



EVIDENCE-BASED BEST PRACTICES FOR THE TREATMENT OF SCHIZOPHRENIA IN SOUTH CAROLINA

Key Messages for Management of Schizophrenia

1. Use an adequate trial of an antipsychotic, consisting of BOTH an adequate medication dosage and duration.
2. Use a rating scale to assess symptom severity before initiating medication; then repeat scale at regular intervals to assess patient response and determine if further dose adjustments are needed.
3. Talk with the patient and family about the importance of medication adherence and collaborate to provide symptom relief and minimize side effects.

BACKGROUND

A mental health panel of 4 psychiatrists and 5 clinical pharmacists from different geographic regions of the state was created to consensually agree on evidence-based best practices for the treatment of schizophrenia in South Carolina. The panel recommended detailed treatment algorithms as the core of their best practices. **The evidenced-based materials and algorithms developed and implemented in the Texas Medication Algorithm Project (TMAP) were the panel's primary source of information.**¹⁻³ Supplemental information included specific recommendations from a review of primary literature and personal opinion from the SCORxE mental health panel members. Modifications were made (with permission) to the TMAP content and algorithms as necessary for the SCORxE project, based on the panel's consensus or vote. This document highlights the major elements of the SCORxE mental health panel's best practices report.

The information contained in this summary is intended to supplement the knowledge of clinicians regarding best practices and drug therapy to treat schizophrenia in non-pregnant individuals ages 18-64. This information is advisory only and is not intended to replace, nor should it be regarded as, a substitute for individualized diagnosis and treatment, based upon sound clinical judgment.

The following symbols, found in parentheses following statements, indicate the level of evidence for the statements, with Level a, Level b and Level c representing the TMAP authors' assessment, and Level d representing recommendations from the SCORxE mental health panel that differ from TMAP or other references:

- (Level a) - Strong empirical trials using randomization and blinding
- (Level b) - Open label trials, cohort studies, and epidemiologic studies
- (Level c) - Few case reports and/or consensus among the TMAP panel
- (Level d) - Consensus among SCORxE mental health panel

SCHIZOPHRENIA TREATMENT AT-A-GLANCE

- Whenever possible, patients should receive an adequate trial of each antipsychotic. An adequate trial of an antipsychotic consists of BOTH an adequate dose and adequate duration.
 - Patients need *at least 4 weeks* of therapeutic doses of an antipsychotic (excluding clozapine) before they can be classified as “non-responders” to the medication. Clozapine requires up to 3 months.
 - Assessing the full effects of an antipsychotic can take 12 weeks or longer.
 - When possible, avoid changing antipsychotics after only a short (1-2 weeks) treatment trial.
 - During acute relapses, multi-week 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.
 - When a patient who has been stable on antipsychotic medication has an acute exacerbation, a change in medication may not be necessary. Often the exacerbation is due to nonadherence (e.g., substance abuse, environment or social stressors).
- At each visit where medications are evaluated, decisions should be based on objective as well as subjective assessments of patient response. Use a rating scale to assess symptom severity before initiating medication; then repeat scale at regular intervals to assess patient response and determine if further dose adjustments are needed.
 - Physicians should assess core symptom severity, other symptoms (e.g., anxiety, mood) and side effects.
 - Patients should provide a global self report of symptoms and side effects.
 - Administer brief positive and negative rating scales.
 - Talk with the patient and family about the importance of medication adherence and collaborate to provide symptom relief and minimize side effects.
- Persistent positive or negative symptoms, unacceptable side effects, or the need for multiple medications to handle antipsychotic side effects indicate that a medication change may be necessary.
 - When possible, avoid changing antipsychotics after only minimal side effects.
 - To reduce the likelihood of relapse, avoid stopping antipsychotic medication after the acute positive psychotic symptoms have been reduced.
 - It is preferable to exhaust reasonable antipsychotic monotherapy before progressing to combination therapy if a patient has failed or refused clozapine (Level c). (see Figure 1)
- The SCORxE mental health panel recommends weekly visits for monitoring of compliance and side effects during an acute episode.
- No algorithm addresses all clinical situations. When a clinician judges that a patient’s treatment should differ from the algorithm’s recommendations, it is valuable to document the rationale in the patient’s chart.
 - Documentation is a critical factor to ensure that patients receive optimal care in the future, as they move throughout the healthcare system. It is common for clinicians to assume they will remember the reasons for medication management decisions, but as caseloads grow it becomes more difficult. Such documentation is also useful for others who may treat the patient.

ANTIPSYCHOTIC ALGORITHM

Description of Stages, Tactics and Critical Decision Points (CDPs)

Each stage of the Antipsychotic Algorithm (Figure 1) represents a trial of a different antipsychotic. The algorithm's strategies are the medication options that clinicians and patients choose from within each stage. While medications are the algorithm's "strategies", specific recommendations concerning medication use (e.g., dose titration, measurement of treatment response, trial duration) are the algorithm's "tactics". In clinical practice, variations from these detailed recommendations may be necessary.

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). The same CDP time intervals are recommended for Stages 1,2,4,5, and 6 (Figure 2). Stage 3 (Figure 3), which addresses the use of clozapine, suggests different CDP time intervals.

At each CDP, clinical rating scales are very valuable to assess the patient's level of response to the antipsychotic. The clinician can then make a therapeutic decision with the help of the results of the clinical rating scales, patient global self report, and ratings of 'other symptoms'. When addressing goals of treatment for an individual patient, clinicians should consider initial response and resolution of symptoms, and even remission.

First Generation Antipsychotics (FGAs) versus Second Generation Antipsychotics (SGAs)

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study I (CUtLASS I) studies have raised critical questions about the relative value of newer versus older antipsychotics for treatment of chronic schizophrenia.⁴⁻⁸ These recent studies failed to show advantages for SGAs over FGAs. All subjects in the CATIE study and most in the CUtLASS study were diagnosed with chronic schizophrenia, questioning whether the results of these studies can be extrapolated to treatment of a first episode schizophrenia; therefore, FGAs are not included in Stage 1 of the treatment algorithm. Based on data from these clinical trials, FGAs have been included in Stage 2 of the algorithm. The risk of tardive dyskinesia (TD) and metabolic side effects should be considered when choosing between FGAs and SGAs.

MEDICATIONS AND DOSING

Medication Maintenance

Maintenance antipsychotic medication is a key aspect of successful treatment. Schizophrenia is an illness of exacerbations and remissions. Doses that are just sufficient during quiescent periods of illness are likely to be inadequate during periods of active illness. The optimal maintenance dose is likely to be somewhat higher than the dose that prevents symptoms under the best of circumstances. A maintenance dose that is too high elevates side effects without therapeutic gain; therefore, each patient requires a balance in dosing according to each individual patient's needs.

Medication Dosing

Tables 1 and 2 summarize the usual initiation and maintenance dosing of FGAs and SGAs to treat schizophrenia.

Decision to Change An Antipsychotic Medication

- Persistent positive symptoms that are more than mild in intensity should lead to a medication change (Level a).
- Patients with persistent negative symptoms should be evaluated for depression and medication side effects as contributing factors (Level a). The clinician may decide if it is better to add a treatment (e.g., antidepressant or anticholinergic) or change to another antipsychotic. To clearly evaluate response, make one change at a time (e.g., change antipsychotic or add an antidepressant) (Level c).
- The threshold for deciding to change antipsychotics due to side effects (e.g., extrapyramidal, metabolic, or intolerable side effects) should be low.
- Some side effects are treatable with adjunctive medication. If this tactic is unsuccessful or inadvisable, move the patient to the next stage of the algorithm.
- Some side effects tend to decrease over time (e.g., sedation, postural hypotension). It is reasonable to allow 4 to 6 weeks for these adaptations to occur if the patient is benefiting from the medication and the side effects are not intolerable or dangerous.
- Patients on multiple medications for side effects are candidates for switching to a different antipsychotic.
- In addition to typical extrapyramidal side effects (EPS), consider other complaints about the medication causing physical or mental changes (e.g., dysphoria or zombie-like feeling) as possible reasons for changing antipsychotics (Level b).
- In the case of patients on clozapine, spend considerable effort helping patients cope with side effects, since it is unlikely that they will do better on a different antipsychotic (Level b).
- The SCORxE mental health panel believes there are no efficacy or safety advantage data that recommend the use of paliperidone over risperidone (Level d).

Techniques to Enhance Medication Adherence

(Adapted from references 9-12)

- Use lowest dosing frequency (once daily or twice daily).
- Minimize side effects - especially akathisia.
- Consider long-acting injections for patients unlikely to adhere to oral medication.
- Control negative symptoms because good control is associated with higher patient adherence.
- Consider trying other overall techniques that improve medication adherence, which have not specifically been demonstrated in schizophrenia (e.g., pillboxes, reminders, and taking medication in association with a life activity such as meals).

Non-Adherence

Medication non-adherence is frequently a result of side effects (Level a). The clinician should consider a trial of another first-line SGA before beginning a depot preparation. If the patient is unlikely to adhere with another oral medication, the basis for this conclusion should be documented and the patient put on a depot antipsychotic. These patients can be switched back to a first-line oral antipsychotic when the likelihood of medication adherence has increased.

EVALUATION OF PATIENT RESPONSE

Symptom Evaluation

Symptoms usually 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). Psychotic symptoms gradually decrease over 2-6 weeks or longer. Residual symptoms may continue to improve for 6-12 weeks. Chronic patients may show slower responses of all symptoms (Level c). Response criteria are assessed using the 4-item Positive Symptom Rating Scale (PSRS). Response is considered a 20% reduction in symptoms from initiation of treatment. Response, partial response, and non-response should be based on both objective (rating scales) and subjective data. When addressing goals of treatment for an individual patient, clinicians should consider initial response and resolution of symptoms and continue to evaluate for residual symptoms.

Negative symptoms are not included in the response criteria; however, this does not imply that negative symptoms are not important and do not need to be measured. Negative and cognitive symptoms have more impact on a patient's functional status than the positive symptoms of schizophrenia.

The brief Patient Global Ratings (Self-Report) of Symptom Severity and Side Effects is a quick tool to record how the patient is feeling and to follow overall trends. These ratings apply to symptoms and side effects the patient has experienced during the previous week, and are rated on a scale of 0 to 10, with 0 indicating none and 10 indicating severe.

Evaluation of Non-Response

Before concluding that a patient is a non-responder to an antipsychotic, it is important to consider causes that would indicate a course of action other than changing to a new antipsychotic, such as:

- Medication non-adherence (if due to side effects - try a different antipsychotic; if not due to side effects - consider a long-acting preparation)
- Incorrect diagnosis (consider SCID* interviews of non-responsive patients)
- Substance abuse (if in doubt, get patient consent and check urine)
- 'Covert' side effects (patient feels 'lousy' on medication but does not have typical side effects – consider trial of a different antipsychotic)
- Psychosocial stressors (ask about changes in home, work, finances, etc.)
- Undiagnosed or uncorrected general medical problem (obtain routine labs – complete blood count (CBC), thyroid function tests, chemistry profile)

*(SCID) Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR)

Evaluation of Side Effects

The side effect profiles (Table 3) 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.

Because there is an association between SGAs and obesity, diabetes, dyslipidemia, and cardiovascular disease (CVD), the SCORxE mental health panel recommends special patient monitoring (Table 4).

Figure 1. ANTIPSYCHOTIC ALGORITHM

Choice of antipsychotic (AP) should be guided by considering the patient's clinical characteristics and the efficacy and side effect profiles of the medication. If patient is inadequately adherent at any stage, the clinician should assess and consider a long-acting antipsychotic preparation, such as risperidone long-acting injection, haloperidol decanoate or fluphenazine decanoate.

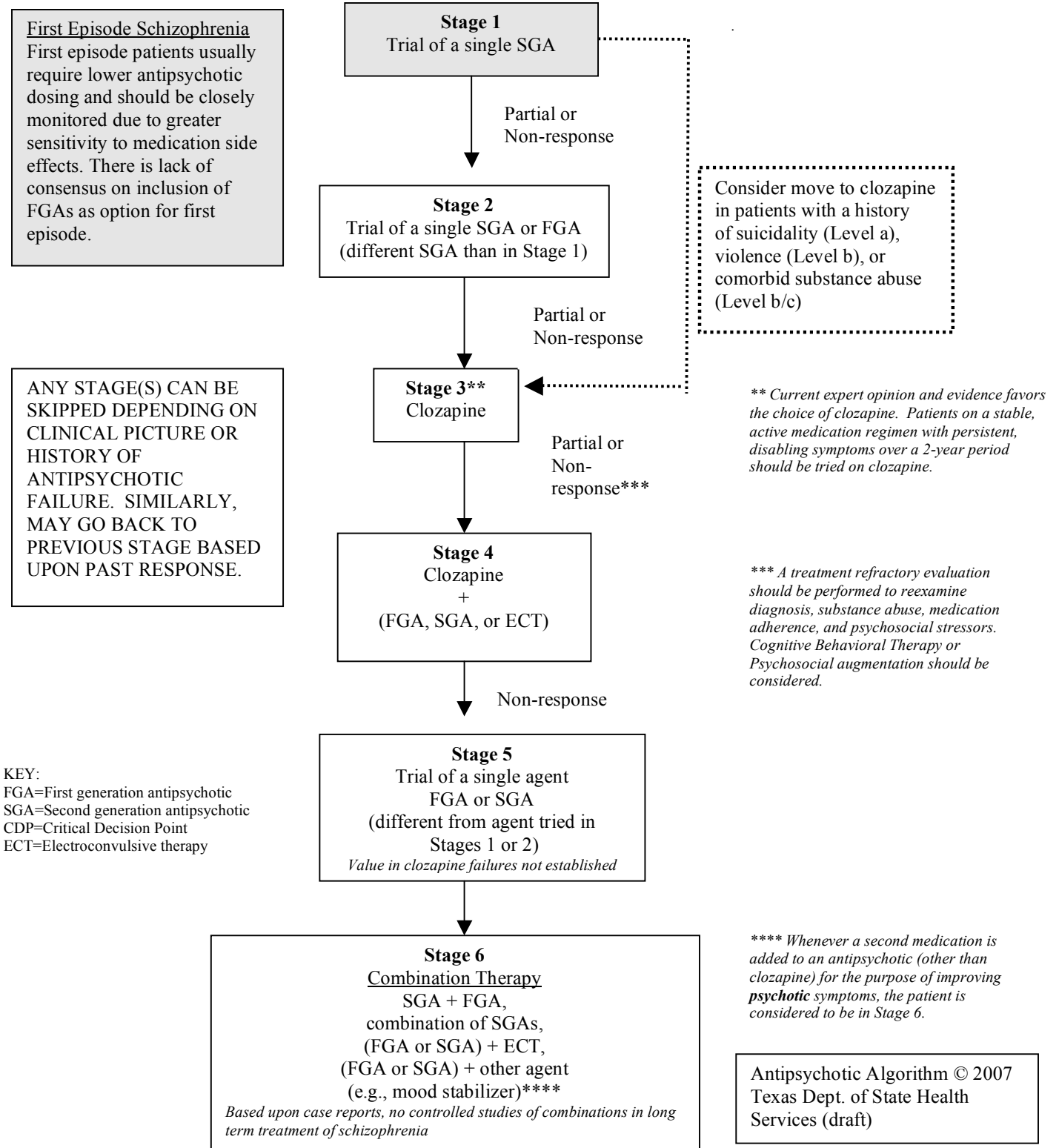


Figure 2. CRITICAL DECISION POINTS (CDPs) FOR STAGES 1, 2, 4, 5, 6 OF ANTIPSYCHOTIC ALGORITHM

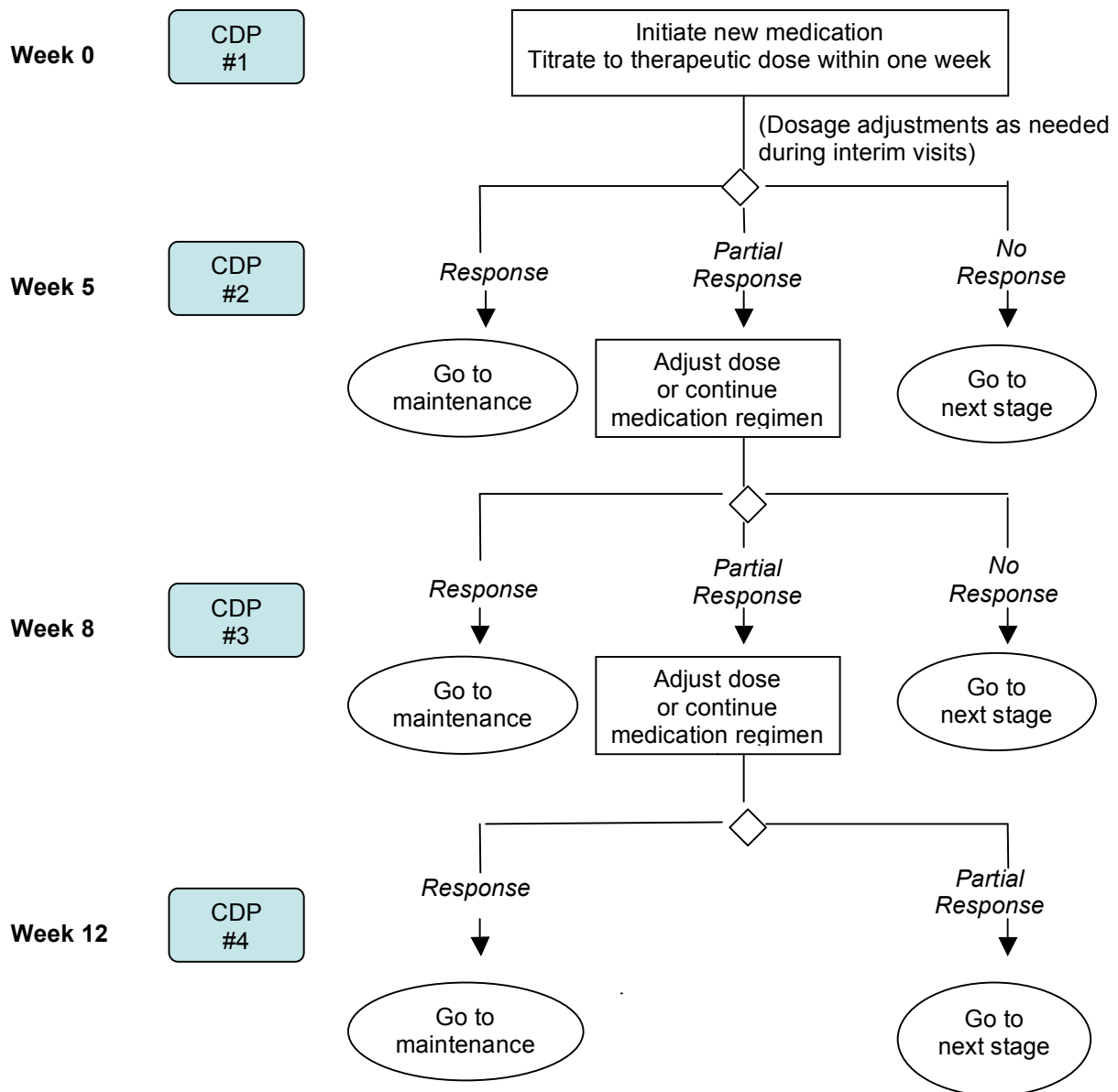
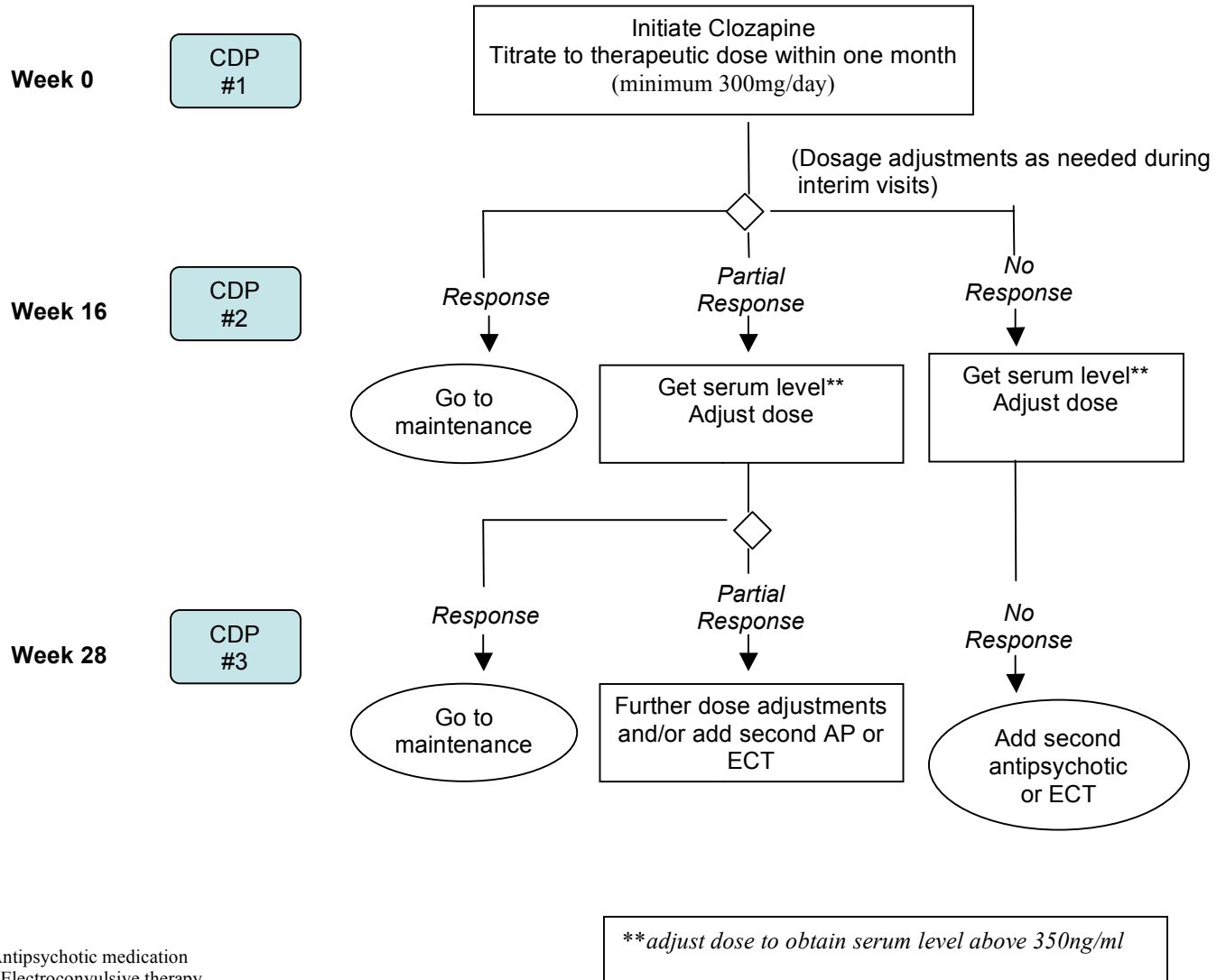


Figure 3. CRITICAL DECISION POINTS (CDPs) FOR STAGE 3* OF ANTIPSYCHOTIC ALGORITHM



* When at a CDP for Stage 3 for patient's taking clozapine, it can be difficult to differentiate between an absolute lack of response versus a partial response. A "non-responder" may be a "partial responder" if a patient's condition deteriorates while clozapine is being tapered and discontinued. The rate of the clozapine taper may cause the re-emergence of psychotic symptoms. Clozapine should be tapered over at least three months. Decreasing the dose too rapidly has been associated with a re-emergence of florid psychosis.

About 50% of patients treated with clozapine do not respond adequately (Level a). 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 is probably the clinician's best option.

Clozapine serum levels should be obtained for the following reasons: (1) partial response or no response with doses of above 300 mg/day (obtain level and adjust dose to achieve serum concentration above 350 ng/ml); (2) non-compliance is suspected; (3) seizure experienced by patient; or (4) dosage above 600 mg/day.

**Figure 4. SCORE SHEET:
4-ITEM POSITIVE SYMPTOM RATING SCALE AND
BRIEF NEGATIVE SYMPTOM ASSESSMENT**

4-Item Positive Symptom Rating Scale

1 = symptom not present, 6/7 = severe/extremely severe, *NA – not able to be assessed

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	SCORE: _____

A response is considered a 20% reduction in symptoms from initiation of treatment. When addressing goals of treatment for an individual patient, clinicians should consider initial response and resolution of symptoms and continue to evaluate for residual symptoms.

The 4-Item PSRS was adapted from the Expanded Version of the BPRS developed by: Ventura J, Lukoff D, Nuechterlein KH, Liberman RP, Green MF, and Shaner, A Manual for the expanded Brief Psychiatric Rating Scale. *International Journal of Methods Psychiatry Research*, 3:227-244, 1993.

4-Item Negative Symptom Rating Scale

1 = symptom not present, 6 = severe

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	SCORE: _____

Source of Information (check all applicable)

- Patient
- Parents/Relatives
- Mental Health Professionals
- Chart

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
- Difficult to assess due to formal thought disorder
- Other _____

Confidence in assessment

___ 1=Not at all - 5=Very confident

The Brief Negative Symptom Assessment was adapted from the Negative Symptom Assessment and the Scale for the Assessment of Negative Symptoms developed respectively by: Alphas and Summerfelt. *The Negative Symptom Assessment: A new instrument to assess negative symptoms of schizophrenia*. Psychopharmacology Bulletin, 1989. 25 (2): p. 159-163 and Andreasen, N. *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): p. 9-102.

Patient Global Self Report

The patient self report is quick tool used to follow overall trends.

Scale 0 to 10 (where 0 = no symptoms/side effects, 5 = moderate symptoms/side effects, 10 = very severe symptoms/side effects)

Symptom severity _____

Side effects _____

Table 1. FIRST GENERATION ANTIPSYCHOTIC (FGA) DOSAGE GUIDELINES

Drug	Starting Dose	Dose Range	Usual Maximum Dose
Chlorpromazine	50-100mg/day	300-1000mg/day	1000mg/day
Fluphenazine	5mg/day	5-20mg/day	20mg/day
Fluphenazine D*	12.5-25mg IM every 2-3 weeks	6.25-50mg IM every 2-4 weeks	100mg IM every 4 weeks
Haloperidol	2-5mg/day	2-20mg/day	20mg/day
Haloperidol D*	25-50mg IM every 2 weeks	50-200mg IM every 2-4 weeks	300mg IM every 3-4 weeks
Loxapine	20mg/day	50-150mg/day	150mg/day
Molindone	20mg/day	50-150mg/day	150mg/day
Perphenazine	4-8mg/day	16-64 mg/day	64mg/day
Thiothixene	5-10mg/day	15-50mg/day	50mg/day
Trifluoperazine	2 mg BID	5-40mg/day	40mg/day

* D = decanoate

Table 2. SECOND GENERATION ANTIPSYCHOTIC (SGA) DOSAGE GUIDELINES

SGA	Starting Dose (I)	Titration	Range	Maximum Dose	Schedule
Aripiprazole	10 mg/day	5-10 mg q 10-14 days	15-30 mg/day	30 mg/day	AM or HS
Clozapine	12.5 mg HS 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 (obtain serum level for doses > 600 mg/day)	900 mg/day	BID Eventual maintenance dose schedule is: BID (1/3in am, 2/3 in pm) Some patients can be maintained on QHS dosing
Olanzapine	5 –10 mg/day	5 mg q 3-7 days	10-20 mg/day	40 mg/day (II)	HS
Paliperidone	3 mg/day	3 mg q day	6-12 mg/day	12mg/day	HS or AM
Quetiapine	100-200 mg/day	50-100 q 2- 3 days	300-800 mg/day	800 mg/day (III)	HS or BID
Risperidone	1-2 mg/day	1-2 mg q 3-7 days	2-6 mg/day	16 mg/day (IV)	HS or AM
Risperidone Long-acting injection	If oral dose ≤ 2 mg, give 25mg IM If oral dose 3-4 mg, give 37.5mg IM If oral dose 5-6 mg, give 50mg IM	25mg q 4 weeks	25-50mg q 2 weeks	50mg q 2 weeks	q 2 weeks
Ziprasidone	80-120 mg/day (V)	40 mg q 2-3 days	80 – 240 mg/day (V) (VI)	240 mg/day (V)(VI)	AM or BID The presence of food can increase ziprasidone's absorption up to two-fold

(I) Starting doses for individual patients may need to be lower. (II) Manufacturer maximum recommended dose is 20mg/day. Some data indicate that olanzapine doses > 20 mg may benefit patients who only partially respond to an adequate trial of olanzapine 20 mg. (references 13,14). (III) Higher doses are used clinically and may provide additional response per the SCORxE mental health panel. (IV) The risk of extrapyramidal side effects is significantly increased by using doses > 6 mg daily. (V) SCORxE mental health panel consensus. (VI) Manufacturer maximum recommended dose is 160mg/day.

Table 3. COMPARISON OF SIDE EFFECTS OF THE DIFFERENT AGENTS

Antipsychotic	EPS	TD	Orthostatic Hypotension	Prolactin	Sedation	Weight Gain	Anti-Cholinergic	Dyslipidemia	Glucose Dysregulation
Chlorpromazine	++	+++	++++	++	++++	++	+++	-	-
Haloperidol	++++	++++	+	+++	+	+	+	-	-
Aripiprazole	+/-	+/-	-	-	+	+/-	+	+/-	+
Clozapine	+/-	-	+++	+/-	++++	++++	++++	++++	+++
Olanzapine	+	+	+	+/-	+++	+++	++	++++	+++
Paliperidone (*)	+/>++	+	+	+++	+	++	+	+	+
Quetiapine	+/-	+/-	++	+/-	++++ (**)	++	+	+	+
Risperidone	+/>++ (***)	+	+	+++	+	++	+	+	+
Ziprasidone	+	+	+	+	+	+/-	+	+/-	-

- = none +/- = mild to none + = mild ++ = moderate +++ = moderately severe ++++ = severe

EPS=Extrapyramidal side effects, TD=Tardive dyskinesia

(*) Paliperidone adverse effects based on available data and risperidone data

(**) During dose titration phase

(***) ++ at doses > 6 mg/day

**Table 4. MONITORING PROTOCOL FOR PATIENTS ON SGAs
(X indicates when to obtain a measure and record it)**

	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually
Personal/Family History	X					X
Weight (BMI)	X	X	X	X	X	
Waist Circumference	X					X
Blood Pressure	X			X		X
Fasting Plasma Glucose	X	X*		X	X*	
Fasting Lipid Profile	X	X*		X		X*

**The SCORxE mental health panel suggests additional monitoring of fasting plasma glucose at 4 weeks and quarterly and fasting lipid profile at 4 weeks and annually. (Level d)*

Adapted from the Consensus Statement endorsed by the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association For The Study of Obesity. **Copyright © 2004 American Diabetes Association, From Diabetes Care®**, Vol. 27, 2004; 596-601. Modified with permission from *The American Diabetes Association*.

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For further information see: <http://www.sccp.sc.edu/SCORxE>

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