials would have had less exposure to the newer medications.

Discussion of including ziprasidone in Stage 1 of the algorithm also focused on the desirability of having a first-line antipsychotic that is less likely to promote weight gain.[22] Moreover, clinicians are becoming increasingly concerned about the association of certain NGAs with diabetes[23,24] and hyperlipidemias.[25]

The need to take ziprasidone twice a day and to take it with food were noted as negative considerations. Pharmacokinetic studies have shown that ziprasidone's absorption is 1.5 to 2 times higher when the medication is taken with food.[15]

Question 2. Should FGAs Remain in the Revised Antipsychotic Algorithm, and, if so, Where Do They Belong in the Sequence of Treatments?

Consensus recommendation (Group consensus, moderate). No empirical basis exists for excluding the FGAs from the revised antipsychotic algorithm, and many clinicians believe that some patients do better on FGA than NGA treatment. There are significant gaps in our knowledge about the appropriate role of FGAs in the era of multiple NGAs. As indicated by the placement of FGAs in Stage 2A, an option for patients with symptoms that are unresponsive to 2 NGAs is to receive a trial of an FGA before moving on to clozapine, if they have not previously had an unsuccessful trial with an FGA. In the case of patients who fail or refuse clozapine, the experts recommended that clinicians use another monotherapy (possibly an FGA) in Stage 5 before resorting to antipsychotic polypharmacy with agents other than clozapine. In Stages 2A and 5, the FGAs are listed as treatment alternatives (as opposed to being the sole treatment). The conference attendees also recommended their use in the following clinical situations:

1. Patients currently taking an FGA who have achieved a good therapeutic response with mini-

mal or no evidence of extrapyramidal symptoms, including tardive dyskinesia.
2. Patients who are candidates for long-term depot therapy (although the future availability of sustained-release injectable forms of NGAs may alter this recommendation).
3. Temporary, adjunctive use in patients who are acutely agitated and potentially violent despite maintenance therapy with an NGA. In the case of short-term use, the treatment stage in the Antipsychotic Algorithm is not affected because the patient is being treated under the Coexisting Symptom Algorithm for Agitation and Excitement.

Background information. Figure 1 shows the algorithm after its revision in 1998. It included FGAs in Stage 4, after a patient had failed trials of 3 NGAs but before a trial of clozapine. The FGAs were not included as first-line treatments in the algorithm because, compared with the NGAs, they cause more acute side effects, have greater potential for producing tardive dyskinesia, are equal or worse for the negative and cognitive symptoms of schizophrenia, and are no more effective for positive symptoms.[6]

Since the 1998 revision, 2 meta-analyses have compared the relative efficacy and tolerability of FGAs and NGAs. One analysis found that, when lower doses of the FGAs were used, they were equal to NGAs in terms of efficacy and overall tolerability, represented by rate of dropout.[26] However, many comments on the article[27–35] have questioned the methods and conclusions of the meta-analysis. The other meta-analysis suggested that, in terms of global improvement in schizophrenic symptoms, risperidone and olanzapine are somewhat more efficacious than haloperidol, while sertindole and quetiapine are equal in efficacy to haloperidol.[36] Both meta-analyses found that NGAs cause fewer extrapyramidal side effects than do FGAs.

No data directly addressed the question posed by the conference organizers, i.e., what proportion of patients who do not respond satisfactorily to one or more NGAs (other than clozapine) will respond adequately to an FGA, if the patient has no history of lack of response to an FGA? In the absence of data, the conference attendees reached their decision (see above) through expert consensus.

Question 3. How Many Antipsychotics Should Be Tried Before Clozapine Is Initiated?

Consensus recommendation (Group consensus, strong). The majority of panel members agreed that clozapine should be promoted to Stage 3 in the updated Antipsychotic Algorithm. The branch point after Stage 2 indicates that, if they so choose, clinicians may attempt a trial of a third antipsychotic (Stage 2A) before initiating clozapine. The experts also concluded that clozapine may be an appropriate Stage 2 drug for patients whom clinicians consider to be at high risk for suicide or violent behavior. The decision to use clozapine at Stage 2 should be the result of shared decision making between clinician and patient.

Background information. There is no universally accepted definition of treatment-resistant schizophrenia.[37] The classic study by Kane et al.[38] defined treatment resistance as failure with at least 2 antipsychotics from 2 different chemical classes. More recently, treatment resistance has been defined as failure with 2 (or even 1) antipsychotics.[39,40]

The 1998 version of the Antipsychotic Algorithm (Figure 1) listed clozapine in Stage 5, after a patient had failed trials of all 3 NGAs and an FGA. Clinicians were given the option of skipping ahead to clozapine if the clinical situation warranted. While it is estimated that anywhere from 20% to 30% of patients with schizophrenia have treatment-resistant illness[41] and would, therefore, be suitable candidates for clozapine, only a modest fraction of patients with treatment-resistant schizophrenia is being treated with clozapine.[41] Clozapine's apparent under-use prompted discussion of whether it should be moved to an earlier stage in the algorithm.

Since the Antipsychotic Algorithm's last revision in 1998, no further data have emerged with regard to how many antipsychotics should be tried in a patient before clozapine is initiated. Moreover, the results of studies that have examined predictors of response to clozapine are conflicting with regard to the effect of duration of illness on the likelihood of response to clozapine.[42,43] The lack of empirical evidence for how soon to use clozapine required that the conference attendees base their recommendation on group consensus. The following paragraphs present the considerations that influenced the experts' decision to move clozapine to Stage 3 (Figure 2) from Stage 5 (Figure 1).

Clozapine's side effects are usually considered to preclude its use as a first-line agent. In addition to undergoing weekly blood monitoring for agranulocytosis, patients who take clozapine often experience bothersome sedation, weight gain, constipation, and sialorrhea. While patients who have not responded satisfactorily to (and have suffered the side effects of) other antipsychotics may be willing to endure some discomfort in exchange for symptomatic relief and increased functionality, many patients who are antipsychotic naive have not yet achieved this perspective.

The conference attendees also discussed the possibility of promoting clozapine to Stage 2. There are no data from randomized controlled trials on the response rate to a second NGA after failure with one. However, almost all practicing psychiatrists who were polled at schizophrenia algorithm training sessions indicated that, in their clinical experience, if a patient fails or only partially responds to one NGA, a second NGA has a substantial likelihood of

being successful. This informal consensus suggests that a second NGA is a reasonable choice before initiating clozapine. Data indicating that clozapine can offer benefits for patients with suicidality[44] and aggression[45,46] may support its earlier use in selected cases.

Patients in Stage 3 of the algorithm who have not responded satisfactorily to at least 2 antipsychotic trials meet the current definition of treatment resistance. Clozapine's effectiveness in patients who do not respond to FGAs is well established,[38] and clozapine appears to be more effective than other NGAs.[39] Clinicians who wish to attempt a trial of another antipsychotic (either NGA or FGA) before starting clozapine may opt to go from Stage 2 to Stage 2A; however, the majority of the conference attendees favored bypassing Stage 2A and going directly from Stage 2 to clozapine. By promoting clozapine to Stage 3, the panel emphasized the proven superiority of clozapine over other antipsychotic treatments for a variety of clinical conditions.

Question 4. What Are the Treatment Options for Patients Who Do Not Respond or Only Respond Partially to Clozapine Monotherapy?

Consensus recommendation (Level C). Augmentation of clozapine remains the best treatment option for patients whose schizophrenic symptoms fail to respond or only partially respond to an adequate trial of clozapine monotherapy. Although the literature is sparse, the bulk of evidence involves using clozapine combined with an FGA, an NGA, or electroconvulsive therapy (ECT) (Figure 2, Stage 4).

Background information. There is no evidence from controlled trials that monotherapy with other antipsychotics is beneficial for partial responders or nonresponders to clozapine monotherapy. Thus, augmentation of clozapine is the preferred treatment option for these patients. The experts' task was to identify augmentation strategies best substantiated by empirical data. It is important to emphasize that, in these cases, the second agent is targeted toward the treatment of refractory psychotic symptoms, not seizure prophylaxis or affective or behavioral symptoms.

One randomized controlled trial of augmentation with sulpiride,[47] open-label studies of augmentation with loxapine[48] and risperidone,[49] and a retrospective analysis of augmentation with pimozide[50] support the addition of a second antipsychotic to clozapine in patients for whom clozapine monotherapy has yielded unsatisfactory results.[41,51] There have been several case reports/series of clinical improvement in patients poorly responsive to clozapine who were treated with the combination of clozapine and ECT.[52–55]

In addition to antipsychotics and ECT, the previous version of the Antipsychotic Algorithm listed mood stabilizers and antidepressants as potential options for clozapine augmentation. The complete lack of evidence to support the use of either of these classes of medications as augmenting agents for clozapine-refractory psychosis prompted the experts to remove them from the clozapine augmentation stage of the algorithm.[41,51]

Question 5. When Should Clinicians Use Combinations of Antipsychotics?

Consensus recommendation (Group consensus, weak). Patients with treatment-resistant illness should receive a trial of clozapine monotherapy before they are treated with combinations of antipsychotics. For patients who refuse to take clozapine or who do not adequately respond to clozapine and clozapine augmentation, clinicians should attempt a final monotherapy trial before using combinations of antipsychotics.

Background information. There is no evidence to support the use of antipsychotic polypharmacy before a trial of clozapine has been attempted.[56] The group was strong in its consensus on this point, but the issue of whether or when to use antipsychotic combinations for persons who have failed clozapine was more debatable. In terms of combination strategies, those involving clozapine and another antipsychotic agent have the most empirical support (see Question 4). There are no controlled data to support the effectiveness of any single antipsychotic or any combination of antipsychotics in patients who refuse to take clozapine or who do not respond adequately to clozapine and to clozapine augmentation.[57] Thus, there was debate over whether to recommend any treatments beyond clozapine augmentation. Recognizing that clinicians have patients who refuse or are nonresponders to clozapine, however, the group opted to provide guidance for their treatment, albeit on the basis of little evidence. Because the use of more than one antipsychotic puts patients at a higher risk for drug interactions and side effects and is more expensive than monotherapy, the experts recommended that clinicians attempt a final trial of monotherapy (Stage 5) before resorting to antipsychotic polypharmacy (Stage 6). However, a person with a failed trial of clozapine, including augmentation, but with a partial response to another antipsychotic, might be a candidate for augmentation of that antipsychotic with another rather than a trial of a fourth or fifth new antipsychotic by itself.

Question 6. Should There Be a Fixed Sequence of Antipsychotics in the Algorithm (i.e., how should clinicians decide which antipsychotic to use first?)

Consensus recommendation (Group consensus, strong). Aside from clozapine's superiority in the treatment-resistant population, there is no consistent evidence supporting differential efficacy among the NGAs and, hence, no basis for specifying a sequence based on efficacy. However, the side effect profiles of the various NGAs differ sufficiently from one another to warrant that

the choice of antipsychotic be guided by the clinical characteristics of the patient and the side effect profile of each agent.

Background information. Studies aimed at establishing differences in efficacy between NGAs have provided inconsistent results.[58,59] Thus, the experts concluded that, while one nonclozapine NGA may work better than another for an individual patient, all of the nonclozapine NGAs are considered to be equally effective. However, the side-effect profiles of the various NGAs are different, and an important aspect of the art of clinical practice is matching patient characteristics with drug profiles.

Question 7. Is There a Preferred Method for Transitioning From One Antipsychotic to Another?

Consensus recommendation (Levels B and C). Planned transitions from one antipsychotic to another can be done by stopping one and starting the other or by overlapping the old and new drugs. Data from studies of several NGAs suggest that the method of cross-titration from one nonclozapine NGA to another does not affect clinical outcomes (Level B), but many clinicians report that they prefer to cross-titrate in some fashion. Elective discontinuation of clozapine should be by gradual tapering over at least a 3-month period to prevent discontinuation symptoms (see the following background information) (Level C).

Background information. The original Schizophrenia Manual recommended employing an "overlap and taper" strategy when transitioning from one NGA to another. Since that publication, studies examining the effects of abrupt versus extended switching have emerged.[21,60] Studies of switching to ziprasidone or aripiprazole from NGAs or FGAs suggest that, for outpatients, results are similar whether the transition is abrupt or done by overlapping the new and old antipsychotic.[21,60] However, many clinicians anecdotally report that patients respond poorly to abrupt medication switches. Investigators have reported discontinuation symptoms, such as psychosis, insomnia, nightmares, headaches, and gastrointestinal disturbances, after the abrupt discontinuation of clozapine.[61,62] A 3-month tapering period is recommended.

Question 8. Should Aripiprazole Be Included as a First-Line Antipsychotic in the Revised Antipsychotic Algorithm?

Consensus recommendation (Level A). Aripiprazole's antipsychotic efficacy and safety profile warrant its inclusion in the algorithm as a coequal Stage 1 option with olanzapine, quetiapine, risperidone, and ziprasidone.

Background information. The FDA approved aripiprazole in November 2002, subsequent to the January 2002 consensus meeting, and it was marketed shortly thereafter. The criteria for considering new antipsychotics for inclusion in the algorithm are at least 6 months postmarketing experience in the United States and at least 50,000 patient exposures.[6] Once aripiprazole met these criteria, the data presented in this section were distributed electronically, for discussion and feedback. A recent article reviews the clinical trials evaluating the safety and efficacy of aripiprazole.[63] Five short-term clinical trials conducted in acutely relapsing inpatients indicate that daily doses ranging from 15 to 30 mg of aripiprazole are more efficacious than placebo[64–66] and as efficacious as haloperidol[67] and risperidone.[68] With regard to preventing relapse of psychotic symptoms, longer-term studies show that aripiprazole is superior to placebo[69,70] and equivalent to haloperidol.[71] A meta-analysis of the inpatient studies indicates that aripiprazole is safe and tolerable with a low liability for extrapyramidal symptoms, weight gain, prolactin elevation, QTc prolongation, and sedation.[72] In preclinical studies, aripiprazole has been characterized as a partial dopamine agonist.[73] Whether this putative mechanism of action translates into differences in its spectrum of efficacy or differences in its suitability for particular patient populations remains to be tested in clinical trials.[74]

CONCLUSION

These recommendations summarize the consensus responses to the questions addressed by the authors. Owing to a lack of data, many of the recommendations are based on expert consensus. One might argue that it is preferable to construct algorithms based solely on level A evidence. Experience in training clinicians, however, has been that they opt for a guiding framework that incorporates expert opinion in dealing with difficult clinical questions, in the absence of definitive evidence.

The questions that have been answered primarily on the basis of expert consensus are not easily addressed by randomized controlled trials, because they require large longitudinal studies of many groups over considerable time periods. Gathering useful data to address questions about the number of different NGAs that should be tried and the value of antipsychotic combinations will require creative experimental designs and, where possible, analysis of large longitudinal databases obtained by behavioral health care organizations.

Drug names: aripiprazole (Abilify), clozapine (Clozaril and others), fluphenazine (Permitil, Prolixin, and others), haloperidol (Haldol and others), loxapine (Loxitane), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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