Schizophrenia in adults: Maintenance therapy and side effect management

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INTRODUCTION

Schizophrenia is a psychiatric disorder characterized by symptoms of chronic or recurrent psychosis. It is commonly associated with impairments in social and occupational functioning [1]. It is among the most disabling and economically catastrophic medical disorders, ranked by the World Health Organization as among the top 10 causes of years lost to disability worldwide for both males and females [2].

Antipsychotic medications are the first-line medication treatment for schizophrenia. They have been shown in clinical trials to be effective in treating symptoms and behaviors associated with the disorder. However, antipsychotic medications have significant side effects. Assessment and management of these adverse effects are an important part of treatment. Evidence-based psychosocial interventions in conjunction with pharmacotherapy can help patients achieve recovery.

This topic addresses the pharmacotherapy of schizophrenia in the maintenance phase of treatment and the management of side effects of medication. Epidemiology, pathogenesis, clinical manifestations, and diagnosis are discussed separately. First-generation antipsychotics, second-generation antipsychotics, long-acting injectable antipsychotics, and psychosocial interventions for schizophrenia are discussed separately.

- (See "Schizophrenia in adults: Epidemiology and pathogenesis".)

- (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)
- (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)
- (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)
- (See "Schizophrenia in adults: Psychosocial management".)
- (See "Schizophrenia in adults: Guidelines for prescribing clozapine".)
- (See "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis".)

GENERAL PRINCIPLES

Objectives of treatment — The goal of maintenance treatment of schizophrenia is to minimize symptoms and functional impairments, minimize side effects of pharmacotherapy, avoid relapses, and promote recovery that allows self-determination, full integration into society, and pursuit of personal goals. (See 'Psychosocial treatments' below and "Schizophrenia in adults: Psychosocial management" and 'Medication adjustments' below.)

Multidisciplinary care — We recommend a multidisciplinary approach to maintenance treatment of patients who have recovered from an acute psychotic episode of schizophrenia. Comprehensive programs provide individualized treatment plans including pharmacotherapy, case management, family intervention, and other community outreach services.

Treatment programs offering multidisciplinary interventions have been associated with lower rehospitalization rates, lower core illness symptoms, and improved interpersonal and everyday living skills in patients recovering from a first episode of psychosis [3]. As an example, a clinical trial randomized 34 community mental health centers in 21 states in the United States to offer people with newly diagnosed, nonaffective psychosis either standard care (181 patients) or a program of intensive treatment (computerized, algorithm-assisted medication management; family psychoeducation; resiliency-focused individual psychotherapy; and supported education/employment; 223 patients) [4]. After two years, subjects receiving the intensive intervention had greater improvement in quality of life, more involvement in school/work, and less psychopathology than the subjects in the standard care group. In this study, rates of hospitalization did not differ between groups.

Limited availability of these programs is the main barrier to broad implementation. (See 'Psychosocial treatments' below.)

Patient education — Patient education is the first step in effective maintenance treatment of patients with antipsychotic medication. To promote adherence to medication regimens, we recommend educating all patients treated with antipsychotics about their side effects (eg, extrapyramidal symptoms, tardive dyskinesia, sedation, dry mouth) and the increased risk of recurrence of symptoms due to premature discontinuation of medications.

Patient education is important because some patients may view side effects as a sign that the medication is not working or is worsening their symptoms. Anticipation of side effects may prevent patients from unilaterally discontinuing their medication.

ANTIPSYCHOTIC THERAPY

Initial management of acute psychosis — Initial management of schizophrenia involves the treatment and stabilization of acute psychosis. Selection and dosing of antipsychotic therapy in the acute setting is discussed in detail elsewhere. (See "Psychosis in adults: Initial management", section on 'Initial management'.)

Medication adjustments

Patient-specific considerations

Full response to pharmacologic therapy — If a patient has fully responded (ie, no longer has clinically significant psychosis) to the antipsychotic initiated for an acute psychotic episode, we continue that medication. We use the lowest effective dose. Duration of antipsychotic therapy is discussed elsewhere. (See 'Duration of antipsychotic therapy' below.)

Partial response or recurrence of symptoms — Some patients, despite having symptomatic improvement with antipsychotic treatment, have persistent residual symptoms (eg, incomplete or partial response). Other patients have full response to antipsychotic treatment but have intermittent symptom recurrence. If the symptoms are bothersome to the patient or impair functioning, we consider the treatment response suboptimal.

Our first step in patients with incomplete response or intermittent symptom recurrence is to assess medication adherence (see 'Nonadherence' below). For those with confirmed adherence, next steps depend on whether the antipsychotic dose is within therapeutic range.

- In patients who have been treated with subtherapeutic doses, we increase their dose until either the patient responds, therapeutic range is reached, or side effects limit further increases (table 1). (See 'Side effect management' below and "Psychosis in adults: Initial management", section on 'Administration'.)

- In patients who have incomplete response or recurrent symptoms despite the medication being in the therapeutic range for an adequate time period (ie, six weeks), data informing the optimal approach are very limited [5]. If the symptoms are bothersome to the patient, we generally suggest switching the medication.

  - For individuals who have only tried one or two other standard antipsychotic agents (ie, not clozapine) in the past, we try a different standard antipsychotic. There are no specific agents that are preferred. As with initial selection of antipsychotic therapy, the choice depends on medication side effects, the patient's comorbidities, history of adherence, and patient preferences. Additionally, if the patient has had a good response to a particular agent in the past, that would be a reasonable choice to try again. Selection of antipsychotic therapy and changing medications are discussed in detail elsewhere. (See 'Implementation of medication changes' below and "Psychosis in adults: Initial management", section on 'Selection'.)

  - For individuals who have chronic symptoms that have not fully remitted despite two or more prior medication trials with standard antipsychotic agents and who are bothered by these symptoms or who have functional impairment, we consider them to have treatment-resistant schizophrenia and evaluate them for clozapine eligibility. Management of treatment-resistant patients is discussed in detail elsewhere. (See 'Treatment-resistant schizophrenia' below.)

We generally do not recommend doses above the therapeutic range. Most studies of antipsychotics dosed above the recommended range have found no clear benefit [6]. If used, trials of higher doses should be limited to three months unless there is clear evidence of benefit. (See "Psychosis in adults: Initial management", section on 'Administration'.)

We typically do not add a second antipsychotic agent in patients who have suboptimal response because little empirical evidence supports this practice [7,8]. Although a national cohort study of over 62,000 patients with schizophrenia in Finland suggested that combination antipsychotic therapy was associated with a lower risk of hospitalization compared with monotherapy overall, the only specific oral combination therapy that was clearly associated with better outcomes than its separate components was clozapine plus aripiprazole [8]. Thus, we generally reserve combining antipsychotic agents to patients on clozapine in whom a therapeutic dose cannot be

achieved. This is discussed elsewhere. (See "Evaluation and management of treatment-resistant schizophrenia", section on 'Augmentation with medication'.)

Persistent suicidality — In patients with schizophrenia who have persistent suicidal ideation despite antipsychotic treatment, we suggest a trial of clozapine [9-11]. Clozapine has been shown in a large randomized trial to reduce suicide attempts in patients with schizophrenia and schizoaffective disorder at high risk for suicide [9] and the US Food and Drug Administration approved it for this use. In this study, 980 patients with schizophrenia or schizoaffective disorder (27 percent refractory to previous treatment and high risk due to prior suicide attempts or current suicidal ideation) were randomly assigned to either olanzapine or clozapine treatment [9]. Less suicidal behavior (attempts or completed suicide) occurred in patients treated with clozapine (hazard ratio 0.76, 95% CI 0.58-0.97). Further, in nationwide observational studies of patients with schizophrenia in Finland (n >61,000) and Sweden (n >29,000), clozapine was the only antipsychotic associated with a decreased risk of suicide attempt or completion compared with use of no antipsychotic (hazard ratio 0.64, 95% CI 0.49-0.84 Finnish cohort; hazard ratio 0.66, 95% CI 0.43-0.99 Swedish cohort) [10]. Guidelines for clozapine prescribing, dosing, monitoring, and side effect management are described separately. Management of suicidal patients is described separately. (See "Schizophrenia in adults: Guidelines for prescribing clozapine" and "Suicidal ideation and behavior in adults".)

Treatment-resistant schizophrenia — Patients with schizophrenia who do not benefit adequately from two or more trials of standard antipsychotic medications despite typically therapeutic doses and treatment durations (eg, six weeks) are considered to have treatment-resistant schizophrenia. We usually evaluate these patients for clozapine eligibility. Randomized trials have shown that clozapine has greater efficacy compared with other antipsychotics in treating patients who have responded poorly to prior antipsychotic trials [12-15]. However, due to its potential toxicity, it is reserved for treatment-refractory cases or cases with high risk for suicide. In the United States, clozapine is the only antipsychotic medication approved for this use. The efficacy of interventions for treatment-resistant schizophrenia, including clozapine, is discussed separately. Guidelines for clozapine prescribing, dosing, monitoring, and side effect management are described separately. (See "Evaluation and management of treatment-resistant schizophrenia" and "Schizophrenia in adults: Guidelines for prescribing clozapine".)

Nonadherence — In patients with poor response to medication or repeated relapses, nonadherence should be considered. We recommend asking patients about their medication adherence in a nonjudgmental fashion. In many cases, side effects may be the cause of nonadherence and may need to be addressed. (See 'Side effect management' below.)

We suggest using long-acting injectable (LAI) antipsychotics for patients with schizophrenia when nonadherence is problematic or leads to frequent relapse. LAI antipsychotics are administered at intervals from 2 to 12 weeks. As an example, risperidone LAI can be administered at a starting dose of 25 mg every two weeks up to a maximum of 50 mg every two weeks. Paliperidone 12-week LAI is another option that can be administered at 12-week intervals after the patient has been adequately treated for at least four months on the four-week version of LAI paliperidone. (See "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)

Other strategies to promote better adherence to antipsychotics include simplifying medication regimens (eg, fewer medications, fewer pills, fewer daily doses) and active engagement of patients in treatment planning (ie, shared decision making).

Implementation of medication changes — Medication changes are usually in response to incomplete or poor response, side effects limiting response to or titration of the medication, or nonadherence to the medication.

We vary the method and rate of change of medications depending on the clinical situation. For example:

- Incomplete or poor response – Continue the ineffective medication at its current dose while titrating the second medication according to its suggested titration schedule (table 2). Once the second medication has reached its target dose, the first medication can be tapered every few days over one to two weeks.
- Side effects – Lower the first medication every few days over one to two weeks while simultaneously titrating the second medication at a similar rate.
- Nonadherence – Begin second medication (eg, LAI antipsychotic) according to usual dosing schedule. (See 'Nonadherence' above and "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)

Duration of antipsychotic therapy — For patients with known or suspected schizophrenia who have recovered from an acute first psychotic episode, we recommend continuing antipsychotics for at least two to three years.

Whether to continue beyond this interval depends on the course and individual features.

- For those with a first episode of psychosis, we base the decision to continue antipsychotic therapy on the symptom intensity, level of psychiatric disruption, response to medications, and support. For those who had psychosis that was extremely disruptive, difficult to

control, or accompanied by violence or suicidal ideation, we favor continuing antipsychotic therapy indefinitely. Otherwise, if it seems that potential relapses can be readily controlled, we explore the possibility of discontinuing medications after two to three years.

- For those who have had multiple episodes of psychosis in the past, we generally recommend continuing antipsychotic therapy indefinitely. However, in patients whose recurrent psychosis has been mild with clear warning signs, a trial of antipsychotic discontinuation may be reasonable. We individualize this decision weighing the potential risks and benefits of indefinite antipsychotic treatment, keeping in mind that antipsychotic treatment may be the reason that recurrences have been mild. We would not consider discontinuing antipsychotic treatment for individuals whose recurrent psychosis has been associated with violence, hospitalization, or other serious disruptions.

If the decision is to discontinue antipsychotic medication, we recommend a gradual reduction in antipsychotic dose and weekly monitoring. We recommend restarting an antipsychotic medication, typically the same medication they were on previously, at the first signs of symptom recurrence.

Discontinuing antipsychotic medications is associated with a higher rate of relapse [16,17]. A meta-analysis of 9145 patients with schizophrenia in 75 randomized trials of 7 to 12 months duration found that patients who continued on an antipsychotic experienced a lower relapse rate compared with patients who were transitioned to placebo (24 versus 61 percent; number needed to treat = 3; relative risk 0.38, 95% CI 0.32-0.45) [16]. Systematic reviews and meta-analysis of randomized trials have found that maintenance antipsychotic medication reduces the risk of relapse after a first episode of psychosis in schizophrenia over a period of up to three years [18-22]. Findings are equivocal for longer periods of treatment.

However, among those who are able to discontinue or reduce the dose of antipsychotic medication, doing so may be associated with better long-term functioning. In a trial of patients with schizophrenia who were randomly assigned to either dose reduction/discontinuation or maintenance, at two years, twice as many patients relapsed with the dose reduction strategy versus maintenance treatment (43 versus 21 percent) [23]. At seven-year follow-up, however, patients in the dose reduction/discontinuation strategy were found to have superior functional remission rates (eg, function across domains including housekeeping, community integration, and vocational functioning) versus those in the maintenance group (40 versus 18 percent) [24]. Additionally, patients in the dose reduction strategy group had lower mean daily antipsychotic dose over the prior two years than those in maintenance group (2.2 mg versus 3.6 mg, haloperidol equivalent dose).

Other trials also demonstrate that a fraction of patients with schizophrenia do not need continuous antipsychotic treatment throughout their lifetimes; however, there are no clear characteristics that can identify these individuals prospectively [25].

PSYCHOSOCIAL TREATMENTS

We recommend comprehensive psychosocial treatment as an adjunct to antipsychotic medications for all patients with schizophrenia. Interventions include cognitive remediation and social skills training, cognitive-behavioral therapy, and family-based interventions. Psychosocial interventions for psychosis and schizophrenia are discussed in detail elsewhere. (See "Schizophrenia in adults: Psychosocial management" and "Psychosis in adults: Initial management", section on 'Psychosocial interventions'.)

MONITORING

Follow-up monitoring should include symptom assessment and review of medications and side effects (table 3). Periodic laboratory testing is needed to address possible metabolic effects of medications. Recommended monitoring and frequency are discussed below.

Frequency of follow-up — Frequency of follow-up for patients whose acute symptoms have stabilized depends on the level of residual symptoms, prior history of recurrence, history of adherence to medications, and level of support available to the patient.

For most patients, we recommend weekly follow-up for the first three months of treatment.

If remission is achieved and continues at three months, we typically lower the frequency of visits to once or twice per month for several months, then once per month. Frequency of follow-up visits can be changed depending on clinical progress and availability of a support system.

Psychiatric symptoms — We recommend assessment of psychiatric symptoms at each visit. This is done primarily through clinical interview and mental status examination of the patient. The interview should be performed in a private setting with minimal distraction to establish or maintain rapport with the patient. While open-ended questioning is often preferred, when necessary, we recommend direct questioning about specific symptoms such as hallucinations, paranoia, mood changes, sleep disturbance, suicidality, and homicidality. (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis", section on 'Clinical manifestations'.)

The mental status examination is a portion of the clinical interview that evaluates cognitive domains including arousal, attention, language, and memory and can be useful to detect underlying cognitive or behavioral abnormalities.

While there are no widely accepted clinical tools for measuring the severity of schizophrenia symptoms, some clinical programs use the modified Colorado Symptom Inventory for this purpose [26]. (See "The mental status examination in adults" and "Psychosis in adults: Epidemiology, clinical manifestations, and diagnostic evaluation", section on 'Diagnostic evaluation'.)

Movement and motor symptoms — All patients treated with antipsychotic medications should be monitored for extrapyramidal symptoms (EPS), for example akathisia, parkinsonism, and dystonia, as well as for tardive dyskinesia (TD) at each visit.

- **Frequency** – Patients starting an antipsychotic medication should be evaluated for EPS weekly until the medication dose has been stable for at least two weeks. Two weekly assessments should follow any change in antipsychotic, addition of an antipsychotic, or significant antipsychotic dose increase [27].

  We recommend checking for TD whenever assessing for EPS. Additionally, formal documentation of TD (eg, using the Abnormal Involuntary Movement Scale (form 1)) is recommended at the following intervals:

  - For patients at high risk of developing abnormal movements (eg, over 55 years old, female, comorbid mood disorder or substance use disorder, on high potency D2 blockers such as first-generation antipsychotics) – Every three months.

  - For all other patients – At least every 12 months.

- **Assessment** – Examination for EPS and TD should include inspection of normal movements and abnormal involuntary movements of orofacial muscles and tongue as well as extremities, including fingers and toes. Muscle tone can be checked by passive flexion and extension of arms, legs, wrists, and ankles. While standing the patients can be observed for abnormal movements of the trunk. Gait should be observed for arm swing, bradykinesia (slowing), and balance.

  Some abnormalities may be severe, reported by the patient, and noted by brief visual inspection. Other symptoms may be very mild, unreported by the patient, and identified only by careful examination. We recommend asking about motor symptoms including

restlessness or pacing, inability to sit still, stiffness or slowness of movements, tremor, or gait change, in addition to direct examination.

Findings can be suggestive of syndromes:

- Akathisia is suggested by a sensation of restlessness, frequent pacing, a compelling urge to move, or an inability to sit still. (See 'Akathisia' below.)
- Parkinsonism is suggested by finding of masked facies, bradykinesia, tremor, or rigidity. (See 'Parkinsonism' below.)
- Dystonia is a tonic contraction of a muscle or muscle group that is typically disturbing to the patient and obvious to the examiner. (See 'Dystonia' below.)
- TD is characterized by the following features (see 'Tardive dyskinesia' below and "Tardive dyskinesia: Etiology, risk factors, clinical features, and diagnosis" and "Tardive dyskinesia: Prevention, treatment, and prognosis"):
  - Sucking, smacking of lips
  - Choreoathetoid movements of the tongue
  - Facial grimacing
  - Lateral jaw movements
  - Choreiform or athetoid movements of the extremities and/or truncal areas

Metabolic dysregulation — We recommend monitoring fasting glucose or hemoglobin A1c, lipid profile, weight, and body mass index at regular intervals during the first year and then annually thereafter if normal (table 4).

More frequent measurements may be necessary for individual patients with significant baseline metabolic abnormalities, significant weight gain, or where there is clear evidence of increased risk of insulin resistance [28]. In these cases, we recommend consultation with a primary care clinician, internist, or endocrinologist. Monitoring for metabolic abnormalities in patients taking an antipsychotic drug and/or patients with severe mental illness is reviewed in greater detail separately. (See "Approach to managing increased risk for cardiovascular disease in patients with severe mental illness" and "Metabolic syndrome in patients with severe mental illness: Epidemiology, contributing factors, pathogenesis, and clinical implications".)

Orthostatic changes and tachycardia — We recommend checking pulse and blood pressure at each visit. Orthostatic blood pressure is checked if the patient reports lightheadedness or has tachycardia (eg, greater than 100 beats per minute).

Antipsychotics with alpha-adrenergic blocking effects (eg, clozapine, risperidone, paliperidone, iloperidone) can produce a dose-related orthostatic hypotension and associated tachycardia. These effects are most pronounced during the first days of treatment and occur most frequently with clozapine and iloperidone.

Electrocardiogram — We recommend an electrocardiogram (ECG) prior to starting antipsychotic medications, three months after starting the medication, and yearly thereafter in all patients with baseline risk for QT prolongation. Additionally, we recommend checking ECG at the same intervals in all patients treated with antipsychotic medications associated with QT prolongation (table 3). (See 'Cardiovascular effects' below.)

Other testing in select cases — In some individuals, for example, individuals with pre-existing neutropenia, or in those who report galactorrhea or sexual dysfunction while on medications, it may necessary to check prolactin level or complete blood count more frequently. (See 'Other patient-specific considerations' below and 'Endocrinologic and metabolic side effects' below.)

SIDE EFFECT MANAGEMENT

Extrapyramidal symptoms — Extrapyramidal symptoms (EPS) include akathisia, parkinsonism, and dystonia. While all antipsychotics can cause EPS, they tend to be more common in first-generation antipsychotics (FGAs) than second-generation antipsychotics (table 3) [29]. (See 'Medication adjustments' above and "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Akathisia — Akathisia is the most common form of EPS. It usually presents as motor restlessness with a compelling urge to move or an inability to sit still. Individuals with milder akathisia may describe a subjective feeling of restlessness but not show restless motor behavior.

In patients whose akathisia is intolerable or affects their response to medication we generally suggest cautious reduction of the antipsychotic dose while closely monitoring the patient for exacerbation of psychotic symptoms. In some instances, it may be necessary to address the akathisia pharmacologically rather than lowering the antipsychotic. As examples, when the psychosis was difficult to control or has required several ineffective trials, or when the medications have not yet had time to take effect. The treatment of akathisia in adults receiving antipsychotic medication is in the associated algorithm (algorithm 1).

We suggest individualized treatment depending on the clinical presentation.

- In patients whose akathisia is improved on the lower dose of antipsychotic, we recommend continuing that lower dose of antipsychotic medication.

- In patients with recurrent psychosis on the lower dose, we increase the dose back to prior level to stabilize symptoms. When psychotic symptoms are stable, we suggest switching to another antipsychotic with less propensity to cause EPS (table 3).

- In patients whose akathisia is unimproved on the lower dose, we suggest switching to another antipsychotic with lower propensity to cause akathisia (table 3).

If the above options are tried without success or contraindicated (ie, in patients who cannot have antipsychotic lowered or changed), we suggest treatment of akathisia with medication.

Our preferred choices are propranolol and benztropine. We typically use propranolol to avoid the anticholinergic effects of benztropine. We further individualize the choice based on potential adverse effects and underlying comorbidities. As examples:

- In patients with chronic obstructive pulmonary disease, heart failure, or asthma, we suggest avoiding beta blockers (ie, propranolol).

- In patients with glaucoma or cognitive concerns, we suggest avoiding benztropine.

In small clinical trials, propranolol and benztropine have shown evidence of efficacy in the treatment of akathisia [30-34]. Doses and monitoring are:

- Propranolol – Propranolol should be started to 10 mg orally twice daily. If symptoms do not improve, dosing can be increased weekly to maximum dose of 40 to 60 mg twice daily. Blood pressure should be monitored with the use of propranolol. Fatigue and light-headedness are common.

- Benztropine – Benztropine should be started at 1 mg twice daily and increased up to 3 mg twice daily depending on response. Patients receiving benztropine should be monitored for anticholinergic effects including dry mouth, constipation, urinary retention, blurry vision, and cognitive impairment.

Benzodiazepines are another effective option for reducing akathisia; however, some studies have suggested an increased risk of mortality with benzodiazepine use in schizophrenia [34-36]. Additionally, they are associated with sedation, withdrawal seizures, a potential for addiction, and tolerance. Thus, if used (eg, if there are no other alternatives), patients should receive the lowest dose that reduces akathisia. Lorazepam can be started at 0.5 mg orally twice daily and, if

clinically warranted, increased by 0.5 mg twice daily to a dose of 3 mg twice daily. We do not recommend total daily doses above 6 mg.

Parkinsonism — Symptoms of secondary parkinsonism include masked facies, cogwheel rigidity, tremor, and bradykinesia. These symptoms may range from severe (eg, noted by brief visual inspection of patient) to very mild and unreported by the patient (eg, detected only by careful examination). In severe cases, parkinsonism may significantly impair the patient's quality of life and increase the risk of falls. In these cases, we suggest treatment of the secondary parkinsonism as described below.

Our first treatment intervention is a cautious reduction in antipsychotic dose with close monitoring of the patient for exacerbation of psychotic symptoms.

- In patients whose parkinsonism is improved with lower dose of antipsychotic, we continue the lower dose while monitoring for symptoms and side effects.
- In patients with recurrent psychotic symptoms on a lower dose of antipsychotic, we increase the medication back to its prior dose to stabilize symptoms. When psychosis is stable we suggest switching to another antipsychotic with lower propensity to cause parkinsonism (table 3). In patients who are highly sensitive to parkinsonism, clozapine should be considered.
- In patients whose parkinsonism is unimproved despite lower dose of antipsychotic, we suggest switching to another antipsychotic with lower propensity to cause parkinsonism (table 3).

If the above options are tried without success or contraindicated (ie, in patients who cannot have antipsychotic lowered or changed), we suggest treatment of antipsychotic induced parkinsonism with medications although there is little high-quality evidence supporting the effectiveness of these approaches [37-39]. Choice of medication is based on age of patient, medical comorbidity, current medications, and prior history of treatment for EPS.

Benztropine is our preferred choice for treating antipsychotic induced parkinsonism. We suggest starting at 1 mg twice daily and titrating to 3 mg twice daily if needed. Doses of 1 to 2 mg/day are often effective. Benztropine is an anticholinergic medication that can lead to dry mouth, constipation, blurry vision, urinary retention, and cognitive impairment. These effects may be more severe in patients over 70 years old and in patients on other medications with anticholinergic properties.

If benztropine is ineffective or in patients in which it is not preferred (eg, cognitive concerns, anticholinergic sensitivities), we suggest the N-methyl-D-aspartate-receptor antagonist, amantadine. Amantadine may be given as immediate release 100 mg orally two to three times daily [40]. Once daily forms are available as well for increased adherence. Side effects include hypotension and mild agitation. (See "Initial pharmacologic treatment of Parkinson disease", section on 'Amantadine'.)

Other agents that are less commonly used in the treatment of antipsychotic-induced parkinsonism include diphenhydramine, levodopa, and trihexyphenidyl. Diphenhydramine, an antihistamine, may be given at a dose of 25 to 50 mg orally every six hours. It is less commonly used due to its shorter half-life and sedative properties. Trihexyphenidyl has anticholinergic properties similar to benztropine and is used based on cost and availability.

We advise against using the dopamine agonist levodopa in patients with active psychosis. It has been shown in observational studies to have minimal benefit in the treatment of drug-induced parkinsonism and adverse reactions may include psychosis and agitation [39]. (See "Initial pharmacologic treatment of Parkinson disease", section on 'Nonergot dopamine agonists'.)

Prophylactic use of antiparkinsonian agents is not recommended to prevent antipsychotic-induced parkinsonism. However, it may be useful in patients treated with high doses (eg, greater than haloperidol 10 mg/day or the equivalent dose of other antipsychotics) of high-potency first-generation antipsychotics, or in those patients with known sensitivity to EPS [41,42].

Dystonia — Dystonia is an involuntary contraction of major muscle groups that is highly disturbing to the patient. Some types of dystonia, for example laryngospasm, may be life threatening. Antipsychotic-induced dystonia is usually rapid in onset and is characterized by torticollis, retrocollis, oculogyric crisis, and opisthotonos. Risk factors for dystonia include young age, male sex, use of cocaine, and a history of acute dystonic reaction.

For treatment of acute dystonia secondary to antipsychotic, use we recommend treatment with diphenhydramine or benztropine, as described below. We prefer diphenhydramine.

- Diphenhydramine – We suggest a dose of 50 mg intravenously (IV) or intramuscularly (IM) acutely followed by 50 mg orally every four to six hours. Milder cases may be treated with 50 mg orally two to three times daily.

- Benztropine – We suggest a dose of 1 to 2 mg IM or IV acutely followed by 1 to 2 mg orally daily. Milder cases may be treated with oral benztropine 1 to 2 mg once or twice daily.

The emergence of a dystonia should lead to reevaluation of the patient's antipsychotic regimen. After acute dystonia we suggest continuing the daily dose of benztropine or diphenhydramine and changing to an antipsychotic with less propensity to cause EPS (table 3).

> Prophylactic treatment with an anticholinergic agent such as benztropine is recommended to prevent an acute dystonic reaction in patients who receive intramuscular haloperidol (eg, in the treatment of acute agitation or psychosis). This is particularly important in patients with little prior exposure to antipsychotics. As an example, intramuscular haloperidol 5 or 10 mg can be accompanied by intramuscular benztropine 1 or 2 mg.

Tardive dyskinesia — Tardive dyskinesia (TD) is a syndrome consisting of characteristic involuntary movements occurring most often after chronic treatment with antipsychotic medications or another dopamine receptor blocking agent. TD syndromes are more common after sustained exposure to antipsychotic medications; however, they may appear as early as one to six months after initiation of these agents. TD may initially worsen or reappear after lowering or discontinuing medication. (See "Tardive dyskinesia: Etiology, risk factors, clinical features, and diagnosis", section on 'Risk factors'.)

When patients develop TD, clinicians should re-evaluate the current medication treatment. Prevention and treatment of TD are discussed in detail elsewhere. (See "Tardive dyskinesia: Prevention, treatment, and prognosis", section on 'Initial management'.)

Neuroleptic malignant syndrome — Neuroleptic malignant syndrome (NMS) is a life-threatening syndrome that is characterized by a tetrad of clinical features (fever, rigidity, mental status changes, autonomic instability) and can occur in patients taking antipsychotic or other dopamine-blocking agents [43]. Incidence rates range from 0.02 percent to 3 percent. Treatment of NMS involves withdrawal of medication and intensive management for cardiovascular support, control of hyperthermia, fluids, and restoration of electrolyte balance. (See "Neuroleptic malignant syndrome".)

Endocrinologic and metabolic side effects — Most antipsychotic medications are known to cause metabolic side effects including weight gain, hyperlipidemia, hyperglycemia, and hypertension (table 3). These side effects are risk factors for cardiovascular disease. Additionally, they are primary contributors to the early and increased mortality experienced by patients who have severe mental illness or are on antipsychotic medication [44].

Strategies for preventing and treating metabolic side effects of antipsychotic drugs include:

- Changing the antipsychotic regimen

- Lifestyle interventions including diet changes and exercise to reduce weight and metabolic risk factors
- Treating other metabolic risk factors such as hypertension, dyslipidemia, hyperglycemia, diabetes, and tobacco use

Prevention and treatment of metabolic syndromes are presented in detail elsewhere.

- (See "Approach to managing increased risk for cardiovascular disease in patients with severe mental illness".)
- (See "Modifiable risk factors for cardiovascular disease in patients with severe mental illness".)
- (See "Lifestyle interventions for obesity and overweight patients with severe mental illness".)
- (See "Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease".)
- (See "Initial management of hyperglycemia in adults with type 2 diabetes mellitus".)

Cardiovascular effects

- **QT prolongation** – In patients who develop prolonged QT syndrome during treatment with antipsychotic medications, we recommend consultation with a cardiologist and changing to another antipsychotic medication with lower propensity to cause QT prolongation (table 3). (See "Acquired long QT syndrome: Clinical manifestations, diagnosis, and management" and "Psychosis in adults: Initial management", section on 'Cardiovascular risk factors'.)

- **Orthostatic hypotension and tachycardia** – In individuals at risk for orthostatic hypotension, such as older adult or frail patients, we recommend starting at the lowest possible dose of the prescribed medication and titrating slowly (table 3). As an example, quetiapine can be started at 25 mg per day and increased by 25 mg per day to the acute therapeutic dose range of 150 to 750 mg depending on clinical response. If orthostatic hypotension develops, we recommend carefully lowering the dose of the antipsychotic medication. If this is not effective or contraindicated, we recommend changing to another antipsychotic with less propensity to cause orthostasis.

  Treatment strategies for tachycardia include reducing the dose of antipsychotic medication and avoiding anticholinergic medications. For symptomatic patients, we recommend referral to a cardiologist.

- **Myocarditis and cardiomyopathy** – These have been reported in patients treated with clozapine. (See "Schizophrenia in adults: Guidelines for prescribing clozapine", section on 'Myocarditis/cardiomyopathy'.)

Other treatment-emergent side effects and their treatment

- **Anticholinergic-related side effects** – These side effects include tachycardia, dry mouth, urinary hesitancy, constipation, visual changes, and cognitive impairment. In patients with problematic anticholinergic side effects, we recommend lowering medication dosing as the first treatment. If this is ineffective, we recommend changing to a medication with less anticholinergic effect. Anticholinergic effects are seen with clozapine, chlorpromazine, olanzapine, and, to a lesser extent, with quetiapine, iloperidone, and loxapine (table 3). These side effects tend to be worse in older patients.

- **Sedation** – We recommend giving antipsychotic medications with high propensity to cause sedation at night. Sedation is usually most severe during the first few weeks of treatment and can be minimized by titrating medications slowly. Although all antipsychotics medications can cause sedation, it is most strongly associated with chlorpromazine, olanzapine, clozapine, and quetiapine (table 3).

- **Agranulocytosis** – Leukopenia, neutropenia, and agranulocytosis have been well documented with clozapine but have been reported with other antipsychotics as well [45]. In the United States and other countries, regulations require routine monitoring of clozapine patients for neutropenia and discontinuation of the drug in severe cases. Monitoring guidelines are discussed in detail separately. (See "Schizophrenia in adults: Guidelines for prescribing clozapine", section on 'Monitoring'.)

  For patients taking other antipsychotics who develop drug-induced neutropenia, we recommend prompt withdrawal of the antipsychotic and consultation with a primary care provider or hematologist.

  We then carefully consider the need for continued antipsychotic treatment. If an antipsychotic is still indicated, then we carefully reintroduce a different antipsychotic.

  For patients who have previously experienced a drug-induced neutropenia or who have a pre-existing low white blood cell count or low absolute neutrophil count (ANC; eg, individuals with Duffy-null associated neutrophil count [DANC]), we recommend monitoring ANC at baseline, after two weeks, and after three to six months. If recurrence of neutropenia is documented, we recommend prompt withdrawal of the antipsychotic and further consultation with primary care provider or hematologist. (See "Schizophrenia

in adults: Guidelines for prescribing clozapine", section on 'Duffy-null associated neutrophil count (DANC)' and "Schizophrenia in adults: Guidelines for prescribing clozapine", section on 'Neutropenia' and "Approach to the adult with unexplained neutropenia", section on 'Normal variants <1500/microL'.)

Restarting an antipsychotic after recurrent antipsychotic-induced neutropenia prompts careful assessment of benefits and risks, and must be done with ongoing consultation with a primary care provider or hematologist.

- **Symptoms of hyperprolactinemia** – All FGAs can elevate plasma prolactin. Among second-generation antipsychotics, risperidone and paliperidone are most likely to elevate plasma prolactin (table 3). This elevation can lead to galactorrhea, menstrual disturbances, and sexual dysfunction in females and gynecomastia and sexual dysfunction in males [46]. In patients reporting these symptoms, we recommend prolactin level to clarify diagnosis and treatment. Patients with elevated prolactin levels with the symptoms described above should be referred to their primary care clinician for further evaluation. (See "Causes of hyperprolactinemia", section on 'Drug induced' and "Clinical manifestations and evaluation of hyperprolactinemia", section on 'Clinical presentation' and "Management of hyperprolactinemia".)

- **Seizures** – Most antipsychotics cause a dose-related reduction in the seizure threshold. If a patient experiences new-onset seizures, antipsychotic drugs should not be assumed to be the etiology, as these rarely cause seizures in a patient not otherwise prone to epilepsy. Usual procedures for evaluation of new-onset seizures should be followed. (See "Evaluation and management of the first seizure in adults".)

  The risk of seizures is greatest with clozapine, which has an adjusted hazard ratio of greater than 3 [47]. As a result, patients with seizure disorders who are on clozapine should be carefully monitored in conjunction with their neurologist. (See "Schizophrenia in adults: Guidelines for prescribing clozapine", section on 'Seizures' and "Overview of the management of epilepsy in adults", section on 'Maximizing the likelihood of a successful outcome'.)

- **Visual disturbances** – Pigmentary retinopathies and corneal opacities have been described with chronic administration of chlorpromazine and thioridazine. Cataract development with quetiapine has been reported from preclinical evidence in beagles [27]. The clinical relevance of this finding in beagles is unclear. Nevertheless, all patients should have routine eye examinations, which are generally recommended every two years for

adults. (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'Cataracts'.)

- **Cholestatic jaundice** – This has been described with chlorpromazine and, rarely, with other FGAs. In most cases, discontinuation of the offending drug is the only treatment required [48].

OTHER PATIENT-SPECIFIC CONSIDERATIONS

Comorbid psychiatric disorders — Comorbid depressive disorders and anxiety disorders can lead to increased morbidity, poor functioning, higher relapse rates, and lower quality of life in patients with schizophrenia. Comorbid disorders may be difficult to distinguish from symptoms of schizophrenia or antipsychotic drug side effects. Properly diagnosed, however, these syndromes can respond to antidepressant and anxiolytic medications [49]. Treatment of comorbid disorders in schizophrenia is discussed elsewhere. (See "Depression in schizophrenia" and "Anxiety in schizophrenia".)

Substance use disorders (SUDs) are highly prevalent in patients with schizophrenia [50]. The combination of a severe mental illness and a SUD is commonly described as "dual diagnosis." Dual diagnosis is associated with increased morbidity, poor functioning, decreased adherence to medication, and higher rates of relapse compared to either disorder individually [51]. Integrated treatment strategies for dual diagnosis that include pharmacotherapy have been developed for individuals with schizophrenia and SUDs. (See "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately.

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer

short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Schizophrenia (The Basics)" and "Patient education: Schizoaffective disorder (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Objectives of treatment** – The goals of maintenance treatment of schizophrenia are to minimize symptoms and functional impairments, minimize side effects of antipsychotic therapy, avoid relapses, and promote recovery that allows self-determination, full integration into society, and pursuit of personal goals. (See 'Objectives of treatment' above.)

- **Response to pharmacologic therapy** – For individuals with known or suspected schizophrenia who have responded to an antipsychotic medication started for an acute psychotic episode, we continue that medication at the lowest effective dose in order to avoid adverse effects. (See 'Full response to pharmacologic therapy' above.)

- **Medication adjustments** – Adjustments in medication or dose may be needed to address specific clinical scenarios:

  - **For partial response or recurrence of symptoms** – For patients with suboptimal response or recurrence due to nonadherence we suggest using a long-acting injectable antipsychotic rather than a daily oral antipsychotic (table 2) (**Grade 2C**). (See 'Nonadherence' above and "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication", section on 'Indications'.)

    For patients who have suboptimal response despite good adherence, we increase the dose to target the therapeutic range, if not already done (table 1). For ongoing suboptimal response despite therapeutic dosing for an adequate time period, we suggest switching the antipsychotic medication rather than further increasing the dose

beyond the therapeutic range or adding a second agent (**Grade 2C**). (See 'Partial response or recurrence of symptoms' above.)

- **Persistent suicidality** – For patients with schizophrenia who have persistent suicidal ideation despite antipsychotic treatment, we suggest a trial of clozapine rather than a change to a different (nonclozapine) antipsychotic medication (**Grade 2B**). (See 'Persistent suicidality' above.)

- **Treatment resistance** – We consider individuals with suboptimal response to two or more adequate trials of standard antipsychotic medications to have treatment-resistant schizophrenia. We evaluate these patients for clozapine eligibility. (See 'Treatment-resistant schizophrenia' above and "Evaluation and management of treatment-resistant schizophrenia", section on 'Management'.)

- **Duration of antipsychotic treatment** – We continue antipsychotic therapy for at least two to three years following recovery from an acute psychotic episode. For patients who have recovered from a first psychotic episode, and for those whose psychosis was mild or readily controlled, and was not accompanied by violence or suicidality, we suggest a cautious trial of gradual reduction and antipsychotic discontinuation after that period (**Grade 2C**). For individuals with suicidality or with disruptive or severe psychosis, we continue antipsychotic medications indefinitely. (See 'Duration of antipsychotic therapy' above.)

- **Monitoring** – We assess current and interval psychiatric symptoms including hallucinations, paranoia, mood changes, sleep disturbance, suicidality, and homicidality at each visit. We typically have stable individuals follow-up weekly for the first three months of treatment then less frequently thereafter depending on clinical symptoms. (See 'Psychiatric symptoms' above and 'Frequency of follow-up' above.)

  We assess all individuals on long-term antipsychotic therapy at regular intervals for side effects such as extrapyramidal symptoms and metabolic derangement (table 4). Additional monitoring is warranted for specific agents or patients with certain risk factors (eg, evaluation for agranulocytosis for those on clozapine). (See 'Monitoring' above.)

- **Side effect management** – Management of side effects depends on the specific side effect, the response to the medication, and the patient's history of response to prior medications. An example of the treatment of akathisia is in an algorithm (algorithm 1). (See 'Side effect management' above and 'Akathisia' above.)

- **Psychosocial treatment** – We recommend comprehensive psychosocial treatment as an adjunct to antipsychotic medications for all patients with schizophrenia. (See 'Psychosocial treatments' above.)

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