The Texas Medication Algorithm Project (TMAP) Schizophrenia Algorithms

Alexander L. Miller, M.D.; John A. Chiles, M.D.; Judith K. Chiles, R.N.; M. Lynn Crismon, Pharm.D., F.C.C.P.; A. John Rush, M.D.; and Steven P. Shon, M.D.

***Background*:** In the Texas Medication Algorithm Project (TMAP), detailed guidelines for medication management of schizophrenia and related disorders, bipolar disorders, and major depressive disorders have been developed and implemented.

***Discussion*:** This article describes the algorithms developed for medication treatment of schizophrenia and related disorders. The guidelines recommend a sequence of medications and discuss dosing, duration, and switch-over tactics. They also specify response criteria at each stage of the algorithm for both positive and negative symptoms. The rationale and evidence for each aspect of the algorithms are presented.

(J Clin Psychiatry 1999;60:649–657)

Received Dec. 9, 1998; accepted April 20, 1999. *From the Department of Psychiatry, The University of Texas Health Science Center, San Antonio (Drs. Miller and Chiles); the San Antonio State Hospital, San Antonio (Ms. Chiles); the College of Pharmacy, The University of Texas at Austin, Austin (Dr. Crismon); the Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas (Dr. Rush); and the Texas Department of Mental Health and Mental Retardation, Austin (Dr. Shon).*

Supported in part by grants from the Robert Wood Johnson Foundation, Meadows Foundation, the Lightner-Sams Foundation, Moody Foundation, Nannie Hogan Boyd Charitable Trust, Texas Department of Mental Health and Mental Retardation, Center for Mental Health Services, National Institute of Mental Health (MH-53799), Abbott Laboratories, Bristol-Myers Squibb Company, Eli Lilly and Company, Forest Laboratories, Glaxo-Wellcome, Inc., Janssen Pharmaceutica, Novartis Pharmaceuticals Corporation, Pfizer Inc, SmithKline Beecham Plc., Wyeth-Ayerst Laboratories, United States Pharmacopoeia Convention, Inc., and AstraZeneca Plc., as well as Mental Health Connections, a partnership between Dallas County Mental Health and Mental Retardation and the Department of Psychiatry, University of Texas Southwestern Medical Center, which receives funding from the Texas State Legislature and the Dallas County Hospital District.

Reprint requests to: Alexander L. Miller, M.D., Department of Psychiatry, The University of Texas Health Science Center, 7703 Floyd Curl Dr., San Antonio, TX 78284-7792 (e-mail: millera@uthscsa.edu).

This article provides a review of the specific strategic and tactical medication treatment recommendations that are being used for patients with schizophrenia in the current phase of the Texas Medication Algorithm Project (TMAP).* TMAP also includes algorithms for bipolar and major depressive disorders. Medication algorithms for these illnesses are being implemented at 12 outpatient public mental health clinics in Texas. Approximately 150 to 200 patients with each of these 3 disorders will be treated for at least a year in accordance with the corresponding algorithm. Clinical outcomes and resource utilization of these patient groups will be compared with those of patients who receive treatment as usual. For detailed descriptions of TMAP, see Gilbert et al. (1998)[1] and Rush et al. (1999).[2]

Each of the TMAP medication algorithms follows the same general format and rules in its construction. Strategies (i.e., which medications to use) are presented in specific stages, with each stage representing a therapeutic trial for the patient. The stage at which a patient enters the algorithm depends on the patient's past history of medication treatments. A clear history of failure on or intolerance to a particular medication treatment means that this stage will be bypassed in the implementation of the algorithm for that patient.

In arriving at the recommended sequence of medications in each algorithm, the developers took into account data on efficacy, safety, and tolerability. The weighting of these factors requires complex judgments about risks to patients of persistent illness (ineffective treatment) versus risks from the treatment itself. For example, clozapine is the single most effective antipsychotic, but it has the risk of agranulocytosis and is quite sedating. Based on efficacy considerations alone, clozapine would be the first choice antipsychotic, but no current algorithm puts it first because of the safety and tolerability concerns. New studies, however, could demonstrate that, for example, efficacy is such a paramount issue early in the course of schizophrenia that clozapine should appropriately be a first-line treatment.

When medications within a group are fairly comparable to one another in efficacy, safety, and tolerability (e.g., atypical antipsychotics other than clozapine), the practical question is How many (or how few) of the group

*The entire guidelines for the algorithms for each disorder may be accessed through the TMAP Web site at *http://www.mhmr.state.tx.us/meds/tmap.htm*. The schizophrenia algorithm and guidelines are found at the same site, using *sczpm3.doc*, *scz3.htm*, and *sczse.htm* instead of *tmap.htm* in the last part of the address. The guidelines are in the public domain and may be downloaded without permission.

should be tried before switching to a different group? Most drug-drug comparisons are made by parallel-group design, which allows comparison of each drug's success rate, but which yields little information about how to treat individual patients who fail to respond to or cannot tolerate a particular drug. Given 2 drugs with response rates greater than 50%, the theoretical likelihood that a patient who fails one will respond to the other ranges from 0% (complete equivalency) to 100%. These crucial data are almost always lacking in the literature on newer drugs, because they are not generated in the U.S. Food and Drug Administration (FDA)–approval process.

Two other general aspects of the algorithms should be noted. First, at each stage there are specific tactical recommendations (e.g., for dosing, duration, use of blood levels). These tactical recommendations are provided to guide practitioners toward "usually appropriate" prescribing practices. Going outside these tactical guidelines is acceptable in treating individual patients, if the practitioner's decision to do so can be justified in terms of, for example, the patient's failure to respond to typical doses. Second, the algorithms also provide clear criteria, using clinical ratings, to define response, partial response, and nonresponse. Much of the literature on response in psychiatry is from treatment trials, where the goal is to set the threshold at the minimum level that is clinically meaningful. In clinical practice, however, the goal is to maximize response. In principle, this means progressively trying different treatments until the patient is symptom free or the maximum achievable response has been identified. In practice, it is usually not feasible to try all treatments, but TMAP has purposely set high standards by which to define response. However, clinicians may decide not to progress to the next step if they believe it is unlikely to add benefit. Patients can always return to an earlier stage if later stages are of no greater benefit. If the criteria for response are set too low, on the other hand, some patients who might do substantially better on another medication would never receive it.

THE SCHIZOPHRENIA ALGORITHMS

There are, at this point in time, a number of published algorithms and guidelines for the treatment of schizophrenia. These include the Expert Consensus Guidelines,[3] the American Psychiatric Association (APA) guidelines,[4] and the Patient Outcomes Research Team (PORT) project.[5] The work described below has drawn from all of these sources, but differs from them in its level of specificity. Thus, for each of the disorders that constitute TMAP, detailed manuals have been developed that attempt to cover the full range of clinical circumstances likely to be encountered by practitioners. This article presents the logical and empirical bases for the specific recommendations regarding both strategies and tactics recommended for schizophrenia.

Unlike typical clinical trials, TMAP includes the entire spectrum of patients with the target diagnosis. Thus, the "schizophrenia" algorithms are also being used for patients diagnosed with paranoid disorders or schizoaffective disorder, except for patients with a documented manic episode (schizoaffective disorder, bipolar type), who are managed with the bipolar algorithms. The practical distinction is between patients needing time-limited, mood-related medication treatments in addition to their maintenance antipsychotics and patients needing mood stabilizers as the major element in maintenance management.

There are 3 medication algorithms for patients with schizophrenia and related psychotic disorders in TMAP: (1) 1 for antipsychotic management, (2) 1 for side effect management, and (3) 1 for the associated symptoms of an illness episode (e.g., insomnia, agitation).

Algorithm for Using Antipsychotics in Schizophrenia

The use of antipsychotics for medication management of schizophrenia and related disorders is central to the schizophrenia medication algorithms. In constructing the algorithm for the use of antipsychotics in schizophrenia, 4 basic principles have been followed:

1. Medication safety, tolerability, and efficacy were all considered in the decision on placement of each medication in the algorithm. The appropriate weighting of these elements in antipsychotic algorithm construction depends on 2 factors: (a) the properties of each antipsychotic relative to others in the class and (b) the consequences of partially or completely ineffective treatment. The algorithm is somewhat weighted in favor of safety and tolerability, in that clozapine would be the fifth drug used for a never-treated patient with schizophrenia. The empirical question is whether 3 to 6 months of ineffective treatments seriously worsen the long-term prognosis of patients responsive to clozapine but resistant to other antipsychotics. (Note: The clinician can skip directly to stage 5 or use only a few of stages 1–4 before beginning clozapine if he/she so decides.) Recent articles about use of placebo treatments have generally concluded that brief (6 weeks or less) placebo treatment has little deleterious effect on long-term course, whereas more than 12 months without treatment is harmful.[6,7] Further evidence for early, long-lasting toxic effects of untreated psychosis would favor changing the algorithm to begin clozapine sooner for unresponsive patients, reserving agents that are easier to use for subsequent trials. As a practical matter, for most patients the delays in receiving clozapine have been administrative (limited resources to provide clozapine) and clini-

cal (failure to expeditiously identify and treat nonresponders). By specifying stringent criteria for response and for duration of each stage, the TMAP algorithm attempts to ensure that patients who need it receive clozapine early in their course of illness.

2. Monotherapies are recommended except for the most treatment-refractory patients. The literature on efficacy of combinations of antipsychotics deals almost exclusively with augmentation of clozapine. Even here, published reports are of open-label, nonrandomized trials using pre-post comparisons,[8–11] with the exception of one randomized controlled trial of sulpiride, which is not available in the United States.[12] In practice, many patients are on other combinations (e.g., typical plus atypical), sometimes resulting from the observation that they did particularly well during the period of overlap in the transition from one antipsychotic to another. For individual patients, such a combination may indeed be optimal. However, (a) there is no way to predict ahead of time which patients fall in this category, (b) there are large numbers of possible combinations, and (c) monotherapy is associated with better compliance. Therefore, this algorithm does not recommend trials of combinations until clozapine has failed, but guides the clinicians to be alert to patient status in the transient medication overlaps between monotherapies and consider a return to the combination if neither monotherapy is as effective as the combination.
3. Psychosocial interventions and factors that might influence the choice of antipsychotic were not incorporated into the algorithm. Antipsychotic choices can be significantly influenced by the availability of psychosocial interventions. For example, intensive case management or participation in a day hospital program may obviate the need to treat an intermittently noncompliant patient with a long-acting decanoate preparation. Unfortunately, large variations in availability of psychosocial interventions exist, and few empirical data are available about how best to integrate them with medication selection. For these reasons, we decided that attempting to add psychosocial interventions to the algorithm would greatly complicate it and make it difficult to apply uniformly across sites, thus making the results less generalizable. At each site, the clinicians use available psychosocial resources according to their clinical judgment. TMAP does provide an intensive patient and family education program, coadministered by a clinical staff member and a patient or family member trained in the materials and group facilitation.
4. Medication costs were not factored into medication choices. Costs of antipsychotics must be balanced against savings in other costs and improvements in quality of life to arrive at valid estimates of the value of antipsychotics to the patient and society. A major aim of TMAP is to measure overall treatment and societal costs or cost savings associated with "best" medication first, regardless of the cost per pill. Thus, a goal of TMAP is to learn if higher medication costs are justified by improved outcomes and/or decreased costs in other areas. Until such data are available from this and other pharmacoeconomic studies, it is not unreasonable for clinicians and administrators to factor cost into decision making about sequence of atypical antipsychotics. As noted below, we conclude that current data justify putting atypicals before typicals.

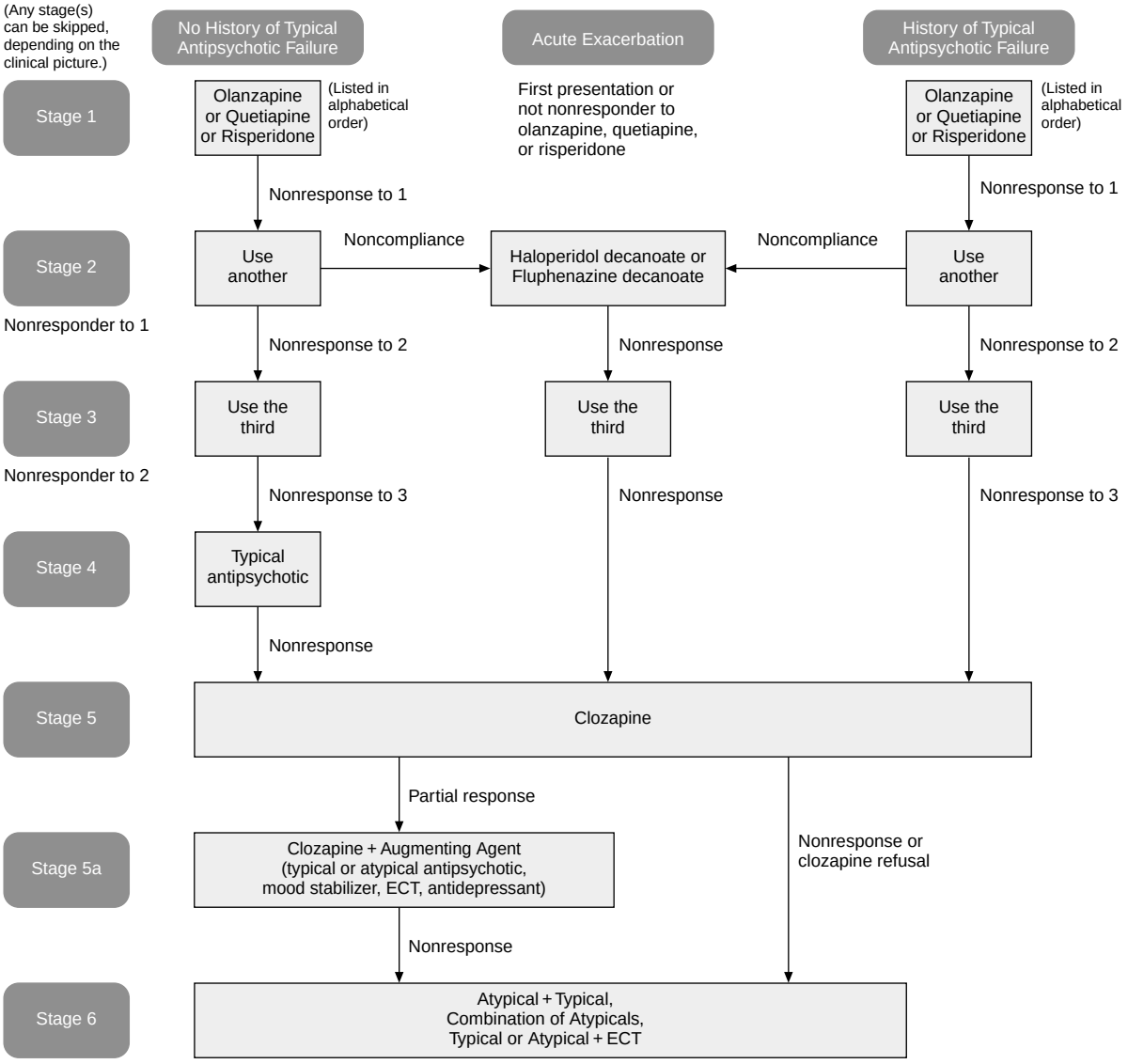
Figure 1 shows the key stages in the schizophrenia antipsychotic algorithm. The rationale for the sequence of medications in the antipsychotic algorithm is as follows:

1. The atypicals (other than clozapine) are preferred over typicals as first-line treatments because they are better tolerated, equal in treating positive symptoms, and equal or better in treating negative symptoms.[13–20] An increasing body of evidence indicates that the atypicals are less likely to cause tardive dyskinesia than typicals. It is debatable if clozapine ever causes tardive dyskinesia.[21,22] Substantially lower incidence rates of tardive dyskinesia have been reported for risperidone[23] and olanzapine compared with typicals.[16] Although no rate has been reported for quetiapine, its very low rate of causing extrapyramidal side effects[18] strongly suggests that it will produce less tardive dyskinesia, since these side effects are associated with the later development of tardive dyskinesia.[21]

   Comparison studies among atypicals are largely lacking. Two studies, using parallel-group design, have compared olanzapine and risperidone.[24,25] They arrive at opposite conclusions as to which drug is superior. Neither study presents data which would justify a recommendation that one or the other of these drugs should routinely be used in preference to the other, although these studies do support the use of lower doses and slower titration of risperidone than was originally recommended.

   There is no information regarding the response rate to one atypical after failure with another. Therefore, the algorithm does not specify which atypical should be used first, but does ask clinicians to try the other atypicals with patients who

Figure 1. Antipsychotic Algorithm[a]



[a]This material is in the public domain and can be reproduced without permission. Abbreviation: ECT = electroconvulsive therapy.

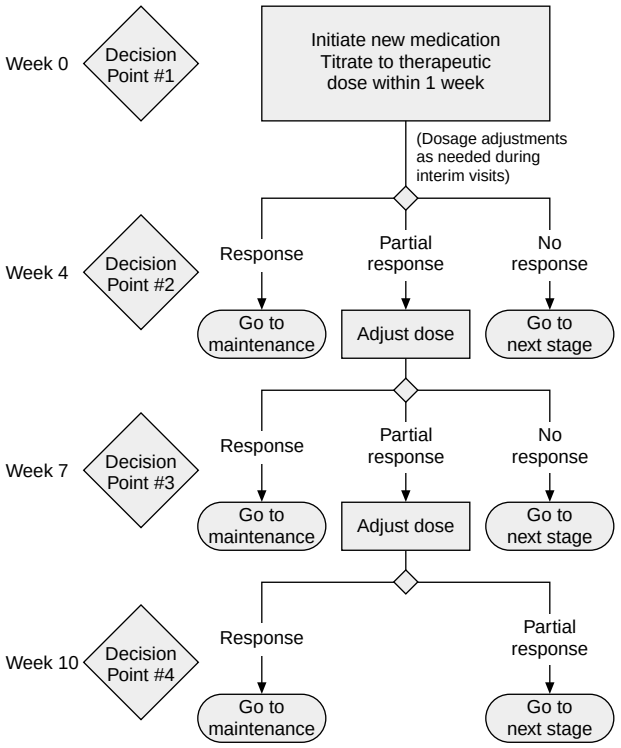
fail one. This approach will produce data on the proportion of patients who fail or are intolerant to one atypical but respond to or tolerate another, and, ultimately, these data will guide revisions to the algorithm (i.e., regarding how many atypicals should be tried for a patient before switching to a typical agent or clozapine).

2. For patients who have failed one or more atypical agents (other than clozapine) and have not failed a typical, should a typical be tried before starting clozapine? No studies have addressed this question. The inclusion criteria for the large, pivotal phase III efficacy trials of the atypicals specified treatment-responsive patients. Since not all such patients then responded to the atypical, by implication there were patients who did better on their prior typical than on the dose of atypical they received in the study. Without knowledge of the quality of prior response to the typical, however, it may not be fair to conclude that there were substantial numbers of patients who had done very well on a typical and then did less well on an atypical. The reasons for placing typicals before clozapine in the algorithm are 4-fold: (a) it is more time efficient to give a trial of a typical than of clozapine (maximum recommended trial duration of 10 weeks vs. 6 months)[26,27]; (b) stopping clozapine to try another antipsychotic requires a very slow taper and long

overlap[28–32]; (c) the greatest risk from typicals (tardive dyskinesia) occurs after the time period of a therapeutic trial,[21,33] whereas the greatest risk from clozapine (agranulocytosis) occurs within the time period of a therapeutic trial[22,34,35]; and (d) clozapine is more inconvenient to take due to blood monitoring. If only very few patients who fail to respond to atypicals respond adequately to a typical antipsychotic, the algorithm will be modified to put clozapine immediately after other atypicals.

3. Clinicians are encouraged to try 2 atypicals before switching noncompliant patients to a decanoate preparation. The rationale here is that the side effect profiles of the atypicals differ from one another, that side effects are a major cause of noncompliance (even when patients do not complain about them), and, therefore, that patients noncompliant with one atypical may be compliant with another.
4. Because clozapine is the only treatment proven effective for patients not responding to other antipsychotics,[20,22] the algorithm includes a variety of agents to augment or combine with clozapine. As noted above, the evidence for these augmenting agents and antipsychotic combinations is almost entirely from open-label case series and case reports. There is a dearth of randomized controlled trials for a group that presumably constitutes about 10% of all patients with schizophrenia (assuming 20% are refractory to drugs other than clozapine and half of this group responds to clozapine).[26] The guidelines given to clinicians in selecting which augmenting agent to use are based on the limited literature and common sense. If depressed mood or mood instability is prominent, then trials of antidepressants (with precautions about drug interactions with selective serotonin reuptake inhibitors [SSRIs]) or mood stabilizers are recommended. The largest number of open-label reports are on augmentation with risperidone or electroconvulsive therapy (ECT).[9,11,36–39] With time, one would expect reports on the combination of clozapine with the more recently available atypicals olanzapine and quetiapine. Community surveys indicate many patients receive both clozapine and a typical antipsychotic,[40] but reports on the efficacy of this combination are lacking. Presumably, the risk of tardive dyskinesia of the antipsychotic combination with clozapine is equal to that of the nonclozapine drug, unless clozapine is protective against development of tardive dyskinesia. Combinations are also an option for patients who are intolerant of therapeutic doses of clozapine. This category of patient (low-dose clozapine plus atypical) was common in one reported series.[11]

Figure 2. Critical Decision Points for Antipsychotic Algorithm Stages 1, 2, 3, and 4[a]



[a]This material is in the public domain and can be reproduced without permission.

5. The literature is even sparser on how to treat patients who fail to respond to clozapine or who refuse it. The combinations given in the algorithm's stage 6 are logical options. Experience with these patients in TMAP may be extensive enough to draw some empirical conclusions about their value.

Duration of Treatment and Dose Adjustments

At each stage, the duration of recommended treatment and the timing of dose adjustments are guided by explicit tactical recommendations at critical decision points. The intent is to ensure that, at each stage, a reasonable balance is struck between the need to have an adequate trial and the need to find an effective treatment as quickly as possible. For the antipsychotics other than clozapine, the recommended minimum trial duration is 3 weeks and the maximum, 9 weeks, after a 1-week titration to a therapeutic dose. The guidelines on length of treatment are targeted toward outpatients, for whom length of stay is not an issue. Dose adjustments can be made as frequently as every week or as infrequently as every 3 weeks. The flow diagrams for the critical decision points in algorithm stages 1 through 4 are illustrated in Figure 2.

Table 1. Antipsychotic Medication Dosing

Antipsychotic	Dosage
Clozapine	300–900 mg/d[a]
Olanzapine	10–20 mg/d
Risperidone	2–6 mg/d
Quetiapine	300–750 mg/d
Chlorpromazine	400–1200 mg/d
Fluphenazine	5–15 mg/d
Fluphenazine decanoate	12.5–75 mg/2–3 wk
Haloperidol	5–15 mg/d
Haloperidol decanoate	50–200 mg/3–4 wk
Thioridazine	300–800 mg/d
Thiothixene	10–30 mg/d

[a]Serum level for doses > 600 mg/d.

Table 2. Clinical Rating Scales[a]

4-Item BPRS
Suspiciousness
Unusual thought content
Hallucinations
Conceptual disorganization
Brief negative symptoms
Prolonged time to respond
Reduced emotion
Reduced social drive
Poor grooming and hygiene

[a]Abbreviation: BPRS = Brief Psychiatric Rating Scale. BPRS items are rated 1–7. Negative symptom items are rated 1–6. For details of ratings, including anchor points, see Appendices J and K in the TMAP Procedural Manual (*http://www.mhmr.state.tx.us/meds/sczpm3.doc*).

Dose ranges are given in Table 1. The algorithm instructions provide some flexibility, particularly with regard to exceeding the upper limit of the dose range if there is evidence that each prior dose increase has produced incremental improvement and if side effects are not a problem. However, the higher dose is maintained only if a patient meets criteria for response (see below) within 3 weeks. If not, treatment progresses to the next stage of the algorithm.

Relatively recent evidence suggests that even with a typical antipsychotic, allowing more time for therapeutic effects to occur may be as beneficial as raising the dose.[41] Moreover, with newer drugs, experience after FDA approval has led to a significant decrease in recommended dose range in one case (risperidone)[42] and reported use of higher doses in another case (olanzapine).[43] Thus, both dose and duration recommendations will be revised as new data are published.

Because of the evidence that clozapine is almost twice as likely to produce a therapeutic response after 3 months as after 6 weeks at therapeutic doses,[26] the recommended duration of a clozapine trial is 3 to 6 months (stage 5). In addition, the options beyond clozapine are complicated and basically unproved, further supporting vigorous efforts to maximize the effectiveness of clozapine for treatment-refractory patients. The recommendations for duration of treatment in stages 5a and 6 are based on those for the individual augmenting or combination agents (stage 5a) or components of the combination (stage 6). Again, there is essentially no literature on this issue. Systematically obtained data would be helpful.

Criteria for Response

The 2 major issues in defining response are (1) What are the domains of response that should guide treatment decisions? and (2) What is a sufficient response in each domain?

There are at least 3 symptom domains in schizophrenia: positive, negative, and cognitive.[44,45] Although elimination of positive symptoms has historically been the desired endpoint of treatment, there is strong evidence that negative symptoms and cognitive deficits are more predictive of long-term outcomes.[46–49] This being the case, one could argue that improvements in negative symptoms and cognitive functioning should be prioritized ahead of reductions in positive symptoms. On the other hand, psychiatrists have much more experience in evaluating positive symptoms in clinical settings, and there is considerably more evidence that medications improve positive symptoms than that they improve core negative symptoms or cognitive deficits. Moreover, assessment instruments, if they are to be of value in typical clinical settings, should be brief, sensitive to change, and easy to administer.

In light of these considerations, we recommended assessment only of positive and negative symptoms to guide implementation of the algorithm. A cognitive assessment was not included because of the lack of an instrument that quickly and easily quantifies cognitive performance, as well as the substantial uncertainty about how much cognitive improvement would be reasonable as an endpoint of treatment. To simplify the task of assessing positive and negative symptoms, we selected the 4 items of the psychosis factor from the Brief Psychiatric Rating Scale (BPRS)[50] and took 4 items from the Negative Symptom Assessment scale[51] and from the Scale for the Assessment of Negative Symptoms,[52] which assess avolition, alogia, asociality, and flat affect. These negative symptom items were chosen based on their large effect sizes in our studies.[53] The anergia factor of the BPRS, often used as a proxy for measuring negative symptoms, had a smaller effect size[53] and does not tap into different aspects of negative symptoms. The items used in the assessment of positive and negative symptoms are shown in Table 2.

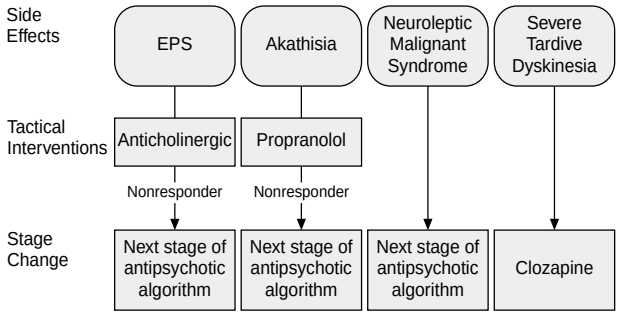
The clinical psychiatric research literature provides much more guidance in defining the minimum change that is clinically meaningful (e.g., BPRS decrease > 20%) than in establishing realistic endpoints for individual patients. Too low an endpoint means that many patients will never get maximum benefit from medication treatment. Too high an endpoint means that many patients will unnecessarily undergo multiple medication trials, with increased risks of relapse, serious adverse events, and so on.

Table 3. Response Criteria[a]

Stage	Positive Symptoms		Negative Symptoms
Stage 1	≤ 6	and	≤ 12
Stage 2	≤ 6	and	≤ 12
Stage 3	≤ 6	and	≤ 12
Stage 4	≤ 6	and	≤ 12
Stage 5	> 20%↓	or	> 20%↓
Stage 5a	> 20%↓	or	> 20%↓
Stage 6	> 20%↓	or	> 20%↓

[a]Stages are shown in Figure 1. Scores are sums of individual scores on items shown in Table 2. Percent decreases are relative to the scores at the prior stage.

Figure 3. Side Effects Algorithms[a]



[a]This material is in the public domain and can be reproduced without permission.

Table 3 recommends criteria for defining an adequate response.

Recent work has shown that virtual absence of positive symptoms is an achievable result in substantial numbers of schizophrenic patients early in the course of treatment.[54] Thus, we opted to establish quite stringent criteria for an adequate response of positive symptoms. The threshold score of ≤ 6 on the 4 BPRS items (each scaled 1–7) means that no item can be of more than mild severity (score = 3), and if 1 item is mild, the others must be normal (score = 1). For negative symptoms, it is less clear what improvements are realistically achievable and how "normal" the nonpsychiatric population is. The cutoff score of ≤ 12 allows the patient to have mild symptoms on each item (scaled 1–6) or even moderately severe symptoms on a couple of items. Experience with these scales in TMAP will provide data to evaluate the utility of these endpoints and modify them if necessary. Duration and severity of illness undoubtedly influence achievable response levels. The response criteria for patients who need clozapine were made less stringent and relative to baseline instead of absolute. Since there is no antipsychotic that has greater efficacy than clozapine, the clinical task is to establish whether it is significantly better than any of the other antipsychotics for the patient. For this purpose, a 20% reduction in symptoms, positive or negative, is considered clinically meaningful. Responses of less than this magnitude probably indicate that the patient should try an additional agent (stage 5a), be moved on to stage 6, or be switched back to the best of the earlier treatments. This decision will depend on the quality of the earlier responses. If they were quite good, nearly meeting criteria for an adequate response, monotherapy with the best agent from an earlier stage may be sufficient (i.e., the patient returns to an earlier stage). If responses were only fair, it may be helpful to augment the best drug of the earlier trials with another agent, as illustrated in stage 6.

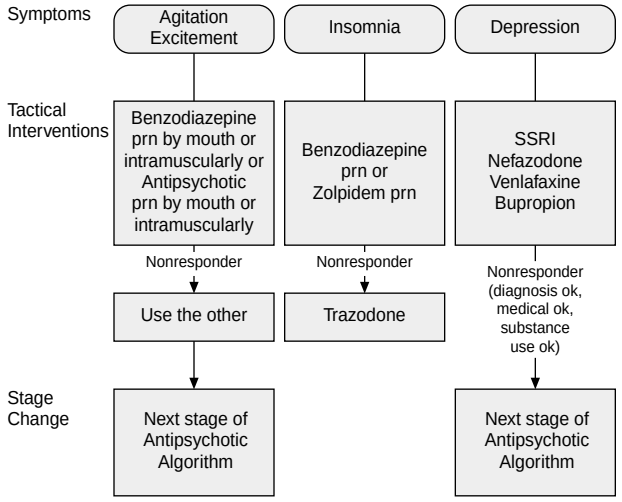
Algorithms for Side Effects and Associated Symptoms

Identification and treatment of side effects have historically been major parts of antipsychotic pharmacotherapy. For typical antipsychotics, the pharmacologic mainstays of side effect treatment are reasonably well established. The algorithms for side effects are shown in Figure 3 and include treatments for extrapyramidal symptoms, akathisia, neuroleptic malignant syndrome, and tardive dyskinesia. With the availability of atypical antipsychotics that are much less likely to produce these side effects, it seems advisable to switch patients with inadequately treated side effects to one of these medications, rather than adding or substituting another side effect treatment, unless there are clinical reasons for not making this switch. The side effect medications have their own problematic side effects, including impairment of cognitive processes. This recommendation to switch to another antipsychotic rather than adding side effect treatments seems logically justified, but is not grounded in empirical studies, which are lacking.

During the development of medication algorithms for associated symptoms (Figure 4), schizophrenia and related psychotic disorders were conceptualized as chronic conditions, requiring maintenance treatment, with superimposed acute symptoms needing short-term treatment. In the case of depression in schizophrenia, it is now generally accepted that antidepressants are the medications of choice.[3–5,55] For the agitation, excitement, and insomnia often associated with illness exacerbations, however, typical antipsychotics have often been used for acute symptom relief as well as for maintenance, blurring the distinction between short-term and longer term treatment goals. With the advent of the atypicals, which lack the heavily sedating properties of, for example, chlorpromazine, and which are not presently available in parenteral forms, it has become more important to separate short- and long-term treatment goals. Thus, while the typicals are listed at stage 4 in the antipsychotic algorithm, they can be used for short periods at any stage for treatment of the associated symptoms of agitation and excitement.

The antipsychotic algorithm for schizophrenia is intended to be very detailed and cover most clinical situa-

Figure 4. Coexisting Symptoms Algorithms[a]



[a]Abbreviation: SSRI = selective serotonin reuptake inhibitor. This material is in the public domain and can be reproduced without permission.

tions. By contrast, the algorithms for side effects and associated symptoms are intended to guide the clinician toward reasonable approaches to typical presentations of these problems, but give wide latitude for exercising clinical judgment about instituting other treatments, including nonmedication ones.

Revising the Algorithm

The medication algorithms used in TMAP and other specific guidelines are dynamic recommendations that require periodic updating and revisions. Reasons for updates and revisions include (1) availability of new medications, (2) evidence that a stage (step) is ineffective, and (3) new published research that better informs strategic choices or tactics.

This is a very active period for studies of new medications for schizophrenia. As new antipsychotics are approved by the FDA, they must be fitted into the algorithm. The clinical trials typically presented to the FDA exclude or limit participation of large segments of the schizophrenic population (drug abusers, medically unstable patients, women, etc.), are not large enough to reliably detect quite rare side effects (the association of clozapine with agranulocytosis only became evident after its use in about 20,000 patients), and have not fully addressed some important clinical issues (optimal switch-over strategies, drug-drug interactions, etc.). Thus, our current procedure is to wait until new drugs have been marketed in this country for at least 6 months and prescribed for at least 50,000 patients before deciding where to place them in the algorithm.

Updates of the algorithms are first developed by the directors of the TMAP schizophrenia module (A.L.M. and J.A.C.) in consultation with experts in the field and then presented to the entire group of TMAP investigators for comments and revisions. After approval by this group, they are distributed to the users and put on the Web site. Thus, revisions are available for others to consider, as they are made. The agreed-upon frequency of revisions is every 6 to 12 months, unless there is a compelling need to incorporate a new finding immediately. This process allows non-TMAP users to be informed rapidly of changes in the algorithms. In dealing with the issue of timely updates, however, the process sacrifices input from a broad range of experts, such as has been incorporated into the Expert Consensus,[3] APA,[4] and POiX[5] guidelines. In the long term, revisions will continue to be predicated on the products of these broad, systematic efforts, as well as on our assessment of important new evidence that has not yet been incorporated into nationally developed guidelines.

SUMMARY

Since 1990, 4 new medications for schizophrenia have been approved for use in the United States. These new treatments are sufficiently different from one another and from the older antipsychotics to justify an algorithmic approach to recommending how they are used. It has also become feasible to separate treatments for schizophrenia and related disorders into those targeted toward short-term symptom control during illness exacerbations and those intended for long-term maintenance of patients.

The medication algorithms developed for the treatment of schizophrenia and related disorders in the Texas Medication Algorithm Project are intended to provide very specific guidelines for clinicians who work with patients suffering from these disorders. They are not intended to substitute for accurate clinical assessments, nor are they intended to inhibit clinicians from individualizing treatment to the particular needs of their patients. The guidelines do ask that clinicians have an explicit clinical rationale for any decisions not to follow the guidelines.

Drug names: bupropion (Wellbutrin), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), nefazodone (Serzone), olanzapine (Zyprexa), propranolol (Inderal and others), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others), thiothixene (Navane), trazodone (Desyrel and others), venlafaxine (Effexor), zolpidem (Ambien).

REFERENCES

1. Gilbert DA, Altshuler KZ, Rago WV, et al. Texas Medication Algorithm Project: definitions, rationale, and methods to develop medication algorithms. J Clin Psychiatry 1998;59:345–351
2. Rush AJ, Rago WV, Crismon ML, et al. Medication treatment for the severely and persistently mentally ill: the Texas Medication Algorithm Project. J Clin Psychiatry 1999;60:284–291
3. Expert Consensus Guideline Series: Treatment of Schizophrenia. J Clin Psychiatry 1996;57(suppl 12B):1–58
4. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Schizophrenia. Am J Psychiatry 1997;154(suppl 4):1–63
5. Lehman AF, Steinwachs DM, and the Co-investigators of the PORT

Project. Translating research into practice: the schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. Schizophr Bull 1998;24:1–10
6. Carpenter WT. The risk of medication-free research. Schizophr Bull 1997;23:11–18
7. Wyatt RJ. Research in schizophrenia and the discontinuation of antipsychotic medications. Schizophr Bull 1997;23:3–9
8. Friedman J, Ault K, Powchik P. Pimozide augmentation for the treatment of schizophrenic patients who are partial responders to clozapine. Biol Psychiatry 1997;42:522–523
9. McCarthy RH, Terkelson KG. Risperidone augmentation of clozapine. Pharmacopsychiatry 1995;28:61–63
10. Mowerman S, Siris S. Adjunctive loxapine in a clozapine-resistant cohort of schizophrenic patients. Ann Clin Psychiatry 1996;8:193–197
11. Henderson DC, Goff DC. Risperidone as an adjunct to clozapine therapy in chronic schizophrenics. J Clin Psychiatry 1996;57:395–397
12. Shiloh R, Zemishlany Z, Aizenberg D, et al. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine; a double-blind, placebo-controlled study. Br J Psychiatry 1997;171:559–573
13. Woerner MG, Sheitman BB, Lieberman JA, et al. Tardive dyskinesia induced by risperidone? [letter] Am J Psychiatry 1996;153:843
14. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825–835
15. Marder SR. Risperidone: clinical development: North American results. Clin Neuropharmacol 1992;15:92A–93A
16. Tollefson GD, Beasley CM, Tamura RN, et al. Blind, controlled, long-term study of comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. Am J Psychiatry 1997;154:1248–1254
17. Beasley CM, Tollefson G, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996;14:111–123
18. Arvanitis LA, Miller BG. Seroquel Trial 13 Study Group: multiple fixed doses of Seroquel (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry 1997;42:233–246
19. Lieberman JA, Saltz BL, Johns CA, et al. The effects of clozapine on tardive dyskinesia. Br J Psychiatry 1991;158:503–510
20. Kane JM, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine/benztropine. Arch Gen Psychiatry 1988;45:789–796
21. Glazer WM, Morgenstern H, Doucette JT. Predicting the long-term risk of tardive dyskinesia in outpatients maintained on neuroleptic medications. J Clin Psychiatry 1993;54:133–139
22. Kane JM. Critical drug appraisal: clozapine. Drug Ther 1991;21:35–40
23. Brecher M, Kane JM, Okamoto A, et al. Low frequency of tardive dyskinesia in elderly patients with dementia exposed to risperidone for up to one year [poster]. Presented at the 151st Annual Meeting of the American Psychiatric Association; May 30–June 4, 1998; Toronto, Ontario, Canada
24. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997;17:407–418
25. Conley RR, Brecher M, and the Risperidone/Olanzapine Study Group. Risperidone versus olanzapine in patients with schizophrenia or schizoaffective disorder. Presented at the 11th European Collegium Neuro-Psychopharmacologicum Congress; Oct 31, 1998; Paris, France
26. Meltzer HY. Duration of a clozapine trial in neuroleptic-resistant schizophrenia [letter]. Arch Gen Psychiatry 1989;46:672
27. Meltzer HY, Bastani B, Kwon KY, et al. A prospective study of clozapine in treatment-resistant schizophrenic patients, I: preliminary report. Psychopharmacology (Berl) 1989;99(suppl):S68–S72
28. Shore D, Matthews S, Cott J, et al. Clinical implications of clozapine discontinuation: report of an NIMH workshop. Schizophr Bull 1995;21:333–338
29. Shiovitz TM, Welke TL, Tigel PD, et al. Cholinergic rebound and rapid onset psychosis following abrupt clozapine withdrawal. Schizophr Bull 1996;22:591–595
30. Still DJ, Dorson PG, Crismon ML, et al. Effects of switching inpatients with treatment-resistant schizophrenia from clozapine to risperidone. Psychiatr Serv 1996;47:1382–1384
31. Gupta S, Daniel DG. Cautions in the clozapine-to-risperidone switch [letter]. Ann Clin Psychiatry 1995;7:149
32. Parsa MA, Al-Lahham YH, Ramirez JR, et al. Prolonged psychotic relapse after abrupt clozapine withdrawal. J Clin Psychopharmacol 1993;13:154–155
33. Kane JM, Woerner M, Lieberman JA. Tardive dyskinesia: prevalence, incidence and risk factors. J Clin Psychopharmacol 1988;8:52–56
34. Alvir JMJ, Lieberman JA, Safferman AZ, et al. Clozapine-induced agranulocytosis: incidence and risk factors in the United States. N Engl J Med 1993;329:162–167
35. Honigfeld G, Arellano F, Sethi J, et al. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. J Clin Psychiatry 1998;59(suppl 3):3–7
36. Safferman AZ, Munne R. Combining clozapine with ECT. Convuls Ther 1992;8:141–143
37. Klapheke MM. Clozapine, ECT and schizoaffective disorder, bipolar type. Convuls Ther 1991;7:36–39
38. Landy DA. Combined use of clozapine and electroconvulsive therapy. Convuls Ther 1991;7:218–221
39. Kales H, Tandon R, DeQuardo JR, et al. Combined electroconvulsive therapy and clozapine in schizophrenia [abstract]. Biol Psychiatry 1995;37:678
40. Naber D, Holzbach R, Perro C, et al. Clinical management of clozapine patients in relation to efficacy and side-effects. Br J Psychiatry 1992;160 (suppl 17):54–59
41. Lieberman JA. Pharmacotherapy for patients with first-episode, acute, and refractory schizophrenia. Psychiatr Ann 1996;26:515–518
42. Luchins DJ, Klass D, Hanrahan P, et al. Alteration in the recommended dosing schedule for risperidone. Am J Psychiatry 1998;155:365–366
43. Sheitman BB, Lindgren JC, Early J, et al. High-dose olanzapine for treatment-refractory schizophrenia [letter]. Am J Psychiatry 1997;154:1626
44. Liddle PF, Barnes TRE, Morris D, et al. Three syndromes in chronic schizophrenia. Br J Psychiatry 1989;155(suppl 7):119–122
45. Mahurin RK, Velligan DI, Miller AL. Executive-frontal lobe cognitive dysfunction in schizophrenia: a symptom subtype analysis. Psychiatry Res 1998;79:139–149
46. Buchanan RW, Kirkpatrick B, Heinrichs DW, et al. Clinical correlates of the deficit syndrome in schizophrenia. Am J Psychiatry 1990;147:290–294
47. Carpenter WT, Heinrich PW, Wagman AMI. Deficit and non-deficit forms of schizophrenia: the concept. Am J Psychiatry 1988;145:578–583
48. Eaton WW, Thar R, Federman B, et al. Structure and course of positive and negative symptoms in schizophrenia. Arch Gen Psychiatry 1995;52:127–134
49. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996;153:321–330
50. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
51. Alphs LD, Summerfelt A, Lann H, et al. The Negative Symptom Assessment: a new instrument to assess negative symptoms of schizophrenia. Psychopharmacol Bull 1989;25:159–163
52. Andreasen NC. Negative symptoms in schizophrenia: definition and reliability. Arch Gen Psychiatry 1982;39:784–788
53. Eckert SL, Diamond PM, Miller AL, et al. A comparison of instrument sensitivity to negative symptom change. Psychiatry Res 1996;63:67–75
54. Lieberman JA, Jody D, Geisler S, et al. Time course and biologic correlates of treatment response in first-episode schizophrenia. Arch Gen Psychiatry 1993;50:369–376
55. Siris SG. Diagnosis of secondary depression in schizophrenia. Schizophr Bull 1991;17:75–98