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Maintenance Treatment of Schizophrenia

VA Clinician's Guide to the Treatment of Schizophrenia from Initial Antipsychotic Selection to Treatment Resistance

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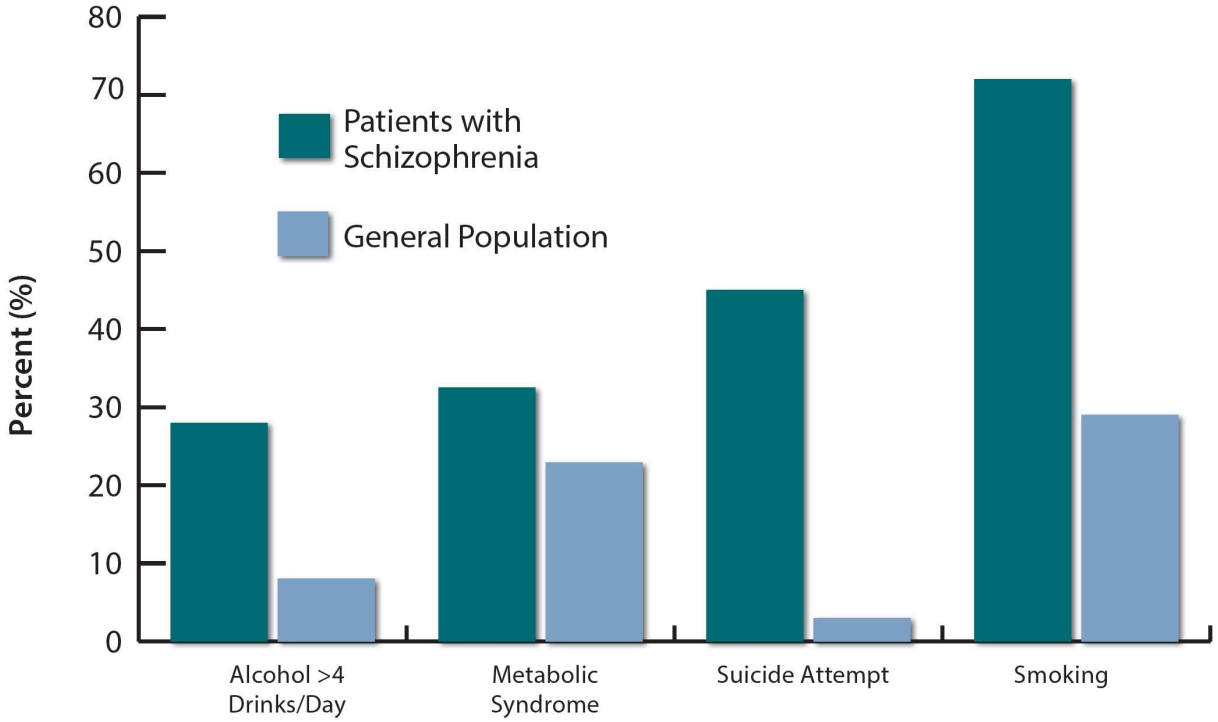
Maintenance Treatment of Schizophrenia

Practical recommendations for the maintenance treatment of schizophrenia from initial antipsychotic selection to treatment resistance.

Schizophrenia is often a lifelong condition that begins in early adulthood and is associated with significant adverse outcomes.

Patients with Schizophrenia vs. General Population[1-5]



Alcohol and smoking data[1], Metabolic syndrome data[2,3], Suicide attempt data[4,5]

Appropriate treatment and monitoring of schizophrenia is essential.

With effective treatment, many patients with schizophrenia can live full and rewarding lives. The ultimate goal is to improve functioning, reduce symptom frequency and exacerbations, and reduce the overall morbidity and mortality from this disorder. This document will provide practical recommendations on the following:

➔ Psychosocial interventions

➔ Initial antipsychotic selection

➔ Treatment resistance and clozapine

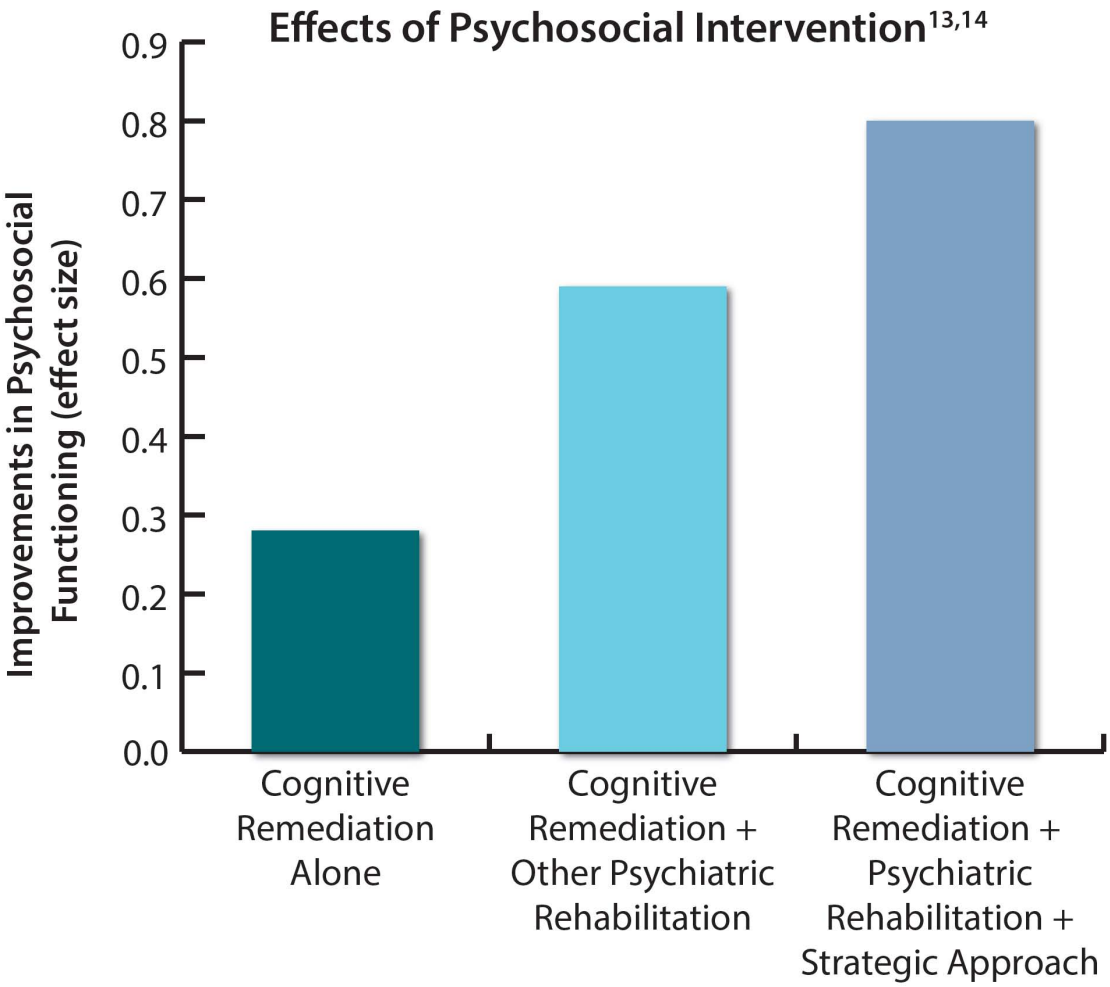
Psychosocial Interventions

Psychosocial interventions should be used in all cases where possible, but may be particularly important for patients with treatment resistant schizophrenia.[6]

Psychosocial Interventions for Patients with Schizophrenia[7,8]	
Intervention	**Description**
Cognitive behavioral therapy (approximately 4–9 months)	Addresses inaccurate or negative thought patterns that underlie emotional responses and maladaptive behavioral patterns. Includes the development of specific cognitive and behavioral strategies to cope with symptoms. Should be offered as adjunct for patients with persistent psychotic symptoms despite adequate pharmacotherapy.
Skills training	Skills needed for everyday activities in order to improve social interactions and independent living. E.g. communication skills: having a casual conversation, making friends, expressing feelings, or obtaining something from another person. Should be offered to patients with schizophrenia who have deficits in skills needed for everyday activities.
Supported employment	Individually tailored job development, searching for a job, the availability of ongoing job supports, and the integration of vocational and mental health services. Should be offered to any person with schizophrenia who has the goal of employment.
Assertive community treatment	Especially helpful for patients who are at risk of repeated hospitalization or have recent homelessness. Key elements include outreach to patients in the community, low patient to staff ratios and high frequency of patient contact. Services should be provided directly by a multi-disciplinary team including a medication prescriber and the caseload should be shared among team members.
Psychosocial interventions for alcohol and substance use disorders	Motivational enhancement and behavioral strategies that focus on engagement in treatment, coping skills training, relapse prevention training, and its delivery in a service model that is integrated with mental health care. Should be offered to patients with schizophrenia and comorbid alcohol or drug use disorders.
Family-based services (approximately 6–9 months)	Beneficial for patients who have regular contact with family members or significant others. Includes illness education, crisis intervention, emotional support, and training in how to cope with illness symptoms and related problems.
Psychosocial interventions for weight management (at least 3 months duration)	For patients who are overweight or obese (BMI ≥25). Psychoeducation focused on nutrition and portion control; behavioral self-management including motivational enhancement; goal setting; regular weigh-ins; self-monitoring of daily food and activity levels; and physical activity modifications.
Token economy interventions	For long-term inpatients or those in the residential care setting. Systems of care based on the principles of operant conditioning and social learning. Utilizes contingent positive reinforcement and the avoidance of punishing consequences for clearly defined target behaviors in order to improve personal hygiene, social interactions and other adaptive behaviors.

Cognitive Deficits and Psychosocial Interventions

Cognitive deficits in schizophrenia are better determinants of outcomes than psychotic symptoms[9] and include impairments in attention, memory, information processing speed, visual learning, verbal learning and reasoning/problem solving.[10] These symptoms often appear before the onset of overt psychosis in the form of subtle difficulties with everyday functioning[11] and become more broad and severe after the onset of schizophrenia.[12]



Combining standard psychiatric care with cognitive remediation and functional skills training targeted to the patient's needs produces the greatest improvements in psychosocial functioning. No particular training program is recommended for patients with schizophrenia; studies are underway in order to obtain FDA approval for standardized cognitive remediation packages for patients with schizophrenia.

Use psychosocial interventions targeted to the specific needs of the patient to augment pharmacotherapy.

Initial Antipsychotic Selection

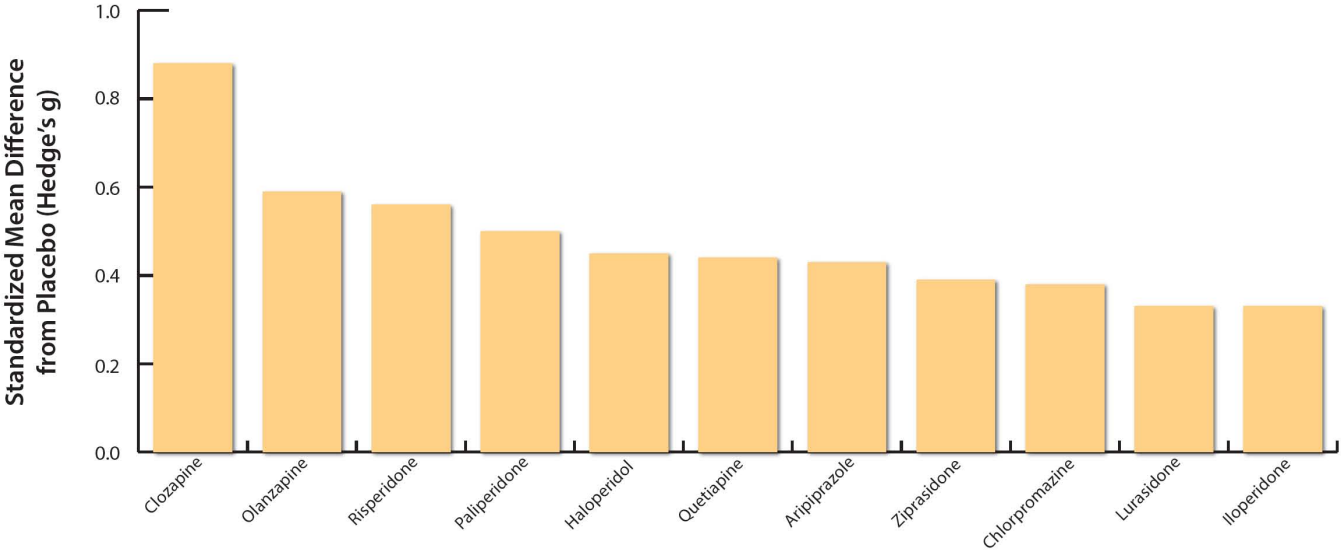
The goal when initially selecting an antipsychotic medication is to achieve maximum effectiveness with minimal side effects.

EFFECTIVENESS:[15,16]

Clozapine has been shown to be significantly more effective than other antipsychotics in treatment resistant schizophrenia.[15] Clozapine may be considered early in treatment for patients with persistent symptoms of hostility or suicidal thoughts and behaviors. However, it is not considered a first line medication for all patients with schizophrenia due to the risk of adverse effects.[7]

There is no consensus in the literature that any non-clozapine antipsychotic is globally superior to another. Therefore, choosing an initial antipsychotic should be guided by side effect profiles in an attempt to reduce adverse outcomes.

Comparison of Antipsychotic Efficacy Relative to Placebo[15]



A recent meta-analysis of 212 studies in 43,049 participants found that all antipsychotic medications studied were superior to placebo and clozapine was significantly more effective than all other antipsychotics. Agents are ranked according to their standardized mean difference (95% credible interval) based on overall change in symptoms of antipsychotic drug vs. placebo.

SAFETY:

While antipsychotics overall have comparable efficacy, there are significant differences in side effect profiles. Antipsychotic selection should take into account individual patient factors in an attempt to minimize risk whenever possible.

Tardive dyskinesia (TD) is a potentially irreversible involuntary movement disorder caused by long-term exposure to antipsychotic medication. Early recognition and withdrawal of the offending agent is vital.

Estimated yearly rate of developing TD:[17]

➔ 5% for first-generation (typical) antipsychotics

➔ 0.74% for second generation (atypical) antipsychotics

Side Effect Profiles of Common Antipsychotic Medications[18–32]								
	Medication	Safety						
		Anti-cholinergic	EPS	QT Prolongation	Sedation	Orthostatic hypotension	Prolactin ⬆	CM side effects
FGA	High potency (haloperidol)	+	++++	++	+	+	+++	+
	Moderate potency (perphenazine)	+	+++	+	+	+	+++	+
	Moderate potency (loxapine)	+	+++	+	++	++	+++	+
	Low potency (chlorpromazine)	+++	+++	++	++++	++++	+++	++
SGA	Asenapine (NF)	+/-	+	+	+	+	+/-	+
	Aripiprazole	+/-	+	+/-	+	+/-	+/-	+
	Brexpiprazole (NF)	+	+	+/-	+	+/-	+/-	++
	Cariprazine (NF)	+/-	+++	+/-	+	+/-	+/-	+
	Clozapine	++++	+/-	+	++++	++++	+/-	++++
	Iloperidone (NF)	+/-	+	++	+	+++	+	++
	Lurasidone (NF)	+/-	++	+/-	+	++	+	+
	Olanzapine	++	++	+	++	++	+/-	++++
	Paliperidone (NF-Oral)	+	++	+	+	++	++++	++
	Quetiapine	+	+/-	++	+++	++	+/-	+++
	Risperidone	+	++	+	+	++	++++	++
	Ziprasidone	+/-	++	++	+	++	+	+/-

CM = Cardiometabolic, EPS = Extrapyramidal Side Effects, FGA = First Generation Antipsychotic, SGA = Second Generation Antipsychotic, +/- = insignificant, + = low, ++ = moderate, +++ = moderately high, ++++ = high. NF = Not currently on VA National Formulary for schizophrenia.

Treatment Resistant Schizophrenia

Treatment resistant schizophrenia (TRS) is defined as suboptimal response to two or more antipsychotic agents at adequate doses for at least 6–8 weeks.[16]

Clozapine is the most effective antipsychotic for TRS.[34–37]

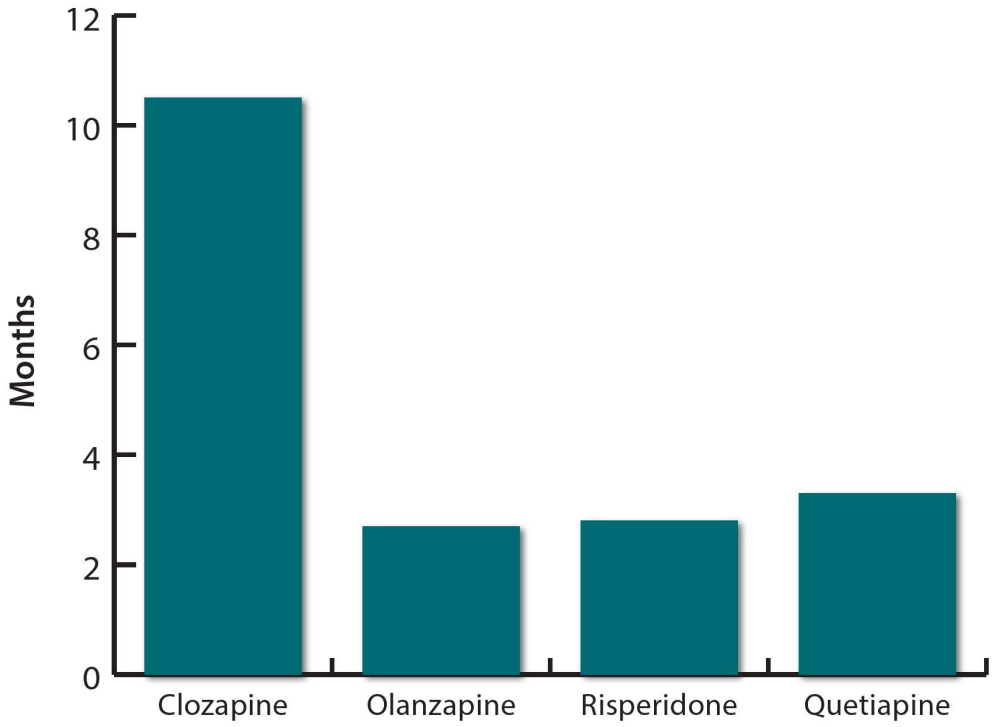
Clozapine has been associated with longer time to discontinuation, greater improvement in symptoms and higher patient subjective ratings than other antipsychotics.[35,36]

Assess for factors that could reduce treatment response.[33]

Examples include:

- ➔ Persistent substance use
- ➔ Incorrect diagnosis
- ➔ Inadequate psychosocial rehabilitation
- ➔ Lack of social support and resources
- ➔ Antipsychotic tolerability issues
- ➔ Poor antipsychotic adherence
- ➔ Drug interactions that decrease antipsychotic levels

CATIE: Median Time to All Cause Treatment Discontinuation[36]



CATIE (US Clinical Antipsychotic Trials of Intervention Effectiveness). Time to discontinuation because of inadequate therapeutic effect was significantly longer for clozapine. Eleven percent of clozapine, 35% of the olanzapine and 43% of both the quetiapine and the risperidone-treated patients discontinued treatment because of lack of efficacy.

Suicidal Behavior and Mortality

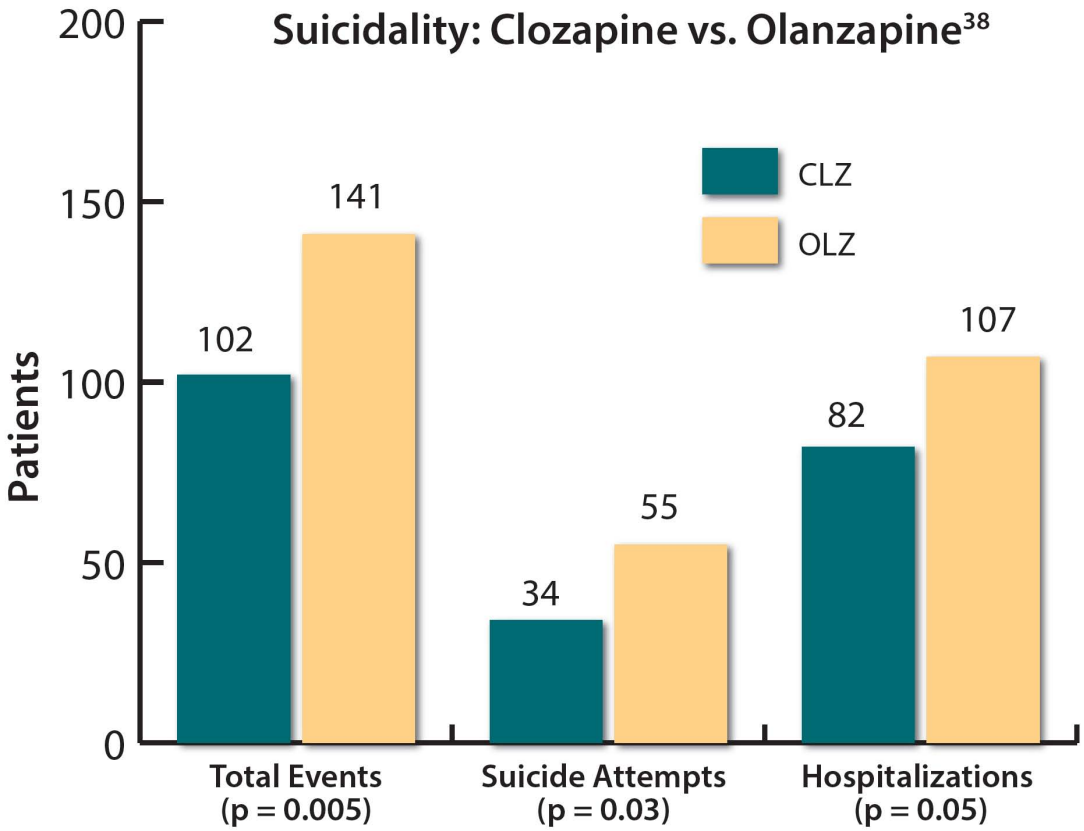
Suicide is a major cause of death among patients with schizophrenia. Suicidal behavior represents a challenge for clinicians and requires appropriate therapy.

➔ Clozapine has been shown to reduce suicidal behavior in patients with schizophrenia[38–42]

➔ Clozapine is associated with a substantially lower mortality compared to other antipsychotic monotherapy and polypharmacy[43–45]

Offer clozapine to your patients who have failed two or more antipsychotics and have no contraindications

Clozapine may also be considered earlier in patients with persistent symptoms of hostility or suicidal thoughts and behaviors.



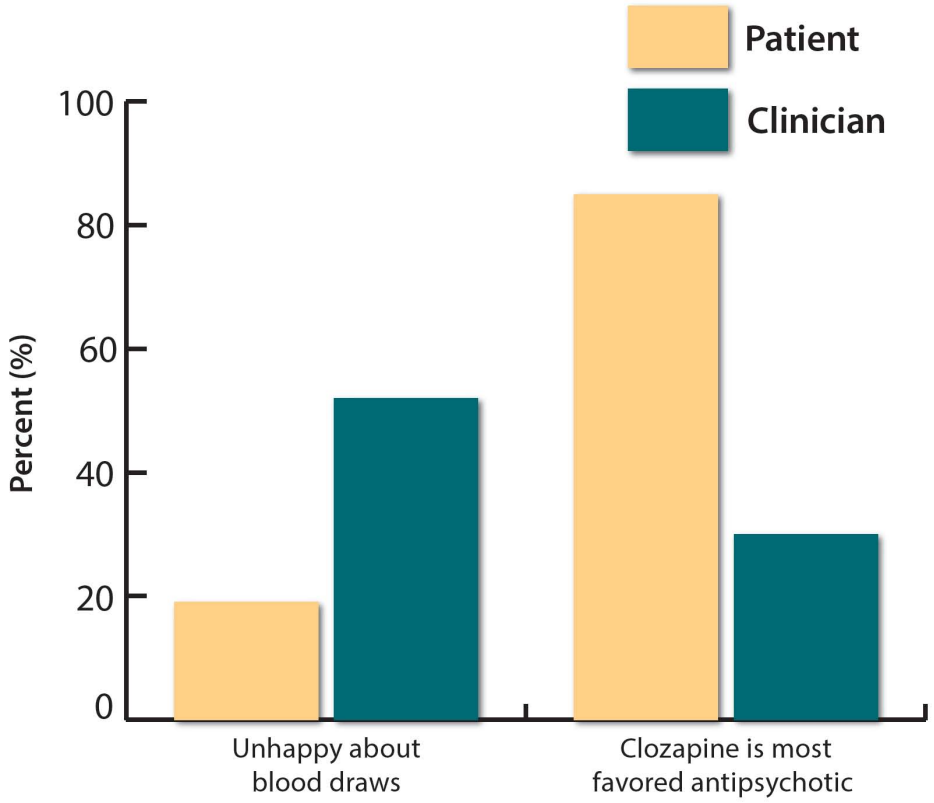
CLZ = clozapine; OLZ = olanzapine. Compared to olanzapine (n = 490), patients treated with clozapine (n = 490) had a 26% reduced risk for suicide attempts or hospitalization to prevent suicide. Total events include total suicide attempts and hospitalizations to prevent suicide.

Potential Barriers to Use of Clozapine

Clozapine remains underutilized despite unsurpassed effectiveness for patients with TRS and established protocols for monitoring side effects. There is evidence to suggest that clinicians may overestimate the impact of side effects and routine blood draws on patients.

Side effects and monitoring requirements are commonly seen as other potential barriers to clozapine use. It is important to monitor for and manage clozapine's side effects.

Clozapine: Views of Patients vs. Clinicians[46]



According to this small study (n = 51), clinicians overestimated how unhappy patients were about routine blood draws. Despite significant side-effects and regular blood tests, patients taking clozapine were more satisfied with clozapine than their clinicians believed they were.

Clozapine Side Effects and Management[18,47–52]			
Side Effect	**Incidence**	**Signs and Symptoms**	**Treatment Options**
Myocarditis	**0.7–1.2%** **Greatest in first month** **Monitoring** for signs and symptoms of myocarditis is important; vitals (every couple days), CRP, and Troponin I/T should be monitored routinely.**	**Unexplained fatigue, dyspnea, fever, tachypnea, chest pain, palpitations, flu like symptoms, electrocardiogram abnormalities, elevated cardiac biomarkers, leukocytosis**	● Discontinue clozapine ● Provide supportive care ● Consult cardiology
Sedation	**44%** **Usually mild and transient in nature**	**Drowsiness/ sedation Dizziness**	**Use minimal dose** **Administer at bedtime** **Avoid other CNS depressants** **Check plasma level**
Sialorrhea	**Varies from 0–80%, with a 31% reported in premarketing tests**	**Increased saliva production** **Inhibition of swallowing reflexes**	**Nonpharmacological** Chewing of sugar-free gum ● Sleep with head propped to avoid choking ● Place towel on pillow **Pharmacological** ● Benztropine 1 mg BID and terazosin 2 mg HS ● Glycopyrrolate 1 mg BID or 2–4 mg HS ● Scopolamine 1.5 mg patch Q 72hrs or 0.3 mg PO HS ● Trihexyphenidyl 5–15 mg HS ● Clonidine patch* (0.1–0.2 mg/day)/ Oral 0.05–1 mg/day ● Botulinum toxin injection 150 units both parotid glands **Anticholinergic medications may add to clozapine anticholinergic side effects.** ***Monitor blood pressure and for worsening mood and psychosis**
Tachycardia	**25%**	**Elevated heart rate (>100 bmp)** **Transient in nature**	**Cardioselective β-blocker** ● Atenolol 25–100 mg/day or metoprolol 25–200 mg BID ● Hold if blood pressure <100/60 or pulse <60 bpm

Clozapine Side Effects and Management[18,47–52]			
Side Effect	**Incidence**	**Signs and Symptoms**	**Treatment Options**
Anticholinergic	14%	Constipation	Increase fluid and fiber intake/exercise Use a stool softener and osmotic or stimulant laxative (e.g. docusate and senna) at first signs of constipation; prolonged stimulant laxative use is not recommended Effective treatment or prevention is essential as death may result
	6%	Dry mouth	Chew sugar-free gum Good oral hygiene to avoid dental carries
Orthostatic Hypotension	9%	With or without syncope Dizziness Transient in nature	Slow titration Advise patient to rise slowly Severe cases consider fludrocortisone
Seizures	1–2%: doses <600 mg/day 5%: doses ≥600 mg/day	Tonic clonic Myoclonic	Discontinue clozapine EEG and neurology consult advised; Rechallenge once seizures under control ● Reinitiate clozapine titration schedule (Do not titrate rapidly) ● Decrease target dose by 50% ● Addition of a anticonvulsant (e.g. depakote, lamotrigine, topiramate) Caution in: Existing seizure disorder; History of head trauma; Drugs that lower seizure threshold
Urinary Incontinence	20% May be underreported	Enuresis (most common); Urinary frequency/urgency or Hesitancy/retention	● Enuresis: Desmopressin 10 mcg per nostril QHS ● Incontinence: Oxbutynin 5 mg BID
Metabolic Syndrome	Not quantified but highly associated	Weight gain; Hyperlipidemia; Elevated plasma glucose	Refer to MIRECC Guidelines : http://vaww.mirecc.va.gov/miamiproject/documents/miami_education_handout.pdf
Severe Neutropenia	0.5–1% (greatest risk 1st 3 months)	Flu-like symptoms	G-CSF can shorten duration

**See clozapine quick reference guide for important guidance on recommended monitoring before and during clozapine administration.

Clozapine Partial Responders

It is estimated that up to 60–70% of patients will have a clinically significant response to clozapine. Despite clozapine's superior efficacy, not all patients will have an adequate response.[53,54]

It's important to check clozapine plasma concentrations:

Response

➔ CLZ plasma concentrations >350–420 ng/mL[55,56]

Relapse

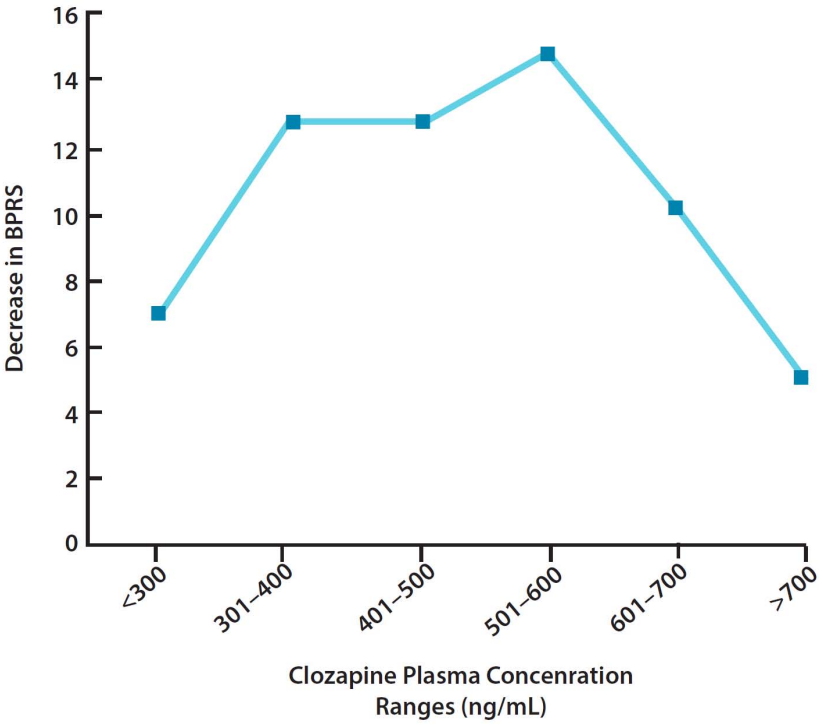
➔ Plasma CLZ below 200 ng/mL[57]

➔ Plasma CLZ reduction of 40-60%[57,58]

CLOZAPINE AUGMENTATION OPTIONS[56, 60–62]

If possible, augmentation should not be tried until after the first 3–6 months of treatment with clozapine to avoid the risk of confusing the effect of the augmenting drug with any late-onset effects of clozapine.[56]

Clozapine Plasma Concentrations and Improvement in BPRS[59]



Sixty one patients with schizophrenia were treated with clozapine 400 mg/day for 6 weeks and assessed with the Brief Psychiatric Rating Scale (BPRS). Clinical improvement was noted at plasma levels >300 ng/mL and diminished at levels >700 ng/mL.

➔ The evidence supporting clozapine augmentation is sparse, often provides conflicting results and improvements, if noted, are minor[56]

➔ Augmentation with lamotrigine, another antipsychotic medication, or an antidepressant for negative symptoms may be beneficial [56,60–62]

Please see 'Clozapine Augmentation Strategies' table for a list of potential clozapine augmenting agents.

Clozapine Augmentation Strategies[60,61,63,64]

Studied Clozapine Augmentation Strategy*	Risks	Benefits	Comments
Antipsychotics			
Risperidone	Cognition worsening ⬆Prolactin ⬆Akathisia	Mixed results ⬇Negative and positive symptoms	• Literature does not support one antipsychotic over another • Benefits of augmentation in meta-analyses have been found to be minimal at most
Ziprasidone	⬆QTc interval	⬇Negative symptoms ⬆Cognitive function	
Aripiprazole	⬆Akathisia	⬇Negative symptoms ⬇Metabolic side effects	
Antidepressants			
Citalopram	QTc monitoring/dose limitations	⬇Negative symptoms	• SSRIs can increase clozapine levels • Mirtazapine and citalopram may be the best antidepressants to improve negative symptoms when combined with clozapine
Fluvoxamine	⬆Clozapine levels	⬆ Global functioning	
Mirtazapine	Weight gain, sedation	⬇Negative symptoms; ⬆Improvement of cognition	
Mood stabilizers/anticonvulsants			
Lamotrigine	Rash, theoretical ⬆risk of severe neutropenia	⬇Negative and positive symptoms	• Meta-analysis found improvements noted with lamotrigine and topiramate diminish when outlier studies were removed • Limited evidence suggests that lithium improves symptoms only for schizoaffective patients • Valproate showed general improvement in a retrospective analysis
Topiramate	Asthenia Sedation	⬇Positive symptoms	
Lithium	Concerns with adverse drug reactions; Neurological symptoms Diabetic ketoacidosis Hypersalivation Orthostatis Weight gain	More effective in schizoaffective patients	
Divalproex sodium	Case reports of over sedation; ⬆risk of neutropenia	⬇ Anxiety ⬇Depressive symptoms	

Table includes studies evaluating treatment of schizophrenia, schizoaffective disorder and psychosis not otherwise specified; Several glutamatergic agents have been studied but are not strongly supported by literature at this time.

Consider augmentation in patients with a partial response to clozapine.

Clozapine Non-responders

If the patient shows no response to clozapine after an adequate trial, reassess for factors that could reduce response (see TRS section above). If no factors are identified, consider discontinuing clozapine and reinstate the best prior antipsychotic and adjunctive therapy.[6]

MULTIPLE ANTIPSYCHOTICS:

Most studies indicate that patients do as well or better on monotherapy vs. multiple antipsychotics.[65–68] However if necessary, a second antipsychotic may be added based on the following clinical rationales.[69] There is a lack of evidence to support use of multiple antipsychotics and the most effective antipsychotic combinations include clozapine.[66]

Rationales to using multiple antipsychotics[69]

- ➔ To manage particular symptoms refractory to antipsychotic monotherapy
- ➔ To avoid high-dose prescribing of an individual antipsychotic that would expose the patient to a higher risk of adverse effects
- ➔ To counteract a particular adverse effect caused by the first antipsychotic—e.g. the addition of aripiprazole has been evaluated to reduce hyperprolactinemia[70]

Use of multiple antipsychotics has been associated with an increased side effect burden[66,71–75]

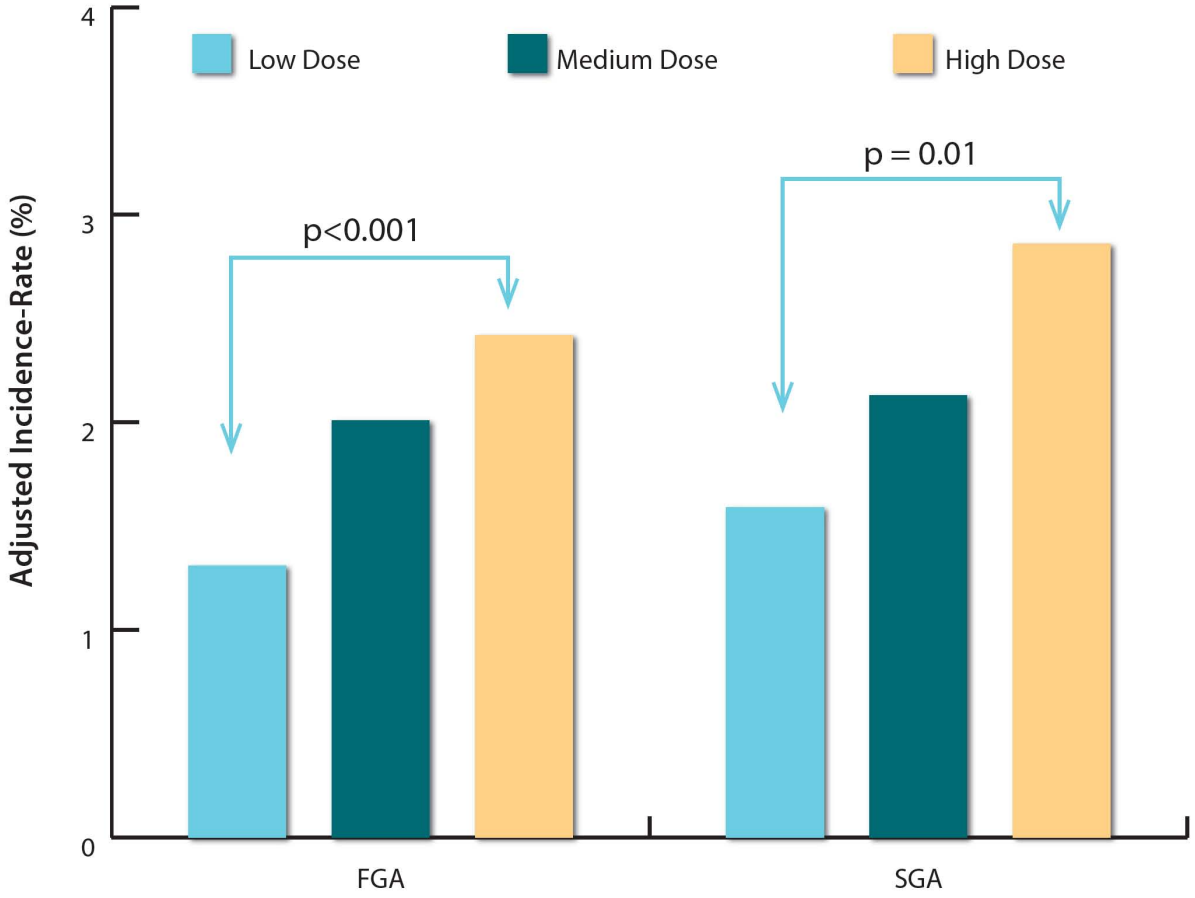
- ➔ Increased sedation, prolactin, glucose, heart rate
- ➔ Decreased working verbal memory
- ➔ Increased risk of meeting criteria for metabolic syndrome in patients on ≥2 antipsychotics, including clozapine, compared with monotherapy (50.0% vs. 34.4%, $p = 0.015$)

Only consider the use of multiple antipsychotics after failure of clozapine, or in patients for whom clozapine is contraindicated.

POTENTIAL CONCERNS WITH EXCEEDING MAXIMUM DOSES[67,72–74,76]

Reviews of dose-response effects of a variety of antipsychotics have revealed no evidence supporting doses above those that are FDA-approved[77,78]

Adjusted Incidence-Rate of Sudden Cardiac Death Among Current Antipsychotic Users[76]



Analysis included 44,218 first generation antipsychotic (FGA) and 46,089 second generation antipsychotic (SGA) subjects and compared them to 186,000 matched schizophrenic controls. Patients on antipsychotic medications had a higher incidence of sudden cardiac death compared to non-users and the risk of cardiac death was found to be dose related for both FGA and SGAs. Low dose: <100 mg chlorpromazine (CPZ); Medium dose: 100–299 mg CPZ; High doses: ≥300 mg CPZ

Risks of exceeding maximum doses include increased mortality, worsened cognition, increased side effects, and increased risk of non-adherence.

Prior to exceeding maximum recommended dose, ensure the following:[79]

- ➔ Adequate time has been allowed for response
- ➔ At least 2 different antipsychotics have been trialed (one SGA)
- ➔ Clozapine non-response, if contraindicated, or not tolerated
- ➔ Adherence is not a concern
- ➔ Adjunctive medications such as antidepressants or mood stabilizers are not indicated
- ➔ Psychological approaches have failed or are not appropriate

High dose antipsychotics have unknown efficacy and risk. Only use high dose antipsychotics when standard treatment options have failed.

Other Treatment Modalities for TRS

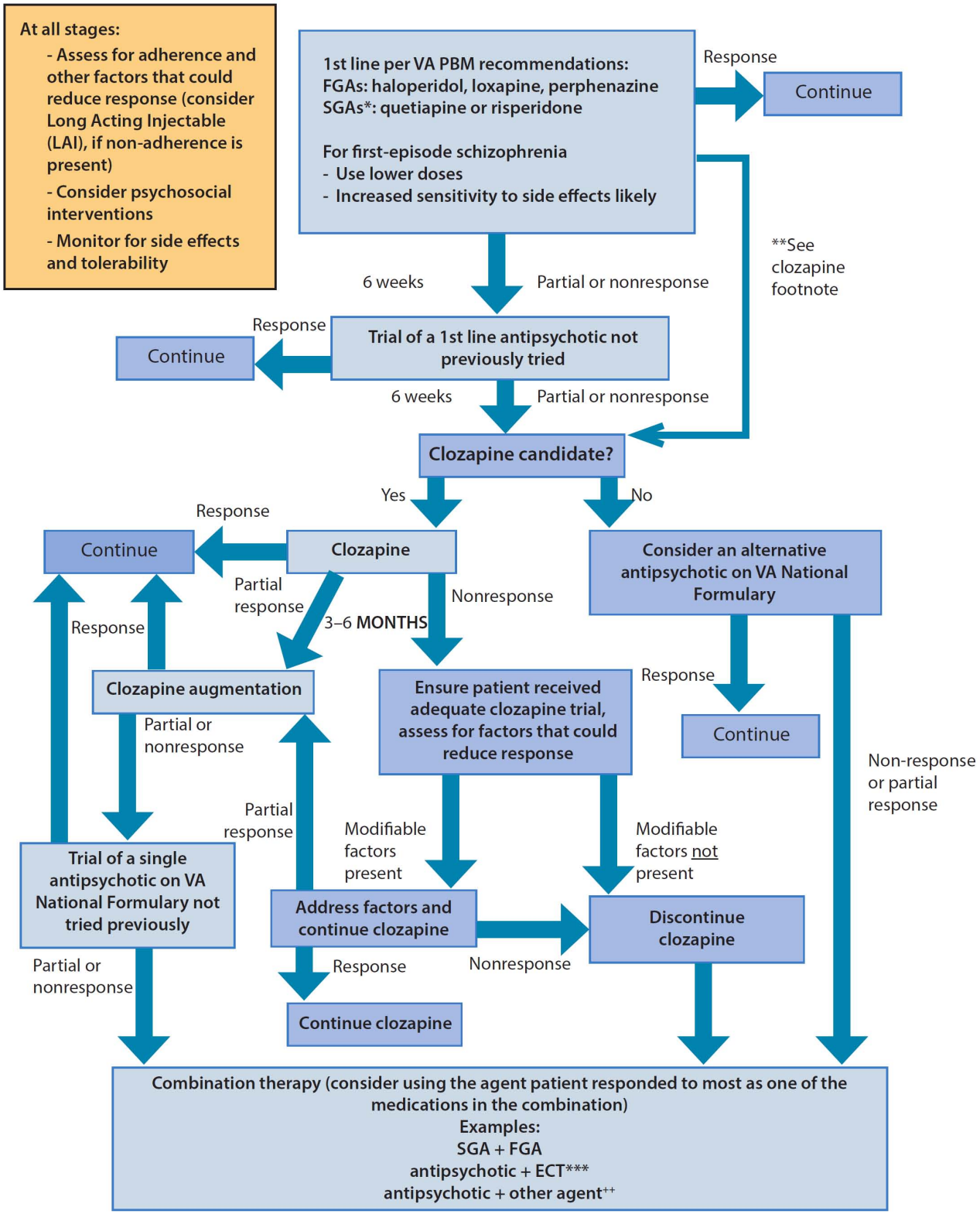
ELECTROCONVULSIVE THERAPY (ECT):

- ➔ A trial of clozapine will generally be indicated before acute treatment with ECT[16]
- ➔ Recommended in combination with antipsychotic medication[80]
- ➔ Recent evidence suggests the combination of clozapine + ECT may be useful in patients with chronic schizophrenia and positive symptoms not adequately responsive to antipsychotic medications, including clozapine[53]
- ➔ ECT should only be continued if rapid global improvement and reduction of acute symptomatology is observed

ECT use in schizophrenia[81]

- ➔ Drug-resistance
- ➔ Catatonia
- ➔ Aggression or suicidal behavior

Treatment of Schizophrenia Algorithm[16,81,82]



*Other SGAs are currently not recommended as an initial treatment option by VA PBM due to side effects and/or cost; **Consider clozapine trial earlier in patients with a history of recurrent suicidality, violence, or comorbid substance abuse; persistence of positive symptoms >2 years warrants and >5 years requires a clozapine trial, independent of number of preceding antipsychotic trials; ***Consider ECT for patients with persistent severe psychosis, catatonia, and/or suicidal ideation or behavior in whom prior treatments including clozapine have failed; ++see clozapine augmentation strategies table on page 11 of this handout.

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Notes

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VA Academic Detailing Service

Real Provider Resources
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This reference guide was created to be used as a tool for VA providers and is available to use from the Academic Detailing SharePoint.

These are general recommendations only; specific clinical decisions should be made by the treating provider based on an individual patient's clinical condition.

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