

Review of the 2020 American Psychiatric Association Schizophrenia Treatment Guidelines

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Schizophrenia is a mental disorder marked by alterations to thought process, perception, and emotion.¹ The exact pathophysiology of the disease is not fully understood but is believed to involve imbalance of one or more neurochemical pathways. Schizophrenia is a lifelong disease typically diagnosed in patients while in their late teens, twenties, and early thirties. The disorder is marked by phases of acute psychosis and remission. Patients can present with positive symptoms such as delusions, hallucinations, and agitation, as well as negative symptoms such as apathy, lack of motivation, and difficulty reading social cues.¹ The goal of treatment is to induce and maintain patients in remission. Nationally, schizophrenia has estimated to affect between one and two million Americans and cost an estimated 23 billion dollars per year to the healthcare system through both direct and indirect costs as of 2008.²

In December of 2019, the American Psychiatric Association (APA) finalized writing the third edition of their treatment guidelines for schizophrenia. These guidelines were made publicly available in September 2020 and utilize the updated Diagnostic and Statistics Manual of Mental Disorders 5th edition (DSM-5) set of criteria for schizophrenia diagnosis.³ The previous edition was released in 2004 and was based off the DSM-4 criteria, making this new set of guidelines as a much needed 16-year update for the treatment of schizophrenia.⁴ The rationale for writing this new edition was to elaborate on an abundance of new literature on both pharmacologic and non-pharmacotherapy-based treatment

modalities as well as discuss a number of new Food and Drug Administration (FDA) approved medications over the past decade and a half.

New to this edition of the guidelines are a series of summary statements. There are 24 numbered statements in total and each fall into one of three categories: 1) assessment and determination of treatment plan, 2) pharmacotherapy, and 3) psychosocial interventions. In addition, each statement is scored by a grading system. Statements can be rated numerically as either one to denote a recommendation or two to denote a suggestion. Statements are also rated alphabetically as A, B, or C to denote the level of evidence behind the statement as strong, moderate, or weak, respectively. The guideline authors consider expert opinion, quantity of relevant literature, and quality of literature when grading these statements. As an example, the recommendation of using an antipsychotic as part of a treatment strategy for schizophrenia is rated 1A, meaning that it is a recommendation that the authors believe is supported by strong evidence. These statements and respective grades serve as an aid to help clinicians in developing treatment plans. Highlights from the pharmacotherapy update (statements four through 14) will be the primary focus of this review.

UPDATED RECOMMENDATIONS

This review will be structured by discussing the ten pharmacotherapy-based statements included within the designated pharmacotherapy category. Primary focus will be directed to areas of change from the previous 2004 guidelines with inclusion of new literature review. A summary of pharmacotherapy changes between editions can be found in **Table 1**.

Statement 4: Antipsychotic Treatment Selection

Level 1A: Recommend patients with schizophrenia be treated with an antipsychotic medication and monitored for effectiveness and side effects.

The idea that patients with schizophrenia should be treated with antipsychotics is not a novel one. This is a recommendation that has not changed. What has changed is which antipsychotic or antipsychotic generation is preferred. Previously, the APA preferred second-generation (also known as atypical) antipsychotics over first-generation antipsychotics. In this newest edition, this is no longer the recommendation. Rather, patients are recommended to be treated with an antipsychotic that will most meet the individual patient needs while minimizing complications with any pre-existing comorbid conditions.³

The two generations of antipsychotics differ primarily in their mechanism of action and side effect profile. First-generation antipsychotics work primarily through dopamine antagonism and therefore are more likely to cause movement disorder-like side effects, such as acute dystonia, parkinsonism, akathisia, or tardive dyskinesia. Second-generation antipsychotics work through antag-

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onism of both dopamine and serotonin and are more likely to cause metabolic based side effects, such as weight gain or hyperglycemia. This difference in side effect profile is what lead the authors of the previous edition to prefer second-generation antipsychotics.^{3,4}

The authors note the relative lack of head-to-head trials as well as a large degree of heterogeneity in clinical trials as a major pitfall in the literature, thus making recommending one antipsychotic over another difficult. The only area of note where head-to-head comparisons have been made is between select second-generation antipsychotics for treatment of initial episodes.⁵ Here they concluded that there was not sufficient evidence of significant advantage of one over another. In an Agency for Healthcare Research and Quality (AHRQ) systematic review by McDonagh et al., the following statistically significant differences in response rate between antipsychotics were seen: olanzapine versus haloperidol (risk ratio (RR): 0.86, 95% confidence interval (CI): 0.78-0.96, favors olanzapine), olanzapine versus quetiapine (odds ratio (OR): 1.71, CI: 1.11-2.68, favors olanzapine), and risperidone versus quetiapine (OR: 1.41, CI: 1.01-2.00, favors risperidone).⁵ Additionally, olanzapine was shown to have a statistically significant advantage over haloperidol in terms of remission rate. All other study comparisons, including haloperidol versus risperidone, haloperidol vs aripiprazole, and haloperidol versus ziprasidone, yielded statistically insignificant results.⁵ The strength of evidence for these findings was considered low by the guideline authors which yielded a 1A recommendation for any patient-specific treat-

ment instead of a specific generation.³

Statements 5 & 6: Continuation of Antipsychotic Medications

Level 1A: Recommend patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with an antipsychotic medication.

Level 2B: Suggest patients with schizophrenia whose symptoms have improved with an antipsychotic medication continue to be treated with the same antipsychotic medication.

Once treatment with an antipsychotic has been deemed successful, the guideline authors recommend that it be continued. This is of course contingent on tolerability of the chosen antipsychotic. However, adjustments in dose may be warranted in some patients. Continued use of antipsychotic medications past the acute phase has shown reduced rates of relapse, hospitalization, and death. Published in 2018, Tiihonen et al. found that risk of death was 2.74 times more likely in those who discontinued antipsychotic therapy as compared to those who continued.⁶ In addition, the risk of rehospitalization was 7.28 times higher in those who discontinued antipsychotic treatment.⁶ The authors suggest dose adjustment may be warranted to reduce side effect burden for continuation of therapy. Of note, the APA does suggest that patients who have responded well to and tolerate antipsychotic medications stay on the same antipsychotic medication used for treatment during the acute phase of disease. These recommenda-

Table 1 | Highlighted Pharmacotherapy Difference Between Editions^{3,4}

Statement ³	Subject Matter	Guidance from Third Edition ³	Guidance from Second Edition ⁴
4	Choice of antipsychotic	No preference for any one antipsychotic or generation of antipsychotic	Consider preferring second generation antipsychotics over first generation antipsychotics
7, 8, 9	Clozapine use	Recommends use for the following indications: High risk of suicide High degree of hostile behavior Treatment resistant schizophrenia Suggests use for the following indication: Severe parkinsonism	Consider use for the following indications: High risk of suicide High degree of hostile behavior Treatment resistant behavior
10	Long-acting injectable antipsychotic use	Suggests use of a long-acting injectable antipsychotic in patients with known or suspected poor adherence	Consider use of a long-acting injectable antipsychotic in patients with poor adherence
11	Management of antipsychotic-induced acute dystonia	Recommends use of anticholinergic or antihistaminic agents for management of acute dystonia	Recommends delay of treatment. Consider use of anticholinergic or antihistaminic agents for management
12	Management of antipsychotic-induced parkinsonism	Suggests lowering the dose of the current antipsychotic, changing to a new antipsychotic, or using an anticholinergic for management of parkinsonism	Recommends lowering the dose of the current antipsychotic followed by changing to a new antipsychotic or using an anticholinergic for management of parkinsonism
13	Management of antipsychotic-induced akathisia	Suggests lowering the dose of the current antipsychotic, changing to a new antipsychotic, using a benzodiazepine, or using a β -blocker for management of akathisia	Consider use of a benzodiazepine or β -blocker for management of akathisia
14	Management of antipsychotic-induced tardive dyskinesia	Recommends using a VMAT2 ^a inhibitor for management of moderate to severe tardive dyskinesia	Recommends lowering the dose of the current antipsychotic or changing to a new antipsychotic

^aVesicular monoamine transporter 2

Table 2 | Currently Available Long-Acting Injectable Medications for Schizophrenia³

Medication	Brand Name	Dosing Interval	Generic Available?	Cost Per Month ^a
Fluphenazine	Prolixin Decanoate [®]	2–4 weeks	Yes	\$7.22—\$231.16
Haloperidol	Haldol Decanoate [®]	4 weeks	Yes	\$37.13—\$262.68
Aripiprazole	Abilify Maintena [®]	4 weeks	No	\$2,847.17
	Aristada [®]	4–8 weeks	No	\$816.36—\$3,315.35
Olanzapine	Zyprexa Relprevv [®]	2–4 weeks	No	n/a ^b
Paliperidone	Invega Sustenna [®]	4 weeks	No	\$1,185.07—\$3,444.65
	Invega Trinza [®]	12 weeks	No	n/a ^b
Risperidone	Risperdal Consta [®]	2 weeks	No	\$1,241.76—\$2,718.94
	Perseris [®]	4 weeks	No	n/a ^b

^aGoodRx, Inc. (October 20, 2021). Pricing Comparisons. www.goodrx.com; ^bNot available

tions remain largely unchanged from the previous edition.

Statements 7, 8, and 9: Clozapine Indications for Use

Level 1B: Recommend that patients with treatment-resistant schizophrenia be treated with clozapine.

Level 1B: Recommend that patients with schizophrenia be treated with clozapine if the risk for suicide attempts or suicide remains substantial despite other treatments.

Level 2C: Suggest that patients with schizophrenia be treated with clozapine if the risk for aggressive behavior remains substantial despite other treatments.

Clozapine is a second-generation antipsychotic developed in 1989, making it one of the oldest second-generation antipsychotics still on the market. As a second-generation antipsychotic, clozapine is believed to work through antagonism of dopaminergic and serotonergic pathways in the brain. Clinicians agree and highlight the value of clozapine in select patients. The new guidelines more strongly recommend that clozapine be used for patients with high suicidality risk, high levels of aggression, treatment-resistant schizophrenia, or antipsychotic-induced parkinsonism resistant to other methods of management.³ The latter is a unique indication to the 3rd edition, based on expert opinion.

Treatment resistant schizophrenia is defined as disease that does not respond to two six-week trials with two different antipsychotics of any generation.⁸ Researchers have found that at least one third of patients with treatment resistant schizophrenia will respond to clozapine.^{9,10} In regard to suicidality, clozapine has been shown in both randomized controlled trials and observational studies to reduce the risk of attempted suicide when compared to other antipsychotics.^{5,11,12} Clozapine has been associated with a 24% decrease (hazard ratio (HR): 0.76, CI: 0.58-0.97) in risk of attempted suicide in high risk patients for over two decades.¹¹ High risk patients were defined as those with a history of attempted suicide, suicidal ideation, or hallucinations for self-harm. A study published in 2013 found similar results, specifically that clozapine significantly reduced risk of suicide over a five year period (OR: 0.29, CI: 0.14-0.63), whereas other antipsychotics produced no change in risk.¹² Lastly, a systematic review by Victoroff

et al. found that clozapine was superior to both first and second-generation antipsychotics including haloperidol, chlorpromazine, and olanzapine, for the treatment of schizophrenia associated with increased aggressive behavior.¹³

Despite some of the known benefits of clozapine, it remains not widely used due to adverse side effects. Weighing the risks and benefits of this medication is key to effective use.

Statement 10: Long-Acting Injectables

Level 2B: Suggest that patients receive treatment with a long-acting injectable antipsychotic medication if they prefer such treatment or if they have a history of poor or uncertain adherence.

Experts suggest that long-acting injectables can be used for patients with known or suspected poor adherence to oral medication therapy. Currently there are two first-generation and seven second-generation antipsychotic products available as long-acting injectables (Table 2). Different products vary in recommended dosing schedules as well as whether oral supplementation is required prior to initiation of the first injectable dose. In a meta-analysis by Kishi et al., long-acting risperidone or paliperidone showed reduced rate of discontinuation due to inefficacy or non-adherence with risk ratios of 0.34 (CI: 0.12-0.92) and 0.3 (CI: 0.11-0.82), respectively, when compared to oral antipsychotic use with haloperidol, aripiprazole, olanzapine, paliperidone, quetiapine, or risperidone.¹⁴ This meta-analysis included a total of five randomized controlled trials with an average duration of 18 months in length. Additional trials also found that long-acting aripiprazole showed lower rates of all-cause discontinuation when compared to oral aripiprazole with a risk ratio of 0.78 (CI: 0.64-0.95).¹⁵

However, these results did not carry over to all other long-acting antipsychotics. Oral olanzapine was found to be superior to long-acting olanzapine for discontinuation due to inefficacy with a risk ratio of 1.52 (CI: 1.12-2.07).¹⁵ Despite somewhat contradictory findings dependent on medication, the recent guideline does

not recommend one long-acting antipsychotic over another, noting that randomized controlled trials may not provide accurate insight into rates of discontinuation due to the increased monitoring frequency.³

Statement 11: Anticholinergic Medications for Acute Dystonia

Level 1C: Recommend that patients who have acute dystonia associated with antipsychotic therapy be treated with an anticholinergic medication.

Acute dystonia is one of many extrapyramidal side effects that can occur with antipsychotics, particularly first-generation antipsychotics. Acute dystonic spasms are prolonged contractions typically seen in the head and neck that occur most frequently at medication initiation and dose adjustment.¹ The authors recommend that intravenous or intramuscular diphenhydramine be used for acute episodes and longer acting benzotropine or trihexyphenidyl for prevention of recurrence.^{16,17} In particular, Arana et al. found that prophylactic use of anticholinergic medications resulted in nearly a two-fold reduction of dystonic episodes with the effect being even greater in patients receiving high-potency antipsychotics. Patients should remain on the anticholinergic for several weeks before discontinuation or decreasing the dose.¹⁸ This practice of prophylactic use of anticholinergics contrasts the previously recommended guidelines suggesting patients should wait out acute dystonia, as it is typically self-limited.

Statement 12: Management of Parkinsonism

Level 2C: Suggest the following options for patients who have parkinsonism associated with anti-psychotic therapy: lowering the dosage of the antipsychotic medication, switching to another antipsychotic medication, or treating with an anticholinergic medication.

Another of the extrapyramidal side effects associated with antipsychotic medication use is antipsychotic-induced parkinsonism. Similar to patients with Parkinson's disease, these patients may develop tremor, muscle rigidity, or slowed movement secondary to medication use.¹ Guideline authors suggest that parkinsonism be managed by either lowering the dose of antipsychotic, switching to a new antipsychotic, or using an anticholinergic. This stands in contrast to the previous recommendations of regimented de-escalation of therapy to negate side effects. Although the authors place no preference for one option over another, they do note that in practice, anticholinergic medications are most often used for patients who are unable to lower their antipsychotic dose or change therapies. As for acute dystonia, benzotropine and trihexyphenidyl are the drugs of choice to manage parkinsonism. Of note the relative lack of high-quality evidence in this area yields a 2C suggestion as this statement is largely based on expert opinion.¹⁹

Statement 12: Management of Akathisia

Level 2C: Suggest the following options for patients who have akathisia associated with antipsychotic therapy: lowering the dosage of the antipsychotic medication, switching to another antipsychotic medication, adding a benzodiazepine medication, or adding a beta-adrenergic blocking agent.

Akathisia is another extrapyramidal side effect defined by a

feeling of restlessness, primary in the lower extremities, that is seen in some patients on antipsychotics.¹ Guidelines currently suggest that for antipsychotic-induced akathisia, clinicians try lowering the dose of medication, switching to a different antipsychotic, or using benzodiazepine or β -blocker adjunctive therapy. In a systematic review conducted by Lima et al., short term benzodiazepine use was found to be highly effective for reduction of acute akathisia with a risk ratio of 0.09 (CI: 0.01-0.6).²⁰ Unfortunately, this review is severely limited by a small sample size of 27 patients across two randomized controlled trials. Lima et al. conducted a similar review with β -blockers but found inconclusive data, lending the statement a 2C suggestion.²¹ As this statement largely holds on expert opinion, continued research into use of benzodiazepines and beta blockers should be considered prior to initiation.

Statement 14: VMAT2 Inhibitor for Tardive Dyskinesia

Level 1B: Recommend that patients who have moderate to severe or disabling tardive dyskinesia associated with antipsychotic therapy be treated with a reversible inhibitor of the vesicular monoamine transporter 2 (VMAT2).

Tardive dyskinesia is a serious extrapyramidal side effect marked by quick involuntary jerking motions, particularly in the head and neck.¹ Treatment for tardive dyskinesia is now recommended with VMAT2 inhibitors. The first VMAT2 inhibitor made its way to market in 2008, and as such, were not addressed in the previous edition of the schizophrenia guidelines. These medications work by inhibiting the release of monoamines, such as serotonin, dopamine, or norepinephrine, from the synapse. While the mechanism of action has been observed, direct correlation into clinical manifestation is still unknown.

To date, there are three VMAT2 inhibitors approved for treatment of tardive dyskinesia associated with antipsychotic medication use. These medications include: tetrabenazine (Xenazine[®]), valbenazine (Ingrezza[®]), and deutetrabenazine (Austedo[®]). With the addition of these medications to market, clinicians now have access to an all-new treatment modality for the management of tardive dyskinesia. Previously, most clinicians relied on lowering the dose of the antipsychotic or switching medications to manage patient concerns. This would lead to complications in overall patient treatment due to side effect mitigation. The current guidelines now recommend VMAT2 inhibitor use to help manage moderate to severe or disabling tardive dyskinesia. In a clinical trial of over 200 patients, deutetrabenazine, the latest of the VMAT2 inhibitors, improved abnormal involuntary movement scores (AIMS) by 2.1 to 3.3 points in patients with tardive dyskinesia.²²

NON-PHARMACOTHERAPY CONSIDERATIONS

Although not the primary focus of this review, it is prudent to briefly mention how the guidelines now approach non-pharmacotherapy-based treatment strategies. The authors of these guidelines emphasize the importance of patient and community or family involvement in developing the treatment plan as well as using evidence based non-pharmacotherapy-based treatment options such as cognitive behavioral therapy. They also recommend that patients who are experiencing their first episode of psychosis be treated as a part of a coordinated specialty care program such as the NAVIGATE program. Coordinated specialty care programs bring in multiple specialties to develop a comprehensive

treatment plan for a patient. They are specifically geared towards patients with first episode psychosis. Patients treated in an evidence-based program have been noted to have lower rates of mortality, hospitalization, and relapse and higher ratings of quality of life and school or work involvement.^{5,23} A full list of psychosocial statements can be found in **Table 3**.

CONCLUSION

The American Psychiatric Association updated their treatment guidelines for schizophrenia in late 2020 after a thorough review of evidence to date. This review manuscript targets the key differences between the newly published third edition guideline update and the previous edition.

Overall differences in the guidelines center around methods involved with the choice of antipsychotic for maintenance treatment, redefining indications for clozapine use, defining indications for long acting injectables, as well as the management of select antipsychotic side effects. In conclusion, these guidelines make a clear attempt to streamline recommendations and provide more definitive statements in important areas of schizophrenia treatment with newly available clinical evidence.

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Table 3 | Relevant Psychosocial Statements³

Statement Number	Level of Evidence	Clinician Guidance
15	1B	Recommend that patients with schizophrenia who are experiencing a first episode of psychosis be treated in a coordinated specialty care program.
16		Recommend that patients with schizophrenia be treated with cognitive-behavioral therapy for psychosis (CBTp).
17		Recommend that patients with schizophrenia receive psychoeducation.
18		Recommend that patients with schizophrenia receive supported employment services.
19		Recommend that patients with schizophrenia receive assertive community treatment if there is a history of poor engagement with services leading to frequent relapse or social disruption (e.g. homelessness; legal difficulties, including imprisonment).
20	2B	Suggest that patients with schizophrenia who have ongoing contact with family receive family interventions.
21	2C	Suggest that patients with schizophrenia receive interventions aimed at developing self-management skills and enhancing person-oriented recovery.
22		Suggest that patients with schizophrenia receive cognitive remediation.
23		Suggest that patients with schizophrenia who have a therapeutic goal of enhanced social functioning receive social skills training.
24		Suggest that patients with schizophrenia be treated with supportive psychotherapy.

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Drug Update:
New Indications and Dosage Forms
November 2021

Dyanavel XR® (amphetamine extended-release) Oral Suspension & Tablets

New Dosage Form: Once daily formulation indicated for treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years of age and older.

Eprontia® (topiramate) Oral Solution

New Dosage Form: Indicated as initial monotherapy or adjunctive therapy for partial-onset or primary generalized tonic-clonic seizures or migraine prevention.

Zoloft® (sertraline) Oral Capsules

New Dosage Form: Selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of major depressive disorder or obsessive-compulsive disorder in adults. Now available in 150mg and 200mg once daily capsules. Initial titration still required with lesser strength when initiating therapy.

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