Appendix I:

Michigan Implementation of Medication Algorithms (MIMA)
Guidelines for Treating Schizophrenia
MIMA Physician Procedural Manual

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2004

This manual is adapted from Alexander L. Miller, Catherine S. Hall, M. Lynn Crismon, and John A. Chiles, *Texas Implementation of Medication Algorithms (TIMA) Procedural Manual, Schizophrenia Module (*January 8, 2003), available on the TIMA website: *http://www.mhmr.state.tx.us/centraloffice/medicaldirector/timasczman.pdf.*

Notice

These guidelines reflect the state of knowledge, current at the time of publication, on effective and appropriate care, as well as clinical consensus judgments when knowledge is lacking. The inevitable changes in the state of scientific information and technology mandate that periodic review, updating, and revisions will be needed. These guidelines (algorithms) do not apply to all patients, and each must be adapted and tailored to each individual patient. Proper use, adaptation, modifications, or decisions to disregard these or other guidelines, in whole or in part, are entirely the responsibility of the clinician who uses the guidelines. The authors bear no responsibility for the use of these guidelines by third parties.

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Overview of MIMA

The Michigan Implementation of Medication Algorithms (MIMA) presented here are part of a broader action plan aimed at encouraging greater use of evidence-based practice (EBP) in mental health care in Michigan. As the name suggests, these medication algorithms for major depression, bipolar disorder, and schizophrenia were adapted from the Texas Implementation of Medication Algorithms (TIMA) project, implemented in that state over the past five years.

Funding for the Michigan EBP project was provided by the Ethel and James Flinn Foundation of Detroit, in partnership with Public Sector Consultants Inc. of Lansing. The project goal, simply stated, was to develop an action plan that would bridge the gap between what is known and what is done in psychiatry, between scientific evidence and actual practice.

Both the MIMA and the action plan of which the algorithms are a part were developed by the project Steering Committee, a diverse group of Michigan mental health experts with demonstrated expertise in EBP. Subcommittees of the Steering Committee reviewed various publicly available algorithms and guidelines and ultimately endorsed those used in Texas on the grounds that they were scientifically sound, had been field-tested and evaluated, were regularly updated, and were part of a broader disease management program.

The disease management component warrants special emphasis. The MIMA should not be viewed in isolation but as part of a program that includes clinical and technical support for physicians and patients, patient/family education, uniform documentation of patient outcomes, and a quality management program. The various components of this multifaceted program will be pilot-tested and evaluated in several Michigan locales over the next few years, with the results informing follow-up EBP programs in the future.

The Michigan EBP project, like other similar projects across the country, was devised in response to accumulating evidence that there is a significant gap between the state of knowledge and the treatment of patients in clinical practice. In many fields of medicine, psychiatry included, practice lags years behind research findings. Research also demonstrates that there are wide variations in practice even within a single state. It is therefore reasonable to conclude that the practices of at least some clinicians vary substantially from what is known to be effective.

Part of the problem is “information overload.” It is impossible for any psychiatrist to keep up with all the developments in his or her field. Another aspect of the problem is the uncritical acceptance of information from sources such as friends and colleagues, flawed studies, or pharmaceutical companies.

EBP has been criticized as a cost-cutting approach that undermines the “art” of medicine. The express intent of the MIMA, however, is actually the reverse. The MIMA in no way trivialize the clinician’s role, but rather formalize what has long been the ideal of practice: the use of science to inform the art of medicine. Clinical expertise continues to play an important role in the MIMA by allowing the clinician to rapidly integrate

research evidence and/or the practice judgments of the broader medical community in making decisions about patient care. Rather than being "cookbook medicine," the MIMA empower clinicians to make their own decisions about patient care, guided by the best available evidence to support those decisions.

Introduction to Algorithm Implementation

Algorithms go beyond guidelines in providing an explicit framework for clinical decision making. Algorithms do not dictate decisions, but rather provide an approach to clinical decision making that should yield similar answers in similar situations. The MIMA are not just general recommendations for medication treatment, they are also a systematic guide to the treatment of individual patients, which includes a number of critical factors: initial medication and dosage, dosage changes, methods and frequency of assessment, and minimum and maximum treatment periods.

Further, algorithms can be divided into *strategies* and *tactics*. Strategies are the various acceptable treatment regimen options for the care of an individual condition. Tactics address how optimally to implement a chosen regimen, and include such considerations as dose, monitoring, and how best to help an inadequately responding patient. Tactics also address the degree of symptom and functional improvement. As was the case with the TIMA, the MIMA presume that the aim of treatment is remission or the maximum possible improvement in cases where remission is not possible.

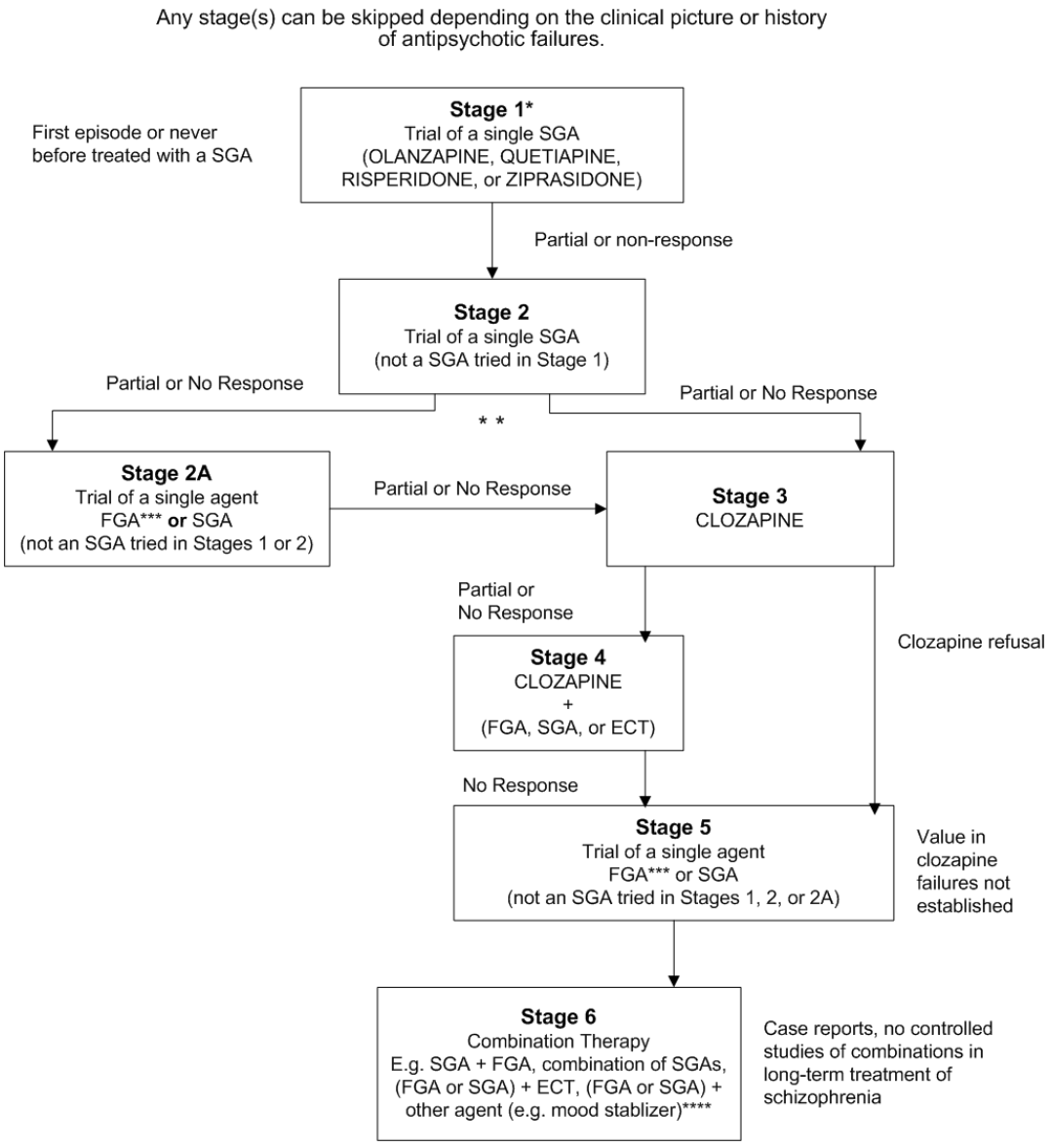
The MIMA approach is informed by the experience of Texas, which demonstrated that the successful implementation of algorithms is a human and social, as well as a technical, consideration. Assuring implementation of a treatment algorithm within a health care organization is a complex endeavor, requiring, in addition to research evidence, integrated changes in health care system design, patient and family education, and evaluation. Recommendations for just such a comprehensive, multifaceted approach are detailed in the Michigan EBP action plan.

Implementation of treatment algorithms is an evolutionary process, and change within systems does not occur without significant planning, goodwill, and effort. Yet the payoff in improved patient care is potentially enormous. Through an explicit process of algorithm implementation, evaluation, and revision, incremental improvements in many areas can result in major improvements in the overall quality of care.

At-a-Glance
Schizophrenia Medication Algorithm

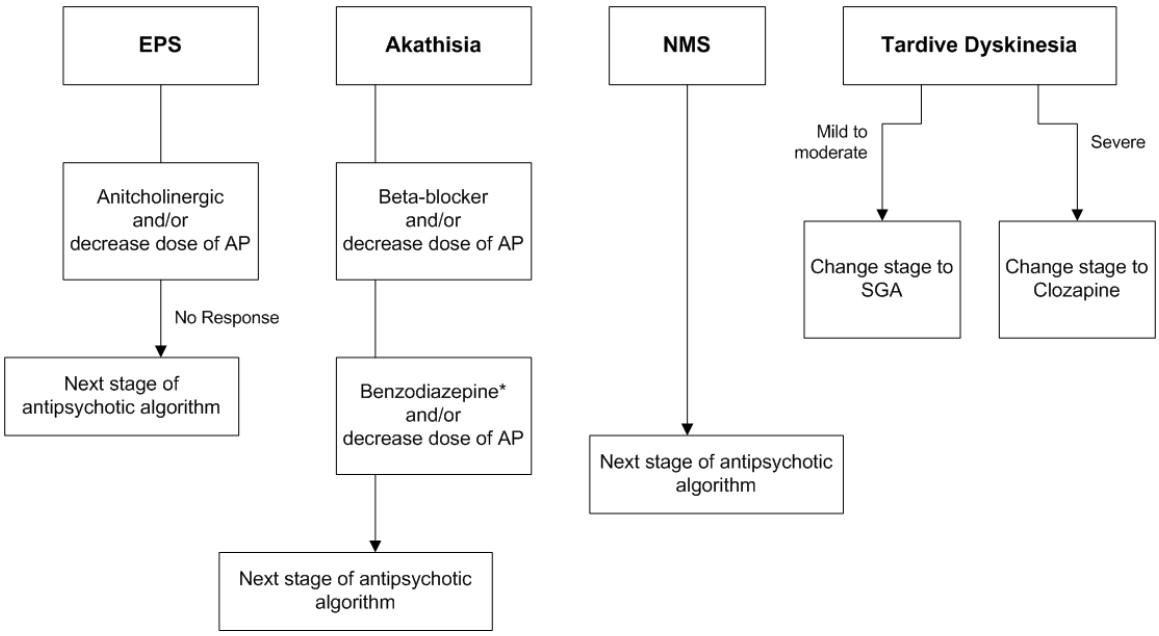
- Optimal implementation of the algorithm calls for a team approach.
- At each visit where medications are evaluated, decisions will be based on objective as well as subjective assessments of patient response.
  - Physicians will assess core symptom severity, other symptoms (anxiety, mood ability, etc.), and side effects.
  - Patients will provide a global self-report of symptoms and side effects.
  - Nonphysician personnel will administer brief positive and negative symptom rating scales and convey results to the psychiatrist who will make the ultimate treatment decision.
- Persistent positive or negative symptoms, unacceptable side effects, or the need for multiple side effect medications indicate that a medication change may be necessary. See the Evaluation of Patient Response section for discussion of using brief positive and negative symptom rating-scale scores.
- As much as possible, patients should receive an adequate trial of each antipsychotic.
  - Patients need at least four weeks of therapeutic doses of an antipsychotic (excluding clozapine) before they can be classified as "nonresponders" to the medication. Clozapine requires more time, up to three months.
  - Assessing the full effects of an antipsychotic can take 12 weeks or longer.
  - During acute relapses, multiweek trials of agents are difficult to sustain. However, failure to respond to an antipsychotic in 1–2 weeks should not eliminate it from future consideration as a possibly effective agent. Another trial may be worthwhile under more elective circumstances.
- No algorithm addresses all clinical situations that will arise in the medication management of schizophrenia.
- Choice of antipsychotic (AP) should be guided by considering the clinical characteristics of the patient and the efficacy and side effect profiles of the medication.

EXHIBIT 1
Algorithm for the Treatment of Schizophrenia



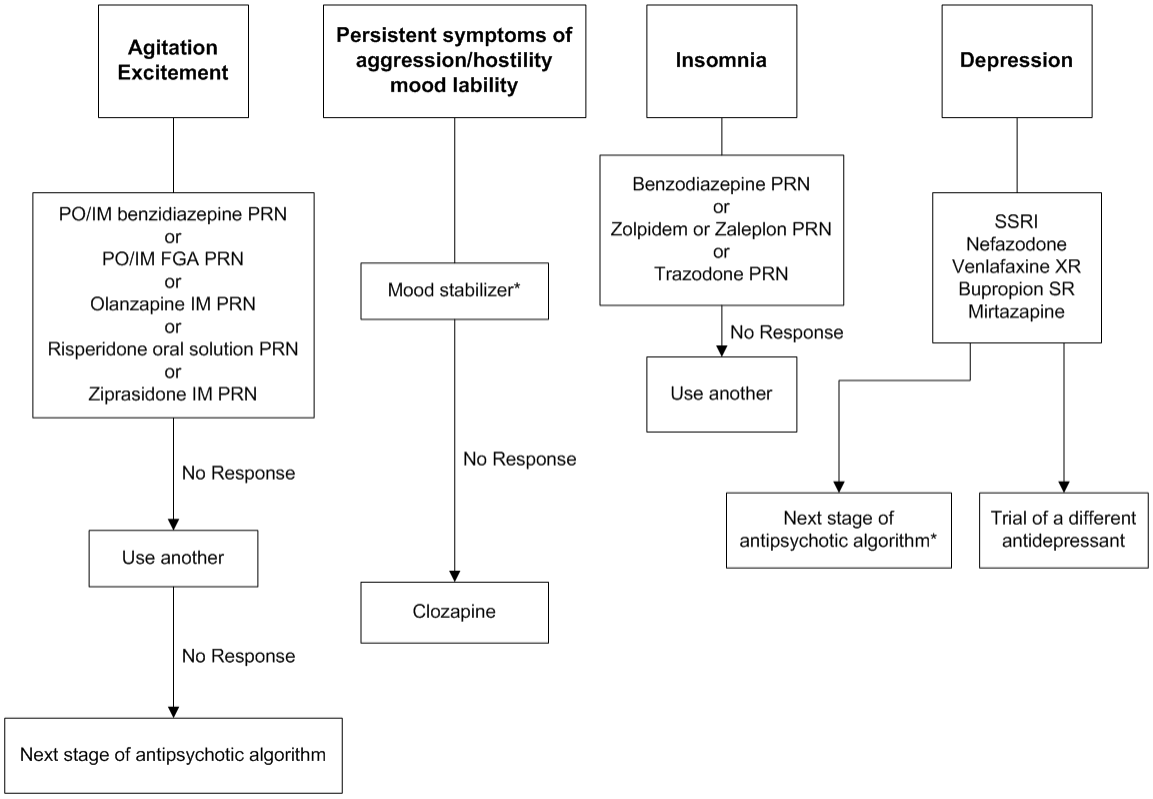
*If patient is nonadherent to medication, the clinician may use haloperidol decanoate or fluphenazine decanoate at any stage, but should carefully assess for unrecognized side effects and consider a different oral AP if side effects could be contributing to nonadherence.
** See text for discussion. Current expert opinion favors choice of clozapine.
***Assuming no history of failure on FGA.
****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. See Description of Tactics and Critical Decision Points section for more explanation.
FGA = First generation AP
SGA = Second generation AP

EXHIBIT 2
Side Effects Algorithms



*Avoid combinations of FGA, anticholinergic, and benzodiazepine.

EXHIBIT 3
Coexisting Symptoms Algorithms



*See Persistent Symptoms of Aggression/Hostility/Mood Lability in Medications and Dosing section.
**Consider clozapine in patients with persistent suicidal behaviors or ideation.

Description of the Stages of the Antipsychotic Algorithm

This section of the manual explains the rationale behind the sequence of stages in the schizophrenia algorithm and highlights some of the changes made at the Schizophrenia Algorithm Update Conference in January 2002.

The antipsychotic algorithm for schizophrenia distinguishes between acute and maintenance treatment. First generation antipsychotics (FGAs),[1] while not recommended at Stage 1 as first-line treatments, may be used short term to help control symptoms of agitation and excitement (see Coexisting Symptoms Algorithms on page 8). The FGAs are not first-line treatments because, compared to the second generation antipsychotics (SGAs),[2] they cause more bothersome side effects, have greater potential for producing tardive dyskinesia, are equal or worse for negative symptoms, are less likely to improve cognitive deficits, and are no more effective for positive symptoms (a).[3] SGAs do have side effects that can be medically serious, but they differ enough from one another in this regard that clinicians can monitor for these side effects and, if necessary, choose another SGA with a different side effect profile.

An important outcome of the update conference was the decision to add ziprasidone (Geodon®) to the list of first-line medications for the treatment of schizophrenia. Ziprasidone was submitted to the FDA in 1997 but was not approved until February 2001 because of concerns over its potential to prolong the QT interval. At the time of the update conference, 150,000 patients had received ziprasidone since its approval by the FDA, and data analysis revealed no increased incidence of sudden death, a marker for fatal arrhythmias. Because it appears that ziprasidone's risk of sudden death and cardiac events is no greater than that of the other agents used as first-line therapy, the experts decided to include ziprasidone as a first-line medication in the antipsychotic algorithm. The case of ziprasidone illustrates the algorithm's policy of requiring widespread utilization of new medications in a variety of clinical settings before their inclusion in the algorithm. As future medications acquire FDA approval, clinicians may use them before they are staged in the algorithm as long as the clinical situation warrants their use and the clinician documents on the clinical record form the rationale for using the new medication.

Although no large-scale research studies have adequately addressed the issue, 90 percent or more of psychiatrists polled at algorithm training sessions indicate that, based on their clinical experience, if a patient fails or only partially responds to one SGA, a trial of another SGA is warranted. For this reason, if a patient does not demonstrate a full

[1] Chlorpromazine, perphenazine, haloperidol, etc.
[2] Clozapine, olanzapine, risperidone, quetiapine, ziprasidone.
[3] The symbols a, b, and c, in parentheses following statements, indicate the authors' assessment of the level of evidence for the statements: (a) denotes recommendations arising from strong empirical trials using randomization and blinding, (b) indicates open label trials, cohort studies, and epidemiologic studies, (c) indicates recommendations based on a few case reports and/or consensus among the consensus panel (Woolf 1992).

response to an adequate trial of a SGA in Stage 1, the patient should receive a different SGA in Stage 2. (See section on Description of Tactics and Critical Decision Points, page 13, for discussion of what constitutes an adequate trial for each agent.) Once a patient has failed to respond or only partially responded to adequate trials of two SGAs, many experts believe that this establishes treatment resistance and that clozapine is the next logical step (Stage 3). Others believe that a trial of a third SGA or, in patients who have never received a trial of a conventional antipsychotic, an FGA may be worthwhile (Stage 2A). While current expert opinion favors using clozapine after Stage 2, the branch point in the diagram after Stage 2 indicates that a trial of a third SGA or an FGA is also a reasonable treatment alternative. If the patient fails to respond or only partially responds to an adequate trial of the Stage 2A medication, the physician should institute a trial of clozapine (Stage 3).

Approximately 50 percent of patients treated with clozapine do not respond adequately to the medication. Since clozapine is the "last best hope" for patients with treatment refractory schizophrenia, adding another antipsychotic or electroconvulsive therapy (ECT) to clozapine in patients who do not adequately respond to monotherapy makes sense and is probably the clinician's best option at this point. One randomized controlled trial (Shiloh et al. 1997) and a number of open label studies support clozapine in combination with a second antipsychotic in patients in whom clozapine monotherapy has yielded unsatisfactory results. For more information on combining ECT with clozapine, see "Electroconvulsive Therapy in Schizophrenia" in the Medications and Dosing section. The definition of adequacy of response to clozapine is discussed in Response, Partial Response, and No Response in the Evaluation of Patient Response section.

After Stage 4 (clozapine plus a second antipsychotic or ECT), there is a paucity of evidence to guide the selection of antipsychotic treatments for nonresponders or clozapine refusers. The general view of the consensus conference attendees was that it is preferable to exhaust reasonable antipsychotic monotherapy alternatives before progressing to combinations of antipsychotics. Stage 5 reflects the expert consensus that if a patient who has failed or refused clozapine has not exhausted all second generation monotherapy options, a trial of monotherapy with a different SGA should be attempted before the patient is started on combination therapy. In addition to the fact that little research evidence supports their use, combination therapies present adherence, safety, tolerability, and financial concerns. Complex medication regimes lead to poorer adherence than simple ones. Combinations also increase the likelihood of risky drug-drug interactions and of unexpected side effects and tolerability problems.

STAGING CONVENTIONS

"Stage 99" is reserved for those patients who insist on returning to the FGA they were taking prior to entry into the algorithm. "Stage 0" indicates a patient that was never entered into the algorithm and has never received an SGA.

Patients who are noncompliant and require a depot preparation are coded as Stage 1-D, 2-D, 2A–D on the clinical record form, the number reflecting which stage they were in at the time noncompliance became an issue, and the "D" indicating that a depot is now being used. The descriptor "R" is reserved for patients who return to an earlier stage.

Therefore, if a patient returns to Stage 2 after an inadequate response in Stage 2A, it would be designated as Stage 2-R.

As mentioned in the notice that appears at the beginning of this manual, these guidelines reflect the state of knowledge at the time of publication. As new studies elucidate different aspects of the medication management of schizophrenia, the algorithm will be periodically revised and updated.

Description of Tactics and Critical Decision Points

Each stage of the antipsychotic algorithm represents a trial of a different antipsychotic, and the medication options that clinicians and patients have to choose from are the algorithm's "strategies." While medications are the algorithm's "strategies," specific recommendations concerning medication use (dose titration, measurement of treatment response, trial duration, etc.) are the algorithm's "tactics." It is in these details of medication management that clinicians most often deviate from expert recommendations. This section of the manual and the following, Evaluation of Patient Response, provide instructions concerning the tactics of medication use.

The critical decision point (CDP) is a point in the course of the medication trial when the clinician decides whether to continue the present medication regimen, adjust the medication dose, or move on to another medication (the next stage of the algorithm). At each CDP, the clinician will use the clinical rating scales to assess the patient's level of response to the antipsychotic. The clinician will then make a therapeutic decision based on the results of the clinical rating scales, patient global self-report, ratings of other symptoms, etc. The response criteria and process measures (tools used to assess patient response) are discussed in the Evaluation of Patient Response section.

EXHIBIT 4
Critical Decision Points (CDPs) for Antipsychotic Algorithm,
Stages 1, 2, 2A, 4, 5, and 6

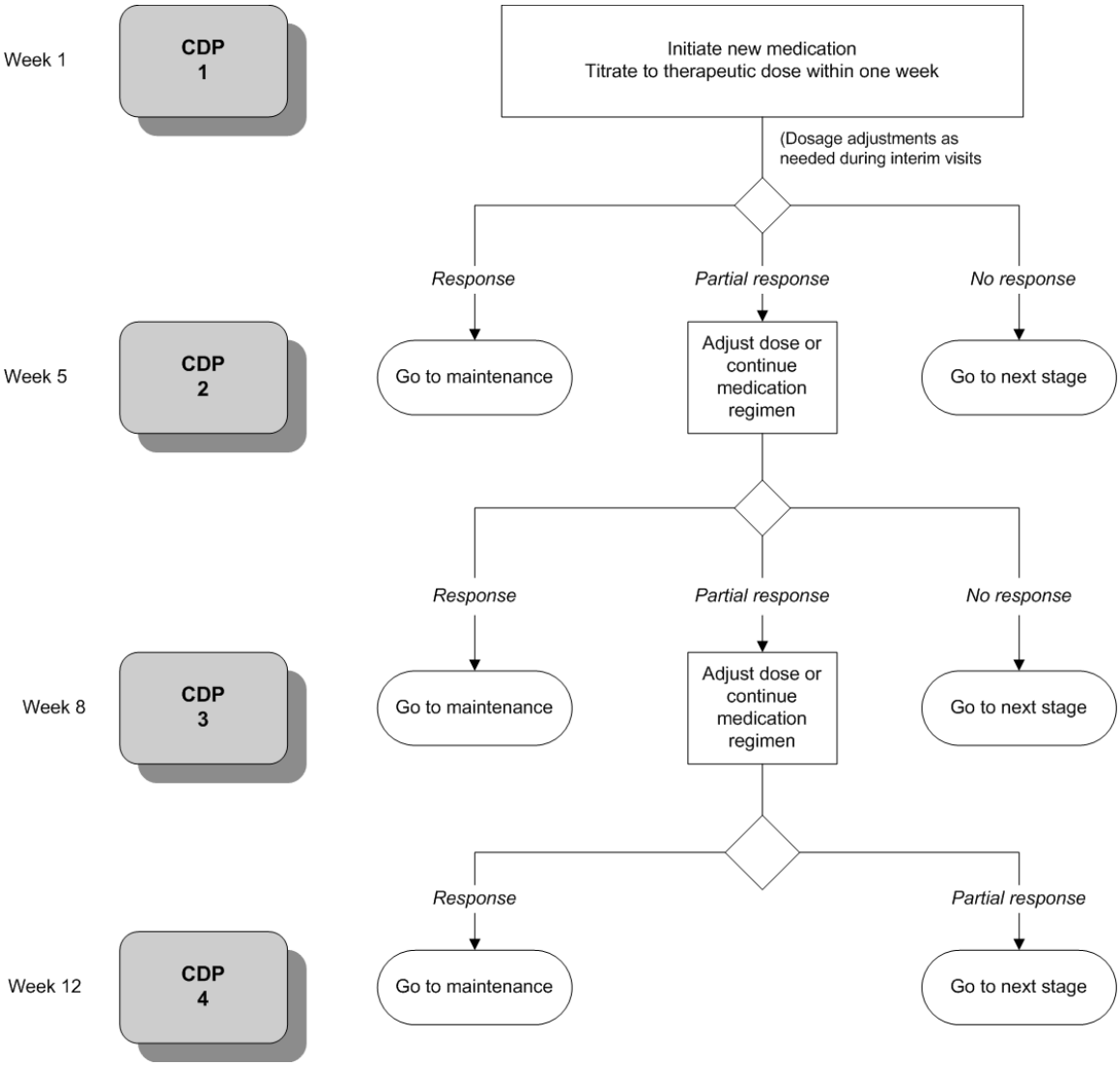
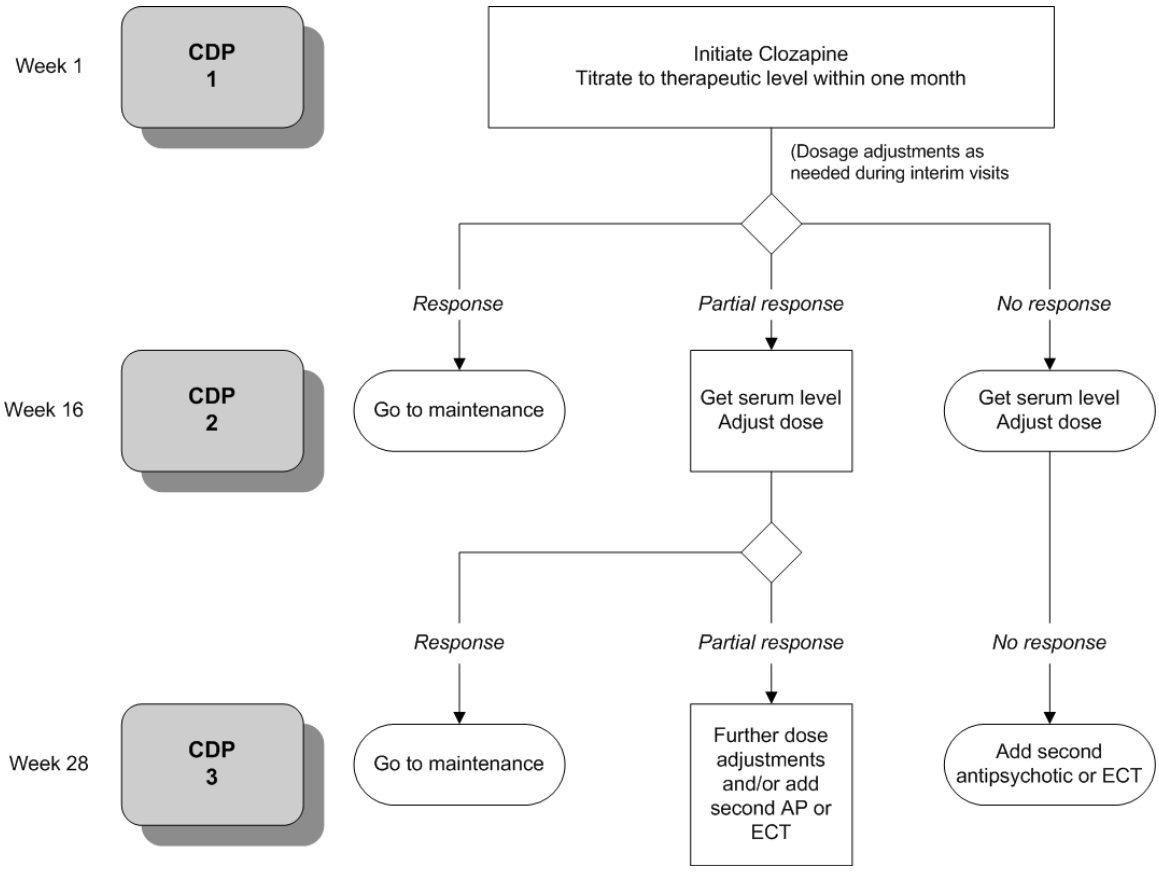


EXHIBIT 5
Critical Decision Points for Antipsychotic Algorithm, Stage 3, Clozapine



SCHEDULE OF CDPS FOR STAGES 1, 2, 2A, 4, 5, AND 6

As stated above, the CDP is a point in the course of medication therapy at which the physician decides whether to continue the present medication regimen, adjust the medication dose, or move on to the next stage of the algorithm. The CDPs are at the same times in treatment stages 1, 2, 2A, 4, 5, and 6.

CDP 1, Week 1

CDP 1 occurs at week 1. This is the point at which the patient enters the algorithm or changes stages in the algorithm. For new patients, decisions need to be made as to what stage of the algorithm the patient will enter and which medication will be prescribed. If the patient enters at Stage 1, the clinician will prescribe olanzapine, quetiapine, risperidone, or ziprasidone.

If the patient has had poor results in the past with any of these antipsychotics, the practitioner should determine if an adequate trial duration at an adequate dose was used before eliminating the possibility of trying that drug again. If any of these drugs can be

used, the physician decides which is preferable. As allowed by the clinical situation, the patient, and when possible, the family should have input into this decision.

The medication should be titrated to a therapeutic dose during the first week, and the patient should be seen weekly for four more visits, if feasible, to evaluate drug tolerability and the need for dosage adjustments. During this five-week medication initiation and dose titration period, it is important to have contact with the patient as frequently as possible to monitor for symptom improvement, possible symptom worsening, and emergent side effects; to encourage medication adherence; and to provide patient/family reassurance. Early intervention may allow management of side effects or symptom worsening, thus possibly preventing hospitalization. If weekly office visits are not possible, nurses or other providers can check on the patient by phone. As symptoms improve, patients can be seen less often for medication visits but should still be seen at least every 2–3 weeks. As stabilization occurs, patient visit frequency can be gradually decreased until eventually a stabilized patient may only need to be seen once every three months.

CDP 2, Week 5

The second critical decision point occurs at about week 5, after titration and after the patient has been on therapeutic doses of medication for four weeks. At this point, the clinical rating scales and other assessment tools are evaluated to determine whether the patient has

- responded adequately enough to continue on the same maintenance dose, or
- had only a partial response requiring dosage adjustment, or
- had a complete lack of response, which indicates moving to the next stage of the algorithm. (Studies suggest that patients who show no response after four weeks of therapeutic doses of medication are not likely to respond after more time on the drug [Marder et al. 2002].)

CDP 2 should be in the time frame of approximately four weeks on a therapeutic dose. Shorter or longer time periods warrant a comment that explains the clinical reasoning.

An issue that may arise at any time is nonadherence. This may require switching to a depot preparation of haloperidol or fluphenazine (or a depot SGA when available). The use of depot drugs requires a trial of at least 8 to 12 weeks and a determination of full response, partial response, or nonresponse. The issue of nonadherence is also discussed in the Medications and Dosing section below.

CDP 3, Week 8

The third CDP occurs at about week 8. Nonresponders and partial responders who are no better at CDP 3 than at CDP 2 should move to the next stage. Partial responders who improve between CDP 2 and CDP 3 may continue another four weeks to CDP 4. The time window for CDP 3 is 7–9 weeks. Shorter or longer periods require a note of explanation. Serum levels of haloperidol and fluphenazine can be useful in deciding if Stage 2A or Stage 5 patients on these medications need dose adjustments.

CDP 4, Week 12

By the twelfth week, failure to achieve an adequate therapeutic response to the medication indicates the need to move on to the next stage (a). The same CDPs repeat for trials of a FGA or any SGA other than clozapine.

FURTHER DISCUSSION OF STAGES 4, 5, AND 6

Stage 4

Since there is no antipsychotic shown to be effective for partial or nonresponders to clozapine, it is worthwhile to try to improve response to clozapine with the addition of another antipsychotic or ECT. These are widely used but understudied tactics.

Although the literature is sparse, the best-supported combination strategies appear to involve adding an FGA, an SGA, or ECT. Patients who, despite an adequate trial of clozapine, still have persistent positive symptoms may benefit from the addition of modest doses of a higher potency typical antipsychotic such as loxitane (Mowerman and Siris 1996) or pimozide (Friedman et al. 1997). (Clinicians should bear in mind pimozide's association with QTc interval prolongation and risk of torsade de pointes.) It should be noted, however, that addition of a typical antipsychotic to clozapine may result in extrapyramidal symptoms (EPS) and potentially decrease some of the benefits of using clozapine (Kapur et al. 2001). A recent report indicates that adding risperidone to clozapine was helpful for ten out of twelve outpatients who were clozapine partial responders (b) (Henderson and Goff 1996). There are several reports of using ECT for patients who are persistently psychotic on clozapine. The combination of ECT and clozapine in these patients produced improvement in a majority of patients with poor or partial responses to clozapine (b). See Electroconvulsive Therapy in Schizophrenia in the Medications and Dosing section.

While mood stabilizers may help patients with schizophrenia with concomitant symptoms of mood instability and/or impulsivity, there is scant evidence to support their role as adjuncts in patients whose positive symptoms only partially respond to clozapine. If clinicians do use mood stabilizers for this purpose, they should carefully monitor the target symptoms and, if no improvement is noted, discontinue the adjunctive mood stabilizer. With regard to staging, if the mood stabilizer is being added to clozapine in an attempt to ameliorate symptoms of psychosis, the patient is in Stage 6. This is because there is virtually no evidence that mood stabilizers enhance the antipsychotic effects of clozapine. Therefore the combination of clozapine plus a mood stabilizer for psychotic symptoms falls in the category of unproven combination treatments. Addition of an anticonvulsant, such as divalproex, to clozapine for another purpose, such as seizure prevention, would not be Stage 6, since only the clozapine is being used as an antipsychotic. If the mood stabilizer is added to clozapine in an attempt to target nonpsychotic symptoms (hostility, mood lability, etc.), the patient is in Stage 3 and the algorithm for coexisting persistent symptoms of aggression, hostility, and mood lability is followed.

The CDPs in this stage of the algorithm reflect the time to response for the medication that is added to clozapine therapy. The augmenting agent should be titrated to a

therapeutic dose in one week with CDPs at weeks 5, 8, and 12. The CDPs for Stage 4 are included above with those for stages 1, 2, 2A, 5, and 6. Due to financial and safety issues (drug interactions, additive side effects) involved in using multiple medications, it is crucial that clinicians use both the clinical rating scales and subjective information (patient self-report, global impressions) to assess the impact of the additional agent and discontinue it if it is not helping the patient.

Stage 5

As mentioned in the Description of Stages of the Antipsychotic Algorithm section, there is practically no evidence to guide antipsychotic selection in patients who either do not respond to or refuse to take clozapine. Stage 5 reflects the expert consensus that if a patient who has failed to respond to or refused clozapine has not exhausted all second generation monotherapy options, a trial of monotherapy with an untried SGA should be attempted before the patient is started on combination therapy. (If there is no history of failure on a FGA, an untried FGA would be another treatment option.) In switching from clozapine to another antipsychotic, the clozapine dose should be tapered down slowly while the new antipsychotic is titrated to a therapeutic dose. If the patient's clinical status worsens during this process, consideration should be given to reinstituting the prior clozapine dose. The CDPs for Stage 5 are included above with those for stages 1, 2, 2A, 4, and 6.

Stage 6

Patients in Stage 6 have persistent psychotic symptoms that warrant the addition of a second agent. (Patients whose nonpsychotic target symptoms [e.g., agitation] require the temporary addition of a second agent would remain in their current algorithm stage and follow one of the coexisting symptoms algorithms.) Long-term combination therapy should be considered a "last resort" for those patients who have exhausted all reasonable monotherapy options. As with combination therapy with clozapine (Stage 4), the CDPs reflect the time to response for the second (or the "added") agent. Due to safety and financial concerns, it is imperative that clinicians use both the clinical rating scales and subjective information to assess the effect of the second medication. If the patient's clinical status has not improved after a 12-week trial of the "added" agent, the second agent should not be continued.

SCHEDULE OF CDPS FOR STAGE 3

There are three critical decision points when using clozapine.

CDP 1

CDP 1 is the point at which the patient has failed at least two antipsychotic trials (by history or trial). At this point clozapine would be started and the dosage titrated to therapeutic levels over one month. For the next three months the patient should be clinically evaluated at least monthly and dosage adjustments made.

CDP 2

CDP 2 for Stage 3 occurs at 16 weeks or after one-month titration and three months at therapeutic doses (minimum of 300 mg/day) (a). If the patient has responded to

clozapine, begin maintenance treatment. If the patient has had a partial response or no response, obtain a serum level and adjust the dose to achieve a serum level above 350 ng/ml.

CDP 3

CDP 3 for Stage 3 occurs at week 28, or after six months of clozapine at therapeutic doses. If the patient has had a partial response, a dosage increase and/or the addition of a second antipsychotic or ECT is indicated. If there has been no response, proceed to Stage 4.

It can be difficult to differentiate between an absolute lack of response versus a partial response to clozapine. It is not uncommon for a clinician to realize that a "nonresponder" was actually a "partial responder" after a patient's condition deteriorates dramatically while clozapine is being tapered and discontinued. However, the clinician must also keep in mind that the rate of the medication taper, not the absence of the drug, may be causing the reemergence of psychotic symptoms. (Clozapine should be tapered down over at least three months; decreasing the dose too rapidly has been associated with a reemergence of florid psychosis.)

Evaluation of Patient Response

Generally speaking, symptoms respond to antipsychotics in somewhat different time frames. Agitation, sleep, and appetite often respond during the first 1–2 weeks, whereas personal hygiene and basic interpersonal socialization may be slower to respond (2–3 weeks), and psychotic symptoms can gradually decrease over 2–6 weeks or longer. Residual symptoms may continue to improve at 6–12 weeks. Chronic patients may show slower responses of all symptoms (c).

The MIMA response criteria are shown below (see Exhibit 6). Descriptions of the process measures used to evaluate patient response begin on page xx.

EXHIBIT 6
MIMA Patient Response Criteria

STAGE 1	Positive symptom score ≤ 6
STAGE 2	Positive symptom score ≤ 6
STAGE 2A	Positive symptom score ≤ 6
STAGE 3	> 20% decrease in positive symptoms
STAGE 4	> 20% decrease in positive symptoms
STAGE 5	> 20% decrease in positive symptoms
STAGE 6	> 20% decrease in positive symptoms

Negative symptoms are no longer included in the response criteria as little evidence exists on which to base realistic goals for negative symptom improvement. Compared to the older agents, the newer medications are thought to be "better" for negative symptoms, but this superiority may be explained by the newer agents' reduced propensity to cause EPS (which can lead to secondary negative symptoms). Several factors (depression, environmental deprivation, positive symptoms) can contribute to negative symptoms and medications may have little effect on *core* negative symptoms.

This in no way implies that negative symptoms are not important and do not need to be measured. On the contrary, recent findings indicate that negative and cognitive symptoms have more of an impact on patients' functional status than the positive symptoms of schizophrenia. At each medication visit, clinicians should perform the Positive Symptoms Rating Scale (PSRS), Brief Negative Symptom Assessment (BNSA), and assessments of "other symptoms" such as mood lability, anxiety, agitation, etc. and incorporate all findings into the clinical decision-making process.

RESPONSE

The goal of stages 1–2A of the antipsychotic algorithm is to achieve control of positive symptoms so that their effects on patient functioning are diminished. Most deterioration in functioning occurs during the first years of the illness; therefore, it is important to aggressively treat symptoms in recent-onset patients.

Control of positive symptoms means that the total score on the four positive symptoms items is six or below. This means that no item can be above mild in severity and that if one item is mild in severity the others must be normal. As mentioned above, the algorithm does not specify a goal for negative symptom response, but it does recommend an approach to their treatment. While evaluating negative symptoms, the clinician should consider the patient's prior history and potential for change. As a guiding principle, the better the premorbid history, the more aggressive one should be in treating negative symptoms, and the worse the history, the less likely that dramatic negative symptom responses will occur (c).

In stages 3–6 of the algorithm, absence of significant positive symptoms may be an unrealistic goal. Therefore, the criteria for response are relative rather than absolute. At least a 20 percent reduction from prior positive symptom levels would justify continuation of the same treatment. Addition of an augmenting agent can be tried in either Stage 4 or Stage 6 in attempt to gain further improvement.

For patients who enter the algorithm at stages 1–2A, these responses can be compared with those in stages 3–6 to decide if there is at least a 20 percent improvement. If not, it is reasonable to return to the best of the earlier antipsychotics if the response in the later stages seems inadequate. For patients who enter the algorithm at Stage 3 or later and are not responding to therapy, and for whom no objective ratings have been done, the clinician is encouraged to try stages 1–2A medications if the history of response to first or second generation antipsychotics is not definitively negative.

It is expected that about half of patients tried on clozapine will not respond (a). The new algorithm recommends combination therapy for nonresponders because, once the patient is on clozapine, it is worth the effort of adding a second agent before going to treatments that have no proven value in clozapine nonresponders. After clozapine discontinuation, it is sometimes found that apparent clozapine "nonresponders" were actually partial responders, a fact that further supports combination therapy in clozapine nonresponders.

PARTIAL RESPONSE

A partial response at any stage of the algorithm is a basis for continuing the patient in that stage, up to the maximum recommended amount of time for that stage. At CDPs there is the option of changing the antipsychotic dose for partial responders. This is not a requirement, however. For many patients, further duration of treatment may be all that is needed (a). There are, unfortunately, no empirical guidelines for deciding when this is the case. As a general rule, prior time to achieve a response in a particular patient is helpful in judging when that patient is likely to respond to the current treatment.

In stages 1–2A, less than a 20 percent reduction in positive symptoms after at least three weeks on the highest recommended dose would mean that the patient is a nonresponder, not a partial responder. If patient and clinician agree that there has been noticeable improvement, however, a partial response may have occurred that is not evident in the PSRS. In this case, continuation of treatment in the same stage is justified, up to the maximum duration recommended.

In summary, a partial responder in stages 1–2A has less than 20 percent improvement in positive symptoms, but his/her absolute positive symptom scores exceeds 6. In stages 3–6, partial response is a clinical judgment that the patient whose symptoms have improved by less than 20 percent is "better." It is not clinically meaningful to try to use scale score changes of less than 20 percent to distinguish between partial responders and nonresponders.

NO RESPONSE

At any stage, before concluding that a patient is a nonresponder to an antipsychotic, the clinician should consider causes of nonresponse that would indicate a course of action other than changing to a new antipsychotic. Included in this list are:

1. Medication nonadherence (If due to side effects, try another SGA. If not due to side effects, consider a depot preparation.)
2. Incorrect diagnosis
3. Substance abuse (Check urine, if in doubt and patient consents.)
4. "Covert" side effects (If patient feels "lousy" on medication but does not have typical side effects, consider trial of a different antipsychotic.)
5. Psychosocial stressors (Ask about changes in home, work, finances, etc.)
6. Undiagnosed or uncorrected general medical problem such as diabetes (Get routine labs—CBC, thyroid function tests, chem profile.)

Process Measures

This section of the manual discusses methods used to evaluate patient response to medication therapy. It covers both physician and provider administered assessments.

PHYSICIAN-ADMINISTERED ASSESSMENTS

The physician can rate the patient at each visit using the scale of 0 = no symptoms to 10 = extreme (see page 26). The areas assessed are core symptom severity, other symptoms, and overall side effect severity.

Provider-Administered Assessments

The following assessments should be completed before the physician sees the patient. The individual performing the following ratings can be a nurse, social worker, or any other mental health professional trained in the administration of the assessments. The administration manual for the clinical rating scales (PSRS, BNSA) is provided in Appendix A. Below is a brief description of each of the three provider-administered assessments.

The Four-Item Positive Symptoms Rating Scale (PSRS)

The four-item PSRS may be administered at each visit. The ratings for the four-item PSRS and the BNSA are on the same score sheet. For the four-item PSRS, the items are ranked on a scale of: N/A = not assessed, 1 = not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = extremely severe.

The four-item PSRS assesses positive symptoms of schizophrenia (suspiciousness, unusual thought content, hallucinations, and conceptual disorganization). These items are from the BPRS (Overall and Gorham 1962) and the expanded version of the BPRS (Lukoff et al. 1993), both of which have been shown to be valid and reliable. Item selection was based, in part, on a factor analysis of the expanded BPRS conducted by Ventura and colleagues in 1995. Included are suggested questions intended to guide the interviewer in obtaining the information required for making the ratings. The interview takes five minutes or less.

The Brief Negative Symptom Assessment (BNSA)

The BNSA may be administered at each visit. The ratings for the four-item PSRS and the BNSA are on the same worksheet (see page XX). For the BNSA, the items are ranked on a scale of 1 through 6. The BNSA is a four-item instrument used to assess a subset of DSM-IV negative symptoms (alogia, amotivation, flat affect, and asociality). The items are based on items from the Negative Symptom Assessment developed by Alphs et al. (1989) and the Scale for the Assessment of Negative Symptoms (SANS) developed by Andreason (1981). The BNSA provides quick assessment of distinct negative symptoms, takes less than five minutes to administer, and is based largely on observation.

Patient Global Ratings (Self-Report) of Symptom Severity and Side Effects

These ratings should apply to the symptoms and side effects the patient has experienced during the past week, and are rated on a scale of 0–10, with 0 indicating none and 10 indicating severe.

Symptom Severity—The provider should ask the patient to make a global rating of symptoms he/she has experienced in the past week where:

0 = no symptoms
5 = moderate symptoms
10 = very severe symptoms

"Which rating best describes any symptoms you might have had in the past *week*?"

Side Effects—The provider should ask the patient to make a global rating of side effects he/she has experienced in the past week where:

0 = no side effects
5 = moderate side effects
10 = very severe side effects

"Which rating best describes any medication side effects you might have had in the past *week*?"

DOSING

The FDA approved product labeling contains dose range information for all marketed antipsychotic medications. These recommendations are based largely upon the results of randomized controlled trials. Evidence that some patients may obtain an enhanced response at doses above the range recommended in the labeling may be found in the medical literature. In the case of risperidone, clinical experience has shown that higher doses (> 6 mg) lead to greater extrapyramidal side effects, and average daily doses have actually decreased over time.

For olanzapine and risperidone, PET data examining D_2 and $5HT_{2A}$ binding in relatively small numbers of patients support the usual dosage range for the average patient.

Studies with first generation antipsychotics indicate that time on drug is often more important than dose escalation above usual doses, and that patients' symptoms on a given antipsychotic may improve with continued drug exposure, with or without a dosage increase. Similar studies with second generation antipsychotics are not yet in the literature.

In a partially, but inadequately responding patient, it may be reasonable to increase the dose above the usual dose range, if the patient has received an adequate trial (8–12 weeks) at higher doses within the usual dosage range. In such cases, the higher dose trial should be time limited (e.g., 4–6 weeks) unless there is evidence of significant clinical benefit. Clinical rating scales should be used to document whether the symptom improvement is greater than that achieved with usual doses. Patients not receiving additional benefit at higher doses within the designated time period should typically be switched to a trial with an alternate agent.

Based on current usage patterns, it is anticipated that:

- The average daily dose of **risperidone** is about 4–5 mg/day. Risperidone doses are usually adjusted in 1–2 mg increments every 3–7 days. Risperidone doses can be taken once daily.
- The average daily dose of **olanzapine** is about 15 mg/day. Olanzapine doses are usually adjusted in 5 mg increments every seven days. The recommended starting dose of olanzapine is 10 mg/day. Higher doses of olanzapine (20 mg) may lead to faster response in positive symptoms (b), but the patient may then do well on a lower maintenance dose once stabilized (c). Olanzapine is usually taken at bedtime.
- **Quetiapine** dosing should be individualized, in the range of 300 mg to 800 mg per day. The starting dose is 25 mg BID, which is titrated up to at least 300 mg (150 mg BID) over 3–7 days. The rate of titration should be adjusted according to side effects. Early postural hypotension and sedation are usually mild and improve with time. The maximum recommended dose is 800 mg/day. Quetiapine has a very low incidence of EPS. When cross-tapering quetiapine and another agent, it is often possible to titrate the quetiapine dose to 300 mg/day before beginning to decrease the old antipsychotic. Some clinicians choose to give most of the quetiapine dose at bedtime, to take

advantage of its sedative properties. This dosing strategy seems reasonable but has not been systematically evaluated.

- **Ziprasidone's** package insert recommends an initial dose of 40 mg/day (20 mg BID). However, many clinicians start the medication at 80 mg/day (40 mg BID) and titrate up to the 120 mg/day target dose over a 3–7 day period. (Doses up to 160 mg/day may be necessary in some patients.) While some patients experience sedation when they start taking ziprasidone, others may transiently feel "activated" or even somewhat agitated. This latter group of patients may benefit from co-prescription of a low-dose benzodiazepine (e.g., clonazepam or lorazepam) during the initial weeks of ziprasidone therapy. The presence of food can increase ziprasidone's absorption up to twofold.
- The recommended first dose of **clozapine** is 12.5 mg (half a 25 mg tablet) on day one. If this dose does not produce symptomatic postural hypotension, progress to 25 mg HS for three days. Further increases at the rate of 25 mg every three days are usually well tolerated. Clozapine should be given in divided doses, with about 1/3 of the dose in the morning and 2/3 at bedtime. Above 100 mg/day, dose increases can be by 50 mg every three days until a daily total dose of at least 300 mg is reached. Subsequent dose increases should be guided by clinical response. The risk of seizures rises from 1 percent at 300 mg/day to 5 percent or more at 900 mg/day.

  Clozapine serum levels are recommended before increasing doses above 600 mg/day. There is no clear threshold, but a reasonable current recommendation is to increase the dose further if the patient is not responding and if the serum level is below 350 ng/ml. Serum clozapine levels should be obtained before the morning dose, approximately twelve hours after the prior dose, and after at least five days on the same daily dose.

EXHIBIT 7
Second Generation Antipsychotic (SGA) Dosage Guidelines

SGA	Starting dose	Titration	Range	Max. dose	Schedule
Clozapine	12.5 mg/day (half a 25 mg tab) Starting day 3, dose increased every 3 days	Day 2: 25 mg HS Day 3: 25 mg BID Day 6: 25 mg AM, 50 mg HS Day 9: 50 mg BID Day 12: 75 mg BID Day 15: 100 mg BID Day 18: 125 mg BID Day 21: 150 mg BID Day 24: 100 mg AM, 200 mg HS	300–900 mg/day (serum level for doses > 600 mg/day)	900 mg/day	BID Eventual maintenance dose schedule is: BID (1/3 in AM, 2/3 in PM)
Olanzapine	5–10 mg/day	5 mg/week	10–20 mg/day	40 mg/day[a]	HS
Quetiapine	25 mg BID	50 mg/day	300–800 mg/day	800 mg/day	BID
Risperidone	1–2 mg/day	1 mg/2–3 days	2–6 mg/day	16 mg/day[b]	HS or AM
Ziprasidone	40–80 mg/day	20–40 mg/2–3 days	80–60 mg/day	160 mg/day	BID The presence of food can increase ziprasidone's absorption up to twofold

[a]Some data indicate that olanzapine doses > 20 mg may benefit patients who only partially respond to an adequate trial of olanzapine 20 mg. (Volavka et al. 2002; Lindenmayer et al. 2001)
[b]The risk of EPS is significantly increased by using doses > 6 mg daily.

EXHIBIT 8
First Generation Antipsychotic (FGA) Dosage Guidelines

Drug	Starting dose	Dose range	Usual max. dose
Chlorpromazine	50–100 mg/day	300–1000 mg/day	1000 mg/day
Fluphenazine	5 mg/day	5–20 mg/day	20 mg/day
Fluphenazine D	12.5–25 mg IM/2–3 weeks	6.25–50 mg IM/2–4 weeks	100 mg IM/4 weeks
Haloperidol	2–5 mg/day	2–20 mg/day	20 mg/day
Haloperidol D	25–50mg IM/2 weeks	50–200 mg/2–4 weeks	300 mg/3–4 weeks
Loxapine	20 mg/day	50–150 mg/day	150 mg/day
Molindone	20 mg/day	50–150 mg/day	150 mg/day
Perphenazine	4–8 mg/day	16–64 mg/day	64 mg/day
Thiothixene	5–10 mg/day	15–50 mg/day	50 mg/day
Trifluoperazine	2 mg BID	5–40 mg/day	40 mg/day

DECISION TO CHANGE ANTIPSYCHOTIC

The decision to change antipsychotic medications can be based on symptomatology or side effects.

1. In general, persistent positive symptoms that are more than mild in intensity should lead to a medication change, unless there is good clinical evidence that further improvement with a medication change is unlikely (a).

2. Patients with persistent negative symptoms should be evaluated for depression and medication side effects as contributing factors (a).

3. The clinician should then decide if it is better to add a treatment (e.g., antidepressant or anticholinergic) or change to another antipsychotic. It is better not to do two things at once (e.g., change antipsychotic and add an antidepressant) (c).

4. The threshold for deciding to change antipsychotics because of side effects should be low, given the favorable side effect profiles of new antipsychotics (a).

5. Some side effects are treatable with adjunctive medication. If this tactic is unsuccessful or clinically inadvisable, move the patient on to the next stage of the algorithm.

6. Some side effects tend to decrease over time (sedation, postural hypotension, for example), and it is worth allowing 4–6 weeks for these adaptations to occur if the patient is benefiting from the medication and the side effects are not intolerable or dangerous.

7. Patients on multiple medications for side effects are candidates for switching to a different antipsychotic if there are other choices that are less likely to produce these side effects and if the side effect medications themselves produce side effects.

8. In addition to typical EPS and akathisia, consider patients' complaints about the medication making them feel physically or mentally uncomfortable (e.g., dysphoric or zombie-like) as possible reasons for changing antipsychotics (b).

9. In the case of treatment-resistant patients on clozapine, it is worth spending considerable effort helping patients cope with side effects, since it is unlikely that they will do better on a different antipsychotic (b).

USE OF FIRST GENERATION ANTIPSYCHOTICS

As discussed in the Description of Stages of the Algorithm section above, FGAs are not recommended as first-line agents because, in general, they are no more effective than the SGAs and have a greater propensity to cause EPS and tardive dyskinesia. There may be times, however, when an FGA is the most appropriate choice for a patient. The following clinical situations may warrant the long-term use of an FGA:

1. Individuals who are currently responding well to an FGA and have no EPS, akathisia, or tardive dyskinesia.
2. Individuals who have a history of responding better to FGAs than to SGAs.
3. Individuals who are candidates for depot therapy (this will likely change as second generation depot antipsychotics become available).

NONADHERENCE

Because medication nonadherence is frequently a result of bothersome side effects (a), clinicians should consider a trial of another first-line SGA before beginning a depot preparation. However, there are instances when the physician can reasonably conclude that the patient is unlikely to comply with another oral medication and that it is not worth trying an alternate SGA (c). In this case, the basis for the conclusion should be documented and the patient put on a depot antipsychotic. These patients can be switched back to a first-line oral antipsychotic at any time if the physician believes that the likelihood of medication compliance has substantially increased (e.g., the patient has gained insight into his/her illness and the need for treatment) and there are current (e.g., EPS) or potential (e.g., TD) problems with the depot treatment. As noted above, criteria for use of depot antipsychotics may change with the advent of depot second generation antipsychotics.

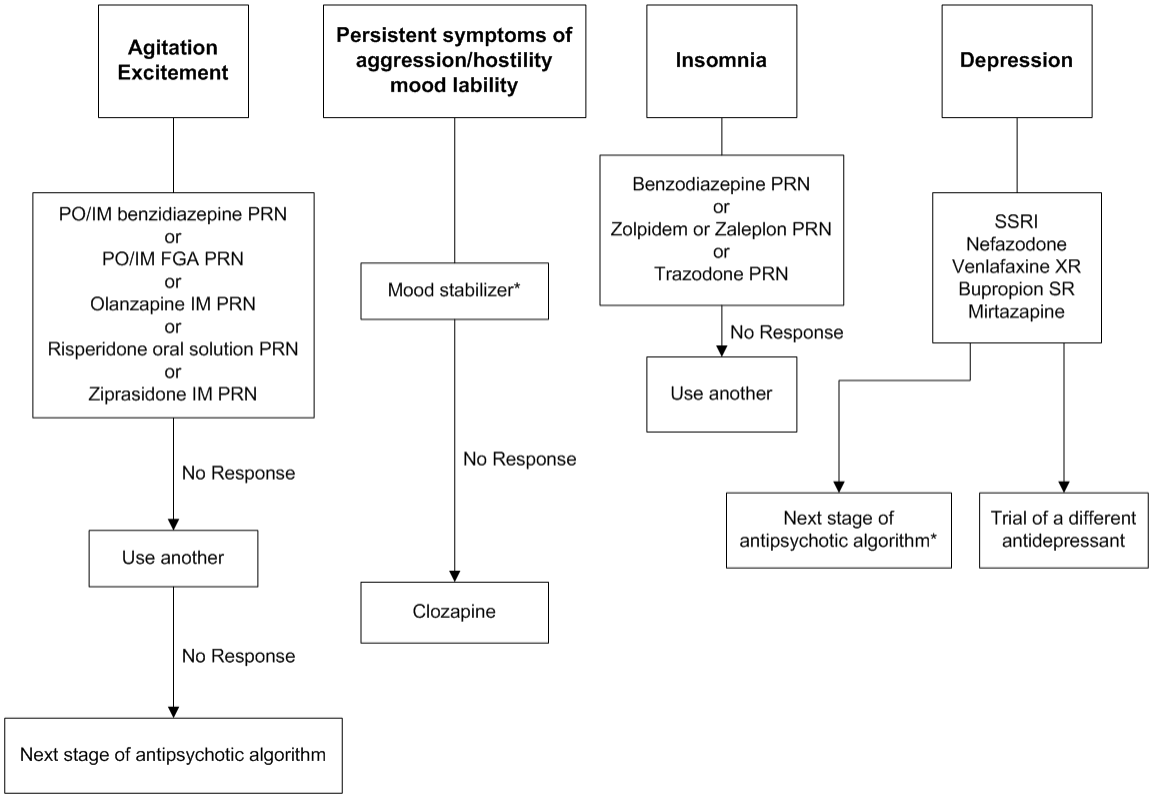
ELECTROCONVULSIVE THERAPY IN SCHIZOPHRENIA

Electroconvulsive therapy (ECT) is a controversial treatment that has been understudied in schizophrenia for the past three decades. Almost all studies have shown beneficial effects of ECT for persistent psychotic states (b), but most of these preceded clozapine and newer second-generation antipsychotics. There are a number of case studies showing improvement when ECT was administered to clozapine-resistant patients kept on clozapine (c). Because of these data, ECT is listed as a choice in stages 4 and 6, in combination with clozapine or another antipsychotic. Lack of ECT availability may be an insurmountable hurdle in some locations, but clinicians who have access to ECT are encouraged to consider it for treatment-resistant patients who fail or refuse clozapine. It is a common clinical impression that when ECT is used for schizophrenia, more treatments are needed (ten or more) and electrode placement should be bilateral (c). There are no controlled studies of ECT for schizophrenia in which number of treatments, duration of treatments, and electrode placement have been systematically evaluated.

MEDICATIONS FOR COEXISTING SYMPTOMS

As used in this algorithm, the term “coexisting symptoms” refers to the nonpsychotic symptoms that frequently accompany an exacerbation of schizophrenia or schizoaffective disorder (excitement, agitation, insomnia) or that frequently complicate the course of these illnesses (depression). The treatments for these symptoms are generally time limited and symptom oriented, in contrast to the maintenance and illness-oriented role of antipsychotics. The algorithms for coexisting symptoms appear below and on page 8. Medications used to manage side effects are discussed in the section of the manual entitled Management of Side Effects on page 40.

EXHIBIT 9
Coexisting Symptoms Algorithms



*Consider clozapine in patients with persistent suicidal behaviors or ideation.

Agitation and Excitement

Agitation and excitement are often the symptoms that lead to recognition of and hospitalization for exacerbations of schizophrenia. Historically, antipsychotics have been used both for these symptoms and for the psychosis, but a number of clinicians report that the SGAs seem less effective for the agitation and excitement of an acute exacerbation. For this reason, the algorithm for these symptoms is separate from the algorithm for psychosis and allows for PRN use of FGAs, benzodiazepines, olanzapine IM, risperidone oral solution or ziprasidone IM. It is important to stress that these PRN treatments should be time limited and discontinued as soon as clinically feasible. In the case of the FGAs this is because of increased risk of EPS, dysphoria, and tardive dyskinesia. In the case of benzodiazepines, the desirability of limiting amount and duration of PRN use relates to the development of tolerance over 2–3 weeks of steady use. On an outpatient basis, benzodiazepines should be used with caution in patients with a recent history of alcohol or drug abuse. Clinician choice of medication for agitation and excitement should be individualized to the needs and circumstances of the patient, guided by past history of response. Outpatients are likely to be more familiar with self-administering benzodiazepines on a PRN basis and may need education on PRN use of one antipsychotic while taking another regularly. Outpatients with a history of EPS should be started on an anticholinergic concurrent with starting a PRN FGA. Olanzapine IM,

risperidone oral solution, and ziprasidone IM act more rapidly than their oral counterparts and their use may be warranted in cases where the patient cannot tolerate or does not respond to FGAs and/or benzodiazepines. The concentration of risperidone oral solution is 1 mg/mL.

If a short course of an adjunctive FGA is being used for agitation, this should not affect the patient's staging in the algorithm. If the combination therapy continues beyond three to four weeks, however, it is no longer considered adjunctive (i.e., the patient is in Stage 6 of the algorithm).

EXHIBIT 10
Medications for Agitation and Excitement

Drug	Starting dose	Range (daily dose)
Lorazepam (Ativan)	0.5–1 mg TID	1–8 mg
Clonazepam (Klonopin)	0.25–0.5 mg BID	0.5–4 mg

Persistent Symptoms of Aggression/Hostility/Mood Lability

While benzodiazepines and FGAs may be used PRN to treat the agitation and excitement of an acute exacerbation of schizophrenia, mood stabilizers may help patients whose schizophrenia is complicated by persistent symptoms of aggression, hostility, and mood lability. In the event that a mood stabilizer is added to clozapine, the clinician should keep in mind that seizures are a risk with clozapine, especially at higher doses, so valproic acid may be safer than lithium. Combination therapy with clozapine and carbamazepine is contraindicated secondary to each agent's bone marrow suppressing effects. Carbamazepine also lowers antipsychotic serum levels secondary to its capacity to induce several different CYP 450 isoenzymes. Due to quetiapine's low bioavailability, carbamazepine's effects on quetiapine are of particular clinical significance. The clinician should periodically assess whether the addition of the mood stabilizer has resulted in a decreased frequency of aggressive, hostile, and/or mood episodes. If there is no discernible change in the clinical picture, the clinician should discontinue the adjuvant mood stabilizer and consider switching the patient to clozapine for persistent symptoms of aggression/hostility.

Insomnia

Insomnia as an acute symptom of psychosis differs in its treatment from the chronic difficulty falling asleep which is common among patients with schizophrenia who have poor sleep hygiene (daytime naps, caffeinated beverages in the evening, etc.). Some treatments for the acute insomnia associated with an exacerbation of psychosis include benzodiazepines, zolpidem (Ambien), zaleplon (Sonata), and trazodone (priapism risk in males). As with the acute interventions for agitation and excitement, PRNSs for insomnia should be time limited in their use.

EXHIBIT 11
Medications for Insomnia

Drug	Starting dose	Range (daily dose)
Zolpidem (Ambien)	10 mg HS	5–10 mg
Zaleplon (Sonata)	10 mg HS*	5–10 mg
Trazodone (Desyrel)	25 mg HS	12.5–100 mg

*May be administered in the middle of the night to reestablish sleep with no next-day hangover.

Depression

Both depression and suicide are common in schizophrenia. Almost half of patients with schizophrenia have major depression at some point in their illness and about 10 percent die by suicide. Medication treatments for depression in schizophrenia are not different from those used in major depressive disorder. For reasons of safety and tolerability, the selective serotonin reuptake inhibitors (SSRIs), bupropion SR, nefazodone, venlafaxine XR, and mirtazapine are recommended as first line treatments for depression in schizophrenia.

If a patient's depressive symptoms do not respond to a trial of one of the aforementioned antidepressants, the clinician should consider whether the patient has been diagnosed correctly, has an undiagnosed medical condition that could precipitate depression, or has been abusing illicit substances. If none of these is the case, there is little evidence to guide the clinician's decision with regard to changing the antipsychotic or trying a different antidepressant. However, a large multinational study showed an advantage for clozapine relative to olanzapine in reducing suicidal behaviors in patients with schizophrenia at increased risk for suicide.

Since some antidepressants can, by themselves, cause akathisia, this side effect should be watched for and not misattributed to the concurrent antipsychotic treatment. (For more information on antidepressant side effects, see the MIMA Guidelines for Treating Major Depressive Disorder). It is worth remembering that failure to respond to one SSRI does not necessarily predict failure on other SSRIs. Duration of treatment should be the same as for any episode of major depression (6–12 months), though this issue has not been well studied in schizophrenia. Recommended doses of antidepressants are listed below (see Exhibit 12).

EXHIBIT 12
Recommended Doses of Antidepressants

Type/Class	Medication	Usual target dose to achieve in weeks 1–3	Usual maximum recommended dose	Recommended administration schedule
SSRI	Citalopram	20 mg/day	60 mg/day	QAM
	Fluoxetine	20 mg/day	40–80 mg/day	QAM
	Paroxetine	20–30 mg/day	40–60 mg/day	QAM
	Sertraline	50–100 mg/day	150–200 mg/day	QAM
Others	Bupropion SR	200–300 mg/day	400 mg/day	BID ≤ 200 mg/dose
	Bupropion	225–300 mg/day	450 mg/day	BID–TID ≤ 150 mg/dose
	Mirtazapine	30 mg/day	60 mg/day	QHS
	Nefazodone	200–400 mg/day	600 mg/day	BID
	Venlafaxine	150–225 mg/day	375 mg/day	BID
	Venlafaxine XR	75–225 mg/day	375 mg/day	QD

DRUG INTERACTIONS

In addition to prior history of response to antidepressant treatment, the selection of an antidepressant agent should take into account potential drug-drug interactions. Of particular concern with regard to drug toxicity are the inhibitory effects of some antidepressants on clozapine metabolism, leading to increased serum levels and risk of seizures. Fluvoxamine (Luvox) can cause large increases in clozapine serum levels and should be avoided. Some other SSRIs and nefazodone may also cause clinically significant increases in clozapine serum levels and should be used carefully in clozapine treated patients. Clozapine serum levels should be monitored after adding one of the above antidepressants to clozapine. Because bupropion itself has an inherent risk of seizures, a pharmacodynamic interaction exists with clozapine. Therefore, the combination of clozapine and bupropion should be avoided.

In order to avoid troublesome drug interactions, Exhibit 13, Antidepressant/Antipsychotic Interactions, should be consulted whenever an antidepressant is added to an antipsychotic or whenever either component of an antidepressant-antipsychotic combination is being changed. **Note:** Venlafaxine (Effexor) increases haloperidol levels, but not by Cytochrome P450 interaction.

EXHIBIT 13
Antidepressant/Antipsychotic Interactions

	Substrate (Drug metabolized by pathway)		
Inhibitor (Inhibits substrate)	**1A2**	**2D6**	**3A3/4**
Bupropion (Wellbutrin)		Phenothiazines (some) Clozapine* Olanzapine*	
Citalopram (Celexa)		Phenothiazines Clozapine* Olanzapine*	
Fluoxetine (Prozac)		**PHENOTHIAZINES** **THIORIDAZINE** Clozapine* Olanzapine*	**Clozapine** **Quetiapine**
Fluvoxamine (Luvox)	**CLOZAPINE** **THIORIDAZINE**** **HALOPERIDOL** **OLANZAPINE** **THIOTHIXENE**		**Clozapine** **Quetiapine**
Nefazodone (Serzone)			**QUETIAPINE** **Clozapine**
Paroxetine (Paxil)		**PHENOTHIAZINES** **THIORIDAZINE** Clozapine* Olanzapine*	
Sertraline (Zoloft)		Phenothiazines Clozapine* Olanzapine*	Clozapine Quetiapine

Regular type = small changes in levels (low probability of clinically significant interaction)
Bold type = moderate changes in levels (moderate probability of clinically significant interaction)
BOLD CAPS = very large changes in levels (high probability of clinically significant interaction)
* = Minor pathway
** Fluvoxamine has been shown to inhibit the metabolism of thioridazine but it is unclear whether the interaction occurs at CYP 1A2 and/or CYP 2C19 (Carrillo et al. 1999).

Risperidone is metabolized through CYP 2D6 to 9-OH-risperidone. Both risperidone and its metabolite are equally potent, however, and the sum of the two remains the same with CYP 2D6 inhibition, usually resulting in no change in clinical effect and no need for reduction of the risperidone dose. There are currently no known inducers of CYP 2D6 (DeVane and Nemeroff 2000).

Quetiapine is a cytochrome P450 3A3/4 substrate and, because of the medication's low bioavailability, clinicians need to be aware of drug interactions that occur through this pathway. It may be necessary to increase the quetiapine dose above 800 mg per day when

quetiapine is used with 3A3/4 inducers such as carbamazepine, phenytoin, phenobarbital, etc.

Ziprasidone is metabolized in the liver, primarily through the aldehyde oxidase enzyme system. These enzymes metabolize approximately two-thirds of ziprasidone and are not known to be significantly inhibited or induced by other medications. Less than one-third of ziprasidone's metabolism is attributable to the cytochrome P450 enzyme system, therefore there should be few problems with pharmacokinetic interactions with ziprasidone. The package insert warns against combining ziprasidone with medications that significantly prolong the QT interval. The drugs to be avoided are listed in the most current package insert and include mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, quinidine, dofetilide, sotalol, moxifloxacin, and sparfloxacin (not a complete list). The package insert also warns about avoiding the use of ziprasidone in conditions in which there may be QT interval prolongation, such as hypokalemia and hypomagnesiumemia (Weiden et al. 2002). For more information on ziprasidone, see the Management of Side Effects section, page 40.

Smoking is a potent inducer of hepatic isoenzymes, especially 1A2, and may decrease the serum levels of multiple different antipsychotics. This should be considered when patients move from a smoke-free environment to an environment where they may resume smoking.

Information on drug interactions is subject to rapid change, based upon new research findings and clinical experiences. Clinicians are encouraged to consult current references for current drug interactions information. A useful, frequently updated website for this information is maintained by Dr. David Flockhart at Indiana University (*http://medicine.iupui.edu/flockhart*).

SIDE EFFECTS ALGORITHMS

Many of our medication efforts in the treatment of schizophrenia and related disorders are targeted toward counteracting the side effects of antipsychotic therapy. Although medications are recommended below (see Exhibit 2) to treat antipsychotic side effects, using a medication to treat a side effect can result in additional adverse effects. In these cases, consideration should be given to changing stages—particularly if the patient's symptoms of illness are not optimally controlled.

Extrapyramidal Symptoms (EPS)

The anticholinergics remain the treatment of choice for acute dystonias and pseudoparkinsonism but have their own set of bothersome side effects (dry mouth, constipation, mild cognitive impairments, etc.). Doses are given in Exhibit 15 below. Intramuscular administration is necessary for prompt relief of emergent symptoms (oculogyric crisis, lingual dystonia, opisthotonus). Failure of the anticholinergic to treat EPS or intolerance of the anticholinergic side effects are both indications for moving to the next stage of the antipsychotic algorithm. The exception would be progression to an FGA from an SGA, since it is likely that EPS will be more problematic. In patients with pseudoparkinsonism, clinicians should also consider reducing the antipsychotic dose or changing stages.

EXHIBIT 14
Anti-EPS Dosing

Anti-EPS	Starting dose	Range (daily dose)
Benztropine (Cogentin)	1 mg BID	2–6 mg
Trihexyphenidyl (Artane)	2 mg BID	4–12 mg

Akathisia

Although akathisia is a form of EPS, it is dealt with separately from the other EPS because it differs in its optimal treatment. The first-line treatment for akathisia is a beta-blocker and, as with pseudoparkinsonism, the clinician should also consider reducing the antipsychotic dose. Though the data on relative frequency of various EPS with SGAs are sparse, a common clinical observation is that one may see akathisia in patients who experience no other EPS. Moreover, these patients may not complain of restlessness, even though they exhibit it (so-called pseudoakathisia). Thus, clinicians should be especially alert to observing restlessness in patients on SGAs. Again, beta-blockers are the first-line treatment. If they fail, or only partially relieve symptoms, benzodiazepines may be a reasonable alternative. Beta-blockers and benzodiazepines can be used in combination for akathisia caused by an SGA, but it is usually preferable to try another SGA rather than having the patient on a three-drug regimen.

In patients taking FGAs who are already on an anticholinergic for EPS, failure of a beta-blocker to relieve akathisia is an indication to change to an SGA rather than trying the alternative of a benzodiazepine for akathisia. This recommendation is based on the premise that the profile of physical and cognitive side effects from the three-drug combination of a FGA, an anticholinergic, and a benzodiazepine will almost certainly be more problematic than the side effects from one of the SGAs.

EXHIBIT 15
Antiakathisia Dosing

Antiakathisia	Starting dose	Range (daily dose)
Propranolol (Inderal)	10 mg QID	20–160 mg

Metoprolol 200–300 mg, nadolol 40–80 mg, pindolol 5 mg, and betaxolol 5–20 mg have all shown efficacy in the treatment of akathisia. (Fleischhacker et al. 1990).

Pulse/blood pressure monitoring may be necessary when using higher doses of beta-blockers.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is frequently undetected in its early stages. Since immediate cessation of the patient's current antipsychotic is the first step and may be all that is needed, early diagnosis is important. Muscular rigidity, change in mental status, hyperthermia, and autonomic instability are the four cardinal symptoms of NMS. Elevated WBC and CPK levels are also frequently seen. Progression of symptoms is a medical emergency requiring supportive medical measures. NMS has been reported with all antipsychotics, so that there is no clear choice for which one to start once the acute episode is resolved. If the patient has been on an FGA, changing to an SGA is reasonable. Re-starting the same antipsychotic is typically not recommended, but there are no studies reporting differential likelihood of NMS across drug classes for such patients. Patients with a history of NMS should be educated about the need to stay well hydrated and avoid strenuous physical activity when outside during hot weather.

Tardive Dyskinesia

It is now generally accepted that the SGAs are less likely to cause tardive dyskinesia (TD) than the FGAs. As mentioned previously, this is one of the reasons why the algorithm does not recommend the older antipsychotics as first-line therapy in the treatment of schizophrenia. Recent studies suggest that changing patients from FGAs to SGAs will lower their risk of developing TD (Tollefson 1997; Jeste 1999).

Clozapine has demonstrated an extremely low (if not absent) risk of TD and is therefore the treatment of choice for the patient with severe TD who needs to be on an antipsychotic. Patients with mild to moderate TD who are still on an FGA should be switched to an SGA because there is some evidence to suggest that the movements may improve when patients are switched to the newer medications.

COMPARING SIDE EFFECTS OF THE DIFFERENT AGENTS

The side effect profiles of the antipsychotics vary from agent to agent. These differences emphasize the importance of using the clinical characteristics of the patient to guide the choice of antipsychotic.

EXHIBIT 16
Comparison of Antipsychotic Adverse Effects

Drug	EPS	TD	Orthostatic hypotension	Prolactin	Sedation	Weight gain	Anti-cholinergic
Clozapine (Clozaril)	+ / –	–	+ + +	+ / –	+ + + +	+ + + +	+ + + +
Risperidone (Risperdal)	+ / + +	+	+	+ + +	+	+ +	+
Olanzapine (Zyprexa)	+	+	+	+ / –	+ +	+ + +	+ +
Quetiapine (Seroquel)	+ / –	+ / –	+ +	+ / –	+ +	+ +	+
Ziprasidone (Geodon)	+	+	+	+	+	+ / –	–
Haloperidol (Haldol)	+ + + +	+ + + +	+	+ + +	+	+	+
Chlorpromazine (Thorazine)	+ + +	+ + +	+ + + +	+ +	+ + + +	+ +	+ + +

– none + mild +/– mild to none ++ moderate +++ moderately severe ++++ severe

In recent years, there has been growing concern about the potential of the newer antipsychotic medications to cause serious medical problems including weight gain, diabetes, hyperlipidemias, cardiac arrhythmias, hyperprolactinemia, and cataracts. Currently, there are no evidence-based guidelines that address which lab tests and/or procedures need to be done to monitor each antipsychotic agent (or how frequently these tests should be performed). The range of expert recommendations is wide. In their marketing, antipsychotic manufacturers tend to emphasize the risks of their competitors' agents, leading to an attitude of wariness and uncertainty on the part of many clinicians. Some mental health agencies have already developed new monitoring guidelines for their clinicians to follow. Until an evidence-based expert consensus on monitoring recommendations is available, clinicians who prescribe in the absence of such guidelines should exercise their own best judgment, recognizing that the costs and inconvenience of increased monitoring must be balanced against the need to ensure patient safety and the wish to avoid liability for harmful side effects.

USE OF PSYCHOTROPIC AGENTS IN PREGNANCY AND LACTATION

Exhibit 17 outlines the effects of medications during various stages of gestation along with descriptions of the potential toxicities of these psychotropic agents.

EXHIBIT 17
Use of Psychotropic Agents in Pregnancy and Lactation

Medication	Trimester 1st	2d	3d	Category*	Summary
Tricyclic antidepressants Desipramine Clomipramine	±	+	+	D C C	Possible association between 1st trimester and limb malformation by some case reports but further studies showed no association. Perinatal syndromes: antidepressant withdrawal with jitteriness and irritability.
Serotonin selective agents	±	+	+	B/C**	Fluoxetine has been the most studied. No higher rates of major congenital malformation in those who took fluoxetine in the 1st trimester than the general population.
Other antidepressants Bupropion	±	+	+	C B	Teratogenicity was not revealed in animals even at much higher doses than that used in humans.
Lithium	ø	+	±	D	Associated with cardiac anomalies when used in 1st trimester. Prematurity associated with use in 2d and 3d trimester. Watch for maternal lithium toxicity after delivery due to volume change—need to decrease dose by half before delivery. Lithium levels may be increased in neonates—risk of "floppy baby" and hypothyroidism
Valproic acid	ø	ø	ø	D	Associated with neural tube defects/1–5% risk of spina bifida
Carbamazepine	±	±	±	D	0.5–1% risk of spina bifida
Other anticonvulsants	±	±	±	C	Gabapentin, lamotrigine, and topiramate were not teratogenic in animal studies but some malformations were observed.
Typical antipsychotics Haloperidol Chlorpromazine Fluphenazine Loxapine Mesoridazine Thioridazine Thiothixene	±	±	±	C	Most common malformations reported include cardiac, genital, skeletal (3.5%). Use of high potency agents is recommended. Avoid low potency agents due to decrease BP and uteroplacental blood flow. Use in 3d trimester associated with neonatal associated extrapyramidal effects such as agitation, tremor, poor sucking, swallowing, primitive reflexes, and hypertonicity/DC drugs 5–10 days prior to delivery to allow fetal drug level to decrease.
Atypical antipsychotics Clozapine	±	±	±	C B	Little information on atypical antipsychotics
Anticholinergics Benztropine Trihexiphenidyl Diphenhydramine	±	± ± +	± ± +	C C B	Main association is suggested cardiovascular effects. Possible association with minor malformations.
Propranolol	±	+	±	C	Has been used to treat pregnancy-induced hypertension and does not appear to be associated with malformations. Neonatal adverse effects have included hyperbilirubinemia, bradycardia, respiratory depression, and low birth weights.
Benzodiazepines	ø	±	±	D	Increased risk of cleft palate in 1st trimester, especially diazepam and alprazolam. 3rd trimester exposure leads to tremors, hypertonicity, failure to feed, cyanosis and apnea. Best avoided but if needed use lorazepam (PRN only).
Buspirone	±	±	±	B	Little information available

*Based on *Drugs in Pregnancy and Lactation*, 5th ed.
ø Use is not recommended
+ May be used (least risk)
± May be used if no other alternative available
**Package insert and *Drugs in Pregnancy and Lactation*, 5th ed., differ.

EXHIBIT 18
FDA Categories

Pregnancy	Category definition
Category A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester and no evidence of a risk in later trimesters. The possibility of fetal harm appears remote.
Category B	Studies in animals have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect that was not confirmed in controlled studies in women in the first trimester.
Category C	Studies in animals have revealed adverse effects on the fetus and there are no controlled studies in women or studies in animals and women are not available. Drugs should be given only if the benefit justifies the potential risk to the fetus.
Category D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk.
Category X	Studies in animal or women have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

ANTIPSYCHOTIC AGENTS IN PREGNANCY

- A number of studies have shown no increase in malformations after first trimester exposure to first generation antipsychotic drugs.
- Two studies found an increase in nonspecific congenital anomalies after exposure to phenothiazines during early pregnancy.
- Available data show no effect of in utero FGA exposure on IQ in humans.
- A mild, transient neonatal withdrawal syndrome of hypertonia, tremor, and poor motor maturity can result after antipsychotic use in late pregnancy.
- Withdrawal dyskinesia, which may include irritability, abnormal hand and trunk posturing, tongue thrusting, and a shrill cry, is a rare reaction to FGA exposure. These symptoms resolve spontaneously over several months with normal subsequent motor development.
- Anticholinergic side effects can be seen in the fetus, neonate, or the pregnant woman.
- Very little information is available concerning the use of atypical antipsychotics during pregnancy.
- Atypical antipsychotics that are prolactin-sparing make implementation of effective contraceptive counseling for seriously ill patients more urgent.
- Glucose intolerance is a problem in pregnancy and the risk may increase with the use of antipsychotics; especially olanzapine and clozapine.
- There are increased risks in pregnancy with the use of clozapine: glucose intolerance in the mother and possible fetal macrosomia, increased anticholingeric type side

effects (constipation) in the mother, increased fatigue and sedation, hypotensive risk in the mother, and neonatal risk for agranulocyctosis.

Guidelines for Using Antipsychotic Agents During Pregnancy

- Agents of choice are haloperidol and trifluoperazine, due to being relatively well studied and having the fewest pregnancy-associated side effects. Atypicals are a possibility, but there are limited data.
- Avoid use during first trimester if possible.
- Use only when benefit clearly outweighs the risk.
- For withdrawal dyskinesias in the newborn, diphenhydramine elixir can alleviate symptoms.
- It is recommended that pregnant women on antipsychotics be given calcium supplementation, which has been shown to reduce EPS, but no other prophylaxis for EPS is indicated.
- Avoid long-acting (depot) preparations of the high-potency group in order to limit the duration of any possible toxic effect in the neonate.

Strategies for Switching Antipsychotics

Even though switching patients between antipsychotics is an extremely common event, there are only a few systematic studies of the process. Comparisons of abrupt versus cross-tapered switching from other antipsychotics to ziprasidone or to aripiprazole found no differences in outcome, regardless of approach (b). Yet, most clinicians favor a crossover strategy that extends over weeks to months, citing instances from their personal experiences of gross decompensations, apparently triggered by too sudden switches. Thus, clinical consensus seems at variance with the modest amount of available evidence. One reason for this discrepancy may be that the switch studies were carried out under controlled conditions, with frequent clinic visits, in contrast to most naturalistic situations.

Some literature-based observations provide helpful guidance to circumstances that favor cross-titration and gradual tapering. Factors considered to favor a more gradual approach include clinical instability, stable response to clozapine, and high doses of "old" agent (b). Abrupt discontinuation of antipsychotics can be associated with withdrawal symptoms such as nausea, sweating and muscle aches, increased motor symptoms, and relapse of psychotic symptoms (b). In switching from a regimen in which anticholinergic treatment was required to an antipsychotic less likely to produce EPS, extending the anticholinergic for at least a few days beyond the last dose of the discontinued antipsychotic is recommended (b). It has been suggested that substitution of agents with overlapping neuropharmacological profiles (e.g., similar relative potency in $5HT_2$ blockade) may lessen withdrawal type symptoms in the switching process (c).

As a practical matter, many antipsychotics can produce distressing side effects if initiated in full therapeutic doses and should be titrated up at rates determined by the urgency of the clinical circumstances and by their tolerability to the patient. Under these conditions, if the patient is at all responsive to the medication that is being discontinued, it makes sense to taper the old medication in such a way as to try to keep the total dose of antipsychotic in the therapeutic range.

A final consideration in switching is the likelihood that the patient will be able to follow a set of complex directions. Given the substantial body of data showing high rates of poor adherence to medication regimens in most chronic illnesses, it seems likely that complicated switching strategies will often not be done as recommended, unless the treatment team provides explicit directions and aids. Thus, written instructions that detail each day's medications during the crossover are useful. For some patients, compartmented medication containers labeled by day of the week can be filled in the office/clinic with the doses of each medication that are to be taken each day.

MEDICATION DISCONTINUATION

A trial period off antipsychotics may be reasonable for some patients early in the course of illness. This, an individualized decision, depends on a number of factors that do not lend themselves to an algorithmic approach. Although research shows increased relapse rates among patients in discontinuation studies, only minimal guidance is provided regarding this treatment decision in patients who responded well to antipsychotics early

in the course of their illness and have maintained a complete remission for a prolonged time period (e.g., more than two years) (c). Thus, the schizophrenia algorithm contains no guidelines for antipsychotic medication discontinuation, which is anticipated to be a rare event in the typical mental health clinic patient population.

MEDICATION MAINTENANCE

The evidence overwhelmingly favors the conclusion that, for most patients, maintenance antipsychotic medication is a key aspect of successful treatment, in preference to discontinuation or intermittent treatment (a). Less clear is what the maintenance dose of antipsychotic medication should be for any individual patient. A common clinical aphorism is that the maintenance dose should be the lowest that will keep the patient relatively symptom free. However, very low doses of maintenance medication are clearly less effective for a proportion of patients than doses in the usual range. Moreover, schizophrenia is an illness of natural exacerbations and remissions. Doses that are just sufficient during periods when the illness is quiescent are likely to be inadequate during periods when an exacerbation threatens. That is to say, the optimal maintenance dose is likely to be somewhat higher than the dose that prevents symptoms under the best of circumstances. On the other hand, too high a maintenance dose elevates side effect risks without therapeutic gain.

TOOLS FOR ALGORITHM IMPLEMENTATION AND ADHERENCE

Patient Algorithm

An individual patient's medication history obtained from patient interview and chart review can be recorded on the personal algorithm form (see Appendix B), and, when kept up-to-date, will provide a quick reference for determining a patient's placement in the algorithm. The most recent start date in an algorithm box should correspond to the current medication. In addition, progress may be numerically tracked with the highest number written in the box indicating the current stage, but it is still recommended that start dates be included to assist in determining length of previous medication trials.

For patients who have had trials of second generation antipsychotics prior to enrollment in the algorithm, "PTE" (prior to enrollment) can be written in the appropriate box accompanied by the date, if known.

Modifications for Inpatient Use

The algorithm recommends that clinicians see patients every week when a new medication is started, approximately every three weeks while the patient is adjusting to the medication, and no less often than every three months once the patient is stable. These recommendations are more applicable to the outpatient than the inpatient setting where, in some facilities, clinicians see their patients every day. **As a general rule, in-patient physicians should fill out a clinical record form for each patient on a weekly basis.** The authors recognize that, compared to outpatients, acutely ill inpatients may require higher antipsychotic doses. After the patient's condition has stabilized, the clinician should attempt to lower the antipsychotic dose (see Medication Maintenance section on page 46). In-patients may also require more adjunctive medications than their outpatient counterparts. Algorithm staging, however, should be based on the maintenance antipsychotic. For example, if a first break patient is taking olanzapine but receiving injections of haloperidol PRN, he or she would be in Stage 1 of the algorithm based on the olanzapine prescription, as long as the use of the adjunct does not exceed a 3–4 week period.

Admission to a psychiatric unit is almost always due to acute circumstances such as imminent danger to self or others, grave disablement, and/or a marked exacerbation of symptoms. The necessity of an inpatient admission signals that a change in treatment should be considered and each admission should trigger a thorough evaluation of algorithm staging. Rarely, a patient is admitted for his or her "first break," and these patients will be started in Stage 1. Far more often, the patient has an extensive medication history and the admitting clinician assumes that the current medication is not working and advances the patient to the next stage of the algorithm. Before changing a stage, however, the clinician should evaluate the following four factors:

1. Has the patient been taking the medication? Nonadherence is a major issue in most chronic diseases. Medication does nothing if not taken and, in order to produce maximum benefits, must be taken as directed. Explore this with the patient. Re-starting the current medication may be the best treatment.

2. Is substance abuse a problem? Drug abuse can cause acute and chronic psychiatric symptoms, which often remit (albeit slowly) when the abuse stops. Always evaluate for symptoms of withdrawal and, if present, help the patient through the withdrawal period before staging the patient in the algorithm. Keep in mind that patients may resort to drugs of abuse to alleviate medication side effects, especially neurological ones.

3. Is the patient experiencing symptoms of depression, anxiety, and/or insomnia? Patients with schizophrenia frequently have coexisting symptoms. Refer to the coexisting symptoms algorithms (page 8) before changing the primary antipsychotic.

4. Is the patient dealing with psychosocial stresses like housing problems, family difficulties, and/or employment uncertainties? If so, the treatment team needs to do what it can to help the patient resolve the problem(s) and a change in

medication may not be beneficial. However, a medication change is probably warranted if the clinician determines that increased symptomatology was one of the major causes of the patient's psychosocial problem(s).

COORDINATING TRANSITIONS BETWEEN INPATIENT AND OUTPATIENT SETTINGS

The transition between inpatient and outpatient care is often unsuccessful. Most inpatient clinicians have dealt with the frustration of discharging a patient only to see him or her return to the hospital within a few weeks as a result of not receiving outpatient follow-up and/or not filling prescriptions. Managed care's insistence on brief stays further aggravates the problem by forcing clinicians to discharge patients before they are truly stabilized. By the same token, outpatient clinicians must constantly revise their treatment plans when the originally formulated plan is not followed by the inpatient physician. The following may improve transitions between the two treatment settings:

1. **Document the treatment plan.** It is imperative that all clinicians document the rationale behind treatment decisions and outline the expected treatment plan. Inpatient clinicians may want to start notes to their outpatient colleagues with "transfer" rather than "discharge" (I am 'transferring' the acute care of this patient…) because the former term implies a continuation of care while the latter suggests a disruption. This plan must be sent to the outpatient clinician before the first outpatient visit.

2. **Follow-up.** Ensure that the patient has an outpatient clinic appointment within one week after discharge and that the patient leaves the hospital with enough medication to last until the first follow-up appointment. The discharge planning process requires communication and coordination between the inpatient and outpatient treatment teams. Physicians and other staff working in both arenas should get to know each other and brainstorm about ways to improve coordination between the two settings. A staff member from the outpatient clinic should attend inpatient treatment team meetings and be actively involved in the discharge planning process. Organized quarterly meetings between key inpatient and outpatient staff members can also be useful in identifying and solving problems involved with transition in care issues.

Appendix A:
Administration Manual
*Four-Item Positive Symptom Rating Scale (PSRS),**
and
*Brief Negative Symptom Assessment (BNSA)***

*The four-item PSRS was adapted from the expanded version of the BPRS developed by: J. Ventura, D. Lukoff, K. H. Nuechterlein, R. P. Liberman, M. F. Green, and A. Shaner, Manual for the expanded Brief Psychiatric Rating Scale, *International Journal of Methods Psychiatry Research* 3 (1993): 227–44.

**The Brief Negative Symptom Assessment was adapted from the Negative Symptom Assessment and the Scale for the Assessment of Negative Symptoms developed respectively by: Alphs and Summerfelt, *The Negative Symptom Assessment: A new instrument to assess negative symptoms of schizophrenia*, *Psychopharmacology Bulletin* 25, no. 2 (1989): 159–63; N. Andreason, Modified scale for the assessment of negative symptoms, *NIMH treatment strategies in schizophrenia study*, Public Health Administration, U.S. Department of Health and Human Services, 1984. ADM (9/85): 9–102.

FOUR-ITEM POSITIVE SYMPTOM RATING SCALE

Scale Items and Anchor Points

1. **SUSPICIOUSNESS:** Expressed or apparent belief that other persons have acted maliciously or with discriminatory intent. Include persecution by supernatural or other nonhuman agencies (e.g., the devil). Note: Ratings of "3" or above should also be rated under Unusual Thought Content.

   Do you ever feel uncomfortable in public? Does it seem as though others are watching you?

   Are you concerned about anyone's intentions toward you?

   Is anyone going out of their way to give you a hard time, or trying to hurt you? Do you feel in any danger?

   If patient reports any persecutory ideas/delusions, ask the following:

   How often have you been concerned that [use patient's description]? Have you told anyone about these experiences?

   1—Not Present

   2—Very Mild
   Seems on guard. Reluctant to respond to some "personal" questions. Reports being overly self-conscious in public.

   3—Mild
   Describes incidents in which others have harmed or wanted to harm him/her that sound plausible. Patient feels as if others are watching, laughing, or criticizing him/her in public, but this occurs only occasionally or rarely. Little or no preoccupation.

   4—Moderate
   Says others are talking about him/her maliciously, have negative intentions, or may harm him/her. Beyond the likelihood of plausibility, but not delusional. Incidents of suspected persecution occur occasionally (less than once per week) with some preoccupation.

   5—Moderately Severe
   Same as 4, but incidents occur frequently, such as more than once per week. Patient is moderately preoccupied with ideas of persecution OR patient reports persecutory delusions expressed with much doubt (e.g., partial delusion).

   6—Severe
   Delusional—speaks of Mafia plots, the FBI, or others poisoning his/her food, persecution by supernatural forces.

   7—Extremely Severe
   Same as 6, but the beliefs are bizarre or more preoccupying. Patient tends to disclose or act on persecutory delusions.

2. **UNUSUAL THOUGHT CONTENT:** Unusual, odd, strange or bizarre thought content. Rate the degree of unusualness, not the degree of disorganization of speech. Delusions are patently absurd, clearly false or bizarre ideas that are expressed with full conviction. Consider the patient to have full conviction if he/she has acted as though the delusional belief were true. Ideas of reference/persecution can be differentiated from delusions in that ideas are expressed with much doubt and contain more elements of reality. Include thought insertion, withdrawal and broadcast. Include grandiose, somatic and persecutory delusions even if rated elsewhere. Note: If somatic concern, guilt, suspiciousness, or grandiosity are rated "6" or "7" due to delusions, then unusual thought content must be rated a "4" or above.

   Have you been receiving any special messages from people or from the way things are arranged around you? Have you seen any references to yourself on TV or in the newspapers?

   Can anyone read your mind?

   Do you have a unique relationship with God?

   Is anything like electricity, X-rays, or radio waves affecting you?

   Are thoughts put into your head that are not your own?

   Have you felt that you were under the control of another person or force?

   If patient reports any odd ideas/delusions, ask the following]:

   How often do you think about [use patient's description]?

   Have you told anyone about these experiences? How do you explain the things that have been happening [specify]?

   1—Not Present

   2—Very Mild
   Ideas of reference (people may stare or may laugh at him), ideas of persecution (people may mistreat him). Unusual beliefs in psychic powers, spirits, UFOs, or unrealistic beliefs in one's own abilities. Not strongly held. Some doubt.

   3—Mild
   Same as 2, but degree of reality distortion is more severe as indicated by highly unusual ideas or greater conviction. Content may be typical of delusions (even bizarre), but without full conviction. The delusion does not seem to have fully formed, but is considered as one possible explanation for an unusual experience.

   4—Moderate
   Delusion present but no preoccupation or functional impairment. May be an encapsulated delusion or a firmly endorsed absurd belief about past delusional circumstances.

   5—Moderately Severe
   Full delusion(s) present with some preoccupation OR some areas of functioning disrupted by delusional thinking.

   6—Severe
   Full delusion(s) present with much preoccupation OR many areas of functioning are disrupted by delusional thinking.

   7—Extremely Severe
   Full delusions present with almost total preoccupation OR most areas of functioning are disrupted by delusional thinking.

3. **HALLUCINATIONS:** Reports of perceptual experiences in the absence of relevant external stimuli. When rating degree to which functioning is disrupted by hallucinations, include preoccupation with the content and experience of the hallucinations, as well as functioning disrupted by acting out on the hallucinatory content (e.g., engaging in deviant behavior due to command hallucinations). Include "thoughts aloud" ("gedankenlautwerden") or pseudohallucinations (e.g., hears a voice inside head) if a voice quality is present.

   Do you ever seem to hear your name being called?

   Have you heard any sounds or people talking to you or about you when there has been nobody around? [If hears voices]: What does the voice/voices say? Did it have a voice quality?

   Do you ever have visions or see things that others do not see? What about smell — odors that others do not smell?

   If the patient reports hallucinations, ask the following:

   Have these experiences interfered with your ability to perform your usual activities/work? How do you explain them? How often do they occur?

   1—Not Present

   2—Very Mild
   While resting or going to sleep, sees visions, smells odors, or hears voices, sounds, or whispers in the absence of external stimulation, but no impairment in functioning.

   3—Mild
   While in a clear state of consciousness, hears a voice calling the subject's name, experiences nonverbal auditory hallucinations (e.g., sounds or whispers), formless visual hallucinations, or has sensory experiences in the presence of a modality relevant stimulus (e.g., visual illusions) infrequently (e.g., 1–2 times per week) and with no functional impairment.

   4—Moderate
   Occasional verbal, visual, gustatory, olfactory, or tactile hallucinations with no functional impairment OR nonverbal auditory hallucinations/visual illusions more than infrequently or with impairment.

   5—Moderately Severe
   Experiences daily hallucinations OR some areas of functioning are disrupted by hallucinations.

   6—Severe
   Experiences verbal or visual hallucinations several times a day OR many areas of functioning are disrupted by these hallucinations.

   7—Extremely Severe
   Persistent verbal or visual hallucinations throughout the day OR most areas of functioning are disrupted by these hallucinations.

4. **CONCEPTUAL DISORGANIZATION:** Degree to which speech is confused, disconnected, vague, or disorganized. Rate tangentiality, circumstantiality, sudden topic shifts, incoherence, derailment, blocking, neologisms, and other speech disorders. Do not rate content of speech.

1—Not Present

2—Very Mild
Peculiar use of words or rambling but speech is comprehensible.

3—Mild
Speech a bit hard to understand or make sense of due to tangentiality, circumstantiality, or sudden topic shifts.

4—Moderate
Speech difficult to understand due to tangentiality, circumstantiality, idiosyncratic speech, or topic shifts on many occasions OR 1–2 instances of incoherent phrases.

5—Moderately Severe
Speech difficult to understand due to circumstantiality, tangentiality, neologisms, blocking, or topic shifts most of the time OR 3–5 instances of incoherent phrases.

6—Severe
Speech is incomprehensible due to severe impairments most of the time. Many PSRS items cannot be rated by self-report alone.

7—Extremely Severe
Speech is incomprehensible throughout interview.

Sources of information (check all applicable):

- ☐ Patient
- ☐ Parents/relatives
- ☐ Mental health professionals
- ☐ Chart
- ☐ Difficult to assess due to formal thought disorder

Confidence in assessment:

- ☐ Rate on a scale of 1–5, where 1 = Not confident at all and 5 = Very confident.

Explain here if validity of assessment is questionable:

- ☐ Symptoms possibly drug-induced
- ☐ Underreported due to lack of rapport
- ☐ Underreported due to negative symptoms
- ☐ Patient uncooperative

Other:_____
_____

BRIEF NEGATIVE SYMPTOM ASSESSMENT SCALE

Items adapted from NSA and SANS

1. **PROLONGED TIME TO RESPOND** (a measure of alogia): Observed throughout communication with the patient. After asking the patient a question, he or she pauses for inappropriately long periods before initiating a response. Delay is considered a pause if it feels as though you are waiting for a response or if you consider repeating the question because it appears that the patient has not heard you. He or she may seem "distant" and sometimes the examiner may wonder if the patient has even heard the question. Prompting usually indicates that the patient is aware of the question, but has been having difficulty in developing his/her thoughts in order to make an appropriate reply. Rate severity on the frequency of these pauses.

   1—Normal
   No abnormal pauses before speaking.

   2—Minimal
   Minimal evidence of inappropriate pauses (brief but not abnormally lengthy pauses occur) may be extreme of normal.

   3—Mild
   Occasional noticeable pauses before answering questions. Due to the length of the pause, you feel the need to repeat yourself once or twice during the interview.

   4—Moderate
   Distinct pauses occur frequently (20–40% of responses).

   5—Marked
   Distinct pauses occur most of the time (40–80% of responses).

   6—Severe
   Distinct pauses occur with almost every response (80–100% of responses).

2. **EMOTION: UNCHANGING FACIAL EXPRESSION; BLANK, EXPRESSIONLESS FACE** (a measure of flat affect): The patient's face appears wooden, mechanical, frozen. Facial musculature is generally expressionless and unchanging. The patient does not change expression, or change is less than normally expected, as the emotional content of discourse changes. Because of this, emotions may be difficult to infer. Disregard changes in facial expression due to abnormal involuntary movements, such as tics and tardive dyskinesia. The two dimensions of importance when making this rating are degree of emotional expression and spontaneity.

1—Normal
Spontaneous displays of emotion occur when expected. Normal degree of expressiveness of emotions is present.

2—Minimal
Spontaneous expressions of emotion occur when expected. However, there is a reduction in degree or intensity of the emotions expressed. May be extreme of normal.

3—Mild
Spontaneous expressions of emotion occur infrequently. When emotions are expressed there is a reduction in degree or intensity displayed.

4—Moderate
Obvious reduction in spontaneous expressions. Spontaneous expressions of emotion may occur very rarely during interaction and only when discussing topics of special interest or humor to the subject.

5—Marked
Facial expression is markedly decreased. There are no spontaneous expressions of emotion unless prompted or coaxed by the interviewer.

6—Severe
There are no expressions of emotion even when attempts are made to elicit an emotional response. The subject's face remains blank throughout the interview.

3. **REDUCED SOCIAL DRIVE** (a measure of asociality): This item assesses how much the subject desires to initiate social interactions. Desire may be measured in part by the number of actual or attempted social contacts with others. If the patient has frequent contact with someone (e.g., family member) who initiates the contact, does the patient appear to desire the contact (i.e., would he or she initiate contact if necessary?)? In making this rating, probe the desire to initiate social interactions, number of social interactions, and the ability to enjoy them.

Assessed by asking the patient questions like:

How have you spent your time in the past week?

Do you live alone or with someone else?

Do you like to be around people?

Do you spend much time with others?

Do you have difficulty feeling close to others?

Who are your friends?

How often do you see them?

Did you see them this past week?

Have you called them on the phone?

When you get together, who decides what to do and where to go?

When you spend time with others, do you ask them to do something with you or do you wait until they ask you to do something?

Is anyone concerned about your happiness or well being?

1—Normal
Normal desire to initiate and normal number of contacts. Social contacts are enjoyable.

2—Minimal
Minimal reduction in either the desire to initiate social contacts or the number of social relationships. May initially seem guarded, but has the ability to establish relationships over time. Social relationships are enjoyable.

3—Mild
Reduction in desire to initiate social contacts. The patient has few social relationships and these social contacts are enjoyable.

4—Moderate
Obvious reduction in the desire to initiate social contacts. The patient has few relationships toward which he or she feels indifference. However, a number of social contacts are initiated each week.

5—Marked
Marked reduction in desire to initiate social contacts. The patient has very few relationships toward which he or she feels indifference. The patient does not initiate social contacts but may maintain a few contacts (such as with family).

6—Severe
Patient does not desire social contact. Actively avoids social interactions.

4. **GROOMING AND HYGIENE** (a measure of amotivation): Observed during interaction with the patient. The patient displays less attention to grooming and hygiene than normal. The patient presents with poorly groomed hair, disheveled clothing, etc. Do not rate grooming as poor if it is simply done in what one might consider poor taste (e.g., wild hairdo or excessive makeup). In addition to observation, one must ask the patient about regularity of bathing, brushing teeth, changing clothes, etc. This is particularly important with outpatients, as the patient may present his or her best grooming and hygiene at their clinic visit. Two dimensions to keep in mind when making this rating are current appearance and regularity of grooming behaviors.

Assess the patient by asking questions like:

How many times in the past week have you taken a shower or bath?

How often do you change your clothes?

How often do you shower and brush your teeth?

1—Normal
Patient is clean (e.g., showers every day) and dressed neatly.

2—Minimal
Minimal reduction in grooming and hygiene, may be at the extreme end of the normal range.

3—Mild
Apparently clean but untidy appearance. Clothing may be mismatched. Patient may shower less often than every other day, or may brush teeth less than every day.

4—Moderate
There is an obvious reduction in grooming and hygiene. Clothes may appear unkempt, rumpled, or the patient may look as if he or she just got out of bed. The patient may to without shower or bathing for two days at a time. The patient may go for two days without brushing their teeth.

5—Marked
There is a marked reduction in grooming and hygiene. Clothing may appear dirty, stained or very unkempt. The subject may have greasy hair or a body odor. The patient may go three days at a time without showering or three or four days without brushing their teeth.

6—Severe
Clothing is badly soiled. Patient has a foul odor. Patient may go more than four days in a row without showering or more than four days in a row without brushing his/her teeth. Poor hygiene may present a health risk.

WORKSHEET
for Four-Item Positive Symptom Rating Scale and
Brief Negative Symptom Assessment

Four-Item Positive Symptom Rating Scale

Use each item's anchor points to rate the patient.

1. Suspiciousness	NA	1	2	3	4	5	6	7	
2. Unusual thought content	NA	1	2	3	4	5	6	7	
3. Hallucinations	NA	1	2	3	4	5	6	7	
4. Conceptual disorganization	NA	1	2	3	4	5	6	7	Total: _____

*** NA – not able to be assessed**

Four-Item Negative Symptom Rating Scale

Use each item's anchor points to rate the patient.

1. Prolonged time to respond	1	2	3	4	5	6	
2. Emotion unchanging facial expression blank, expressionless face	1	2	3	4	5	6	
3. Reduced social drive	1	2	3	4	5	6	
4. Poor grooming and hygiene	1	2	3	4	5	6	Total: _____

Sources of information (check all applicable):

- ☐ Patient
- ☐ Parents/relatives
- ☐ Mental health professionals
- ☐ Chart
- ☐ Difficult to assess due to formal thought disorder

Explain here if validity of assessment is questionable:

- ☐ Symptoms possibly drug-induced
- ☐ Underreported due to lack of rapport
- ☐ Underreported due to negative symptoms
- ☐ Patient uncooperative

Confidence in assessment:

- ☐ 1 = Not at all - 5 = Very confident

Other: _____

The Four-item PSRS was adapted from the Expanded Version of the BPRS developed by: J. Ventura, D. Lukoff, K. H. Nuechterlein, R. P. Liberman, M. F. Green, and A. Shaner, Manual for the expanded Brief Psychiatric Rating Scale, *International Journal of Methods Psychiatry Research* 3 (1993): 227–44.
The Brief Negative Symptom Assessment was adapted from the Negative Symptom Assessment and the Scale for the Assessment of Negative Symptoms developed respectively by: Alphs and Summerfelt, *The Negative Symptom Assessment: A new instrument to assess negative symptoms of schizophrenia, Psychopharmacology Bulletin* 25, no. 2 (1989): 159–63; N. Andreason, *Modified scale for the assessment of negative symptoms. NIMH treatment strategies in schizophrenia study,* Public Health Administration, U.S. Department of Health and Human Services, 1984, ADM (9/85): 9–102

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Appendix B:
Personal Algorithm Form

Fill in boxes using all available past and current information about antipsychotic treatments and responses

SCZ Patient Algorithm for: _____ Clinic ID # _____ Entered: _____