Choosing a Pharmacologic Strategy for Those With a Psychotic Illness:

Balancing Efficacy, Tolerability, and Cost

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Lessons Learned at the Interface of Medicine and Psychiatry

The Psychiatric Consultation Service at Massachusetts General Hospital sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. During their twice-weekly rounds, Dr Stern and other members of the Consultation Service discuss diagnosis and management of hospitalized patients with complex medical or surgical problems who also demonstrate psychiatric symptoms or conditions. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Have you ever wondered which antipsychotic agent you should prescribe to your patient with psychosis? Have you struggled to balance the concepts of efficacy, tolerability, and cost? Have you been uncertain about how to switch from one agent to another without provoking a relapse or triggering intolerable side effects? If you have, the following case vignette and discussion should prove useful.

CASE VIGNETTE

Mr A, a 22-year-old man, developed his first psychotic episode (with auditory hallucinations, paranoia, thought broadcasting, and disorganized thinking), which interfered with his sophomore year of college and interpersonal relationships. He was diagnosed with schizophrenia and started on risperidone, which was gradually titrated to 3 mg twice daily. Over the next 6 months, his symptoms improved dramatically, which enabled him to resume regular activities and fulfill his academic responsibilities.

To improve his medication adherence and outcome, Mr A transitioned from oral risperidone to long-acting injectable (LAI) paliperidone palmitate (Invega Sustenna), starting with a loading dose of 234 mg on day 1 and then adding 156 mg on day 8, with subsequent by-monthly injections. After being stable for more than 4 months on Invega Sustenna, he was transitioned to Invega Trinza (546 mg every 3 months). Although his psychotic symptoms remained under control, he developed significant metabolic side effects, including a 50-lb weight gain (from 130 lb to 180 lb), with his body mass index (BMI) increasing from 18 to 25 kg/m^2. Due to these metabolic changes, Mr A was prescribed metformin, which was gradually titrated to 1,000 mg twice daily. In addition, he complained of cognitive dulling as well as having difficulty initiating and following through with his activities. Mr A also developed elevated prolactin levels (95 ng/mL), which led to erectile dysfunction and gynecomastia that caused him significant distress. To address his hyperprolactinemia, aripiprazole (5 mg daily) was added, which initially reduced his prolactin level to 40 ng/mL and improved his sexual side effects slightly. After 1 month, the aripiprazole dose was increased to 10 mg daily, but at this increased dose, Mr A became anxious, restless, and started to pace (each suggesting akathisia). Due to his frustration and discomfort, Mr A abruptly discontinued his aripiprazole and declined to receive the next scheduled dose of Invega Trinza, which resulted in his relapsing and requiring hospitalization for acute stabilization.

DISCUSSION

Does Everyone With Psychotic Symptoms Have a Psychotic Illness?

Psychosis is an aberration in perceived experiences—at times involving visual and auditory

Clinical Points

- Compared to all other antipsychotics, clozapine has superior efficacy and is the only antipsychotic that is US Food and Drug Administration (FDA) approved for treatment-resistant schizophrenia.
- Long-acting injectables have improved efficacy compared to oral formulations, an observation that is likely related to their enhanced treatment adherence.
- The newest antipsychotic agent, xanomeline-trospium (Cobenfy, Kar-XT), has a novel mechanism of action, acting upstream from the dopamine receptor targeted by the first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs).
- All FGAs and SGAs have an FDA "black box warning" regarding the increased risk of death when used in elderly individuals with dementia.
- Throughout the treatment course, symptoms should be assessed while partaking in therapeutic drug monitoring.

hallucinations, impaired thought processes, delusions, and an inability to discern reality. Psychosis is not a diagnosis per se; instead, it is a descriptor. First-episode psychosis (due to any cause) occurs in approximately 50 of every 100,000 people annually. Its pathophysiology is variable and primarily determined by its etiology, with the common thread being an alteration in the blood-brain barrier that leads to an imbalance of neurotransmitter excitation (via glutamate and dopamine) and inhibition (via γ-aminobutyric acid) with resultant dopamine dysregulation. Only a minority of those who have experienced a first episode of psychosis develop a full-blown psychotic disorder.

When distinguishing between primary and secondary psychoses, the age of the patient, their medical history, as well as the timing of the onset and characteristics of the psychosis are crucial. Typically, primary psychoses (ie, due to psychiatric disorders) begin between the ages of 18 and 35 years and are accompanied by a subtle escalation of symptoms. Moreover, they are more likely to present with auditory hallucinations and to be seen in psychiatric settings.[1]

However, secondary psychoses (ie, due to medical or neurological causes) occur in 11% of individuals with psychosis. The most common causes of secondary psychosis are substance-induced psychoses and psychoses caused by infections or autoimmune conditions. Those with secondary psychoses tend to have symptoms arise acutely after the age of 40 years and develop noticeable changes in their level of functioning. Such conditions are likely to be evaluated in general hospital settings.[1]

When evaluating a patient with psychotic symptoms, their behavior should be observed before beginning the interview or entering the room (if feasible). The clinician should take note of self-dialoging, changes in affect, changes in stance when approached, intensity of eye contact, suspiciousness, psychomotor movements, vital sign abnormalities, and level of alertness when not being stimulated.

A comprehensive evaluation is crucial to reduce the chance that a secondary psychosis will be missed. Recommended assessments include laboratory and imaging tests aimed at detecting metabolic, infectious, inflammatory, endocrine, and toxic etiologies. Table 1 outlines each test and its clinical purpose.

What Types of Medical and Psychiatric Conditions Are Manifest by Psychosis?

Acute onset. The most common cause of psychosis is substance-related psychosis (eg, with intoxication of amphetamine, cannabis, cocaine, phencyclidine, psychedelics, or opiates). Psychosis associated with alcohol withdrawal can lead to alcoholic hallucinosis (with auditory hallucinations, a clear sensorium, and intact cognition) or delirium tremens, which is much more severe and is accompanied by hypertension, tachycardia, diaphoresis, tremors, an altered sensorium, impaired cognition, and auditory and visual hallucinations.[2]

Delirium (toxic-metabolic encephalopathy) also presents with an acute-onset psychosis marked by inattention, impaired arousal, and auditory and visual hallucinations (typically of small animals and bugs), delusions, and significant fluctuations (ie, a waxing and waning course). Delirium is typically secondary to infections, metabolic derangements, or medication effects, and it is best managed by treating the specific etiology.

Epileptic seizures can also lead to an ictal, interictal, or postictal psychosis. Psychotic disorders are 8 times more common in those who carry a diagnosis of epilepsy than in those in the general population.[3] Many cases require use of an antiepileptic drug for seizure control, as well as an antipsychotic to manage psychotic symptoms. Other abrupt-onset psychoses associated with seizures include autoimmune encephalitis, specifically, anti-*N*-methyl-D-aspartate (NMDA) encephalitis, which is manifest as psychosis followed by escalating neurological abnormalities, including seizures and catatonia.[4]

Medication-induced psychoses appear abruptly and are temporally associated with medication changes (eg, of steroids, antiparkinsonian agents, and antibiotics). On occasion, hallucinations arise in the context of severe psychosocial stressors and traumatic experiences (eg, acute and transient psychotic disorders) (Table 2).

Subacute onset. Dementing illnesses (eg, frontotemporal dementia, Lewy body dementia, Alzheimer disease, and vascular dementia) can be manifest by psychosis even years after the onset of insidious symptoms that involve executive dysfunction, memory impairment, and visuospatial impairment. Autoimmune disorders often present weeks to

Table 1.
Recommended Assessment for New-Onset Psychosis

Test	Purpose
Complete blood count	Detects anemia, infection, or hematological abnormalities
Basic metabolic panel	Detects electrolyte imbalances, renal function, dehydration, or uremia
Liver function test	Detects hepatic encephalopathy, liver failure, or substance-induced liver injury
Ammonia level	Rules out hepatic encephalopathy
Erythrocyte sedimentation rate/C-reactive protein	Screens for systemic inflammation or autoimmune conditions
Urine toxicology screen	Detects substance-induced psychosis
HIV testing	Identifies HIV-associated neurocognitive conditions
Rapid plasma reagin	Screens for neurosyphilis
Thyroid-stimulating hormone	Screens for thyroid dysfunction (hyperthyroidism-related psychosis)
Lipid panel	Assesses cardiovascular risk
Brain magnetic resonance imaging	Detects structural lesions, tumors, demyelination, or encephalitis

months after joint pain, pleurisy, nephropathy, or skin involvement, as well as elevated levels of biomarkers. Systemic lupus erythematosus can cause psychosis when the brain is involved (eg, lupus cerebritis).

Primary psychiatric conditions with psychosis include affective disorders (unipolar or bipolar). In unipolar depression (major depressive disorder [MDD]), low mood, neurovegetative symptoms, and mood congruent delusions and hallucinations may appear. Approximately 15% of people with MDD experience psychosis,[5] typically at higher symptom severities (eg, Patient Health Questionnaire-9 score of 20). Bipolar disorder with mania or depression and psychosis may be acute or subacute and have notable mood swings. Schizophrenia typically has an extended prodrome (lasting several months), with significant social withdrawal, cognitive impairment, and auditory and visual hallucinations.

How Has the Care of Psychotic Illnesses Evolved Over the Past Century?

In the first half of the 20th century, state psychiatric hospitals grew significantly due to societal changes (eg, industrialization and urbanization altered household structure, which left the elderly in need of state care). As psychiatric hospitals became overcrowded, care was no longer aligned with moral treatment (that had been pioneered by the asylum reform efforts of Dorothea Dix in the mid-19th century); they had become warehouses characterized by inhumane treatment. The quality of care declined further when trained staff left their hospital positions to serve on the battlefields in World War II.[6]

Subsequently, federal policies and scientific discoveries between 1945 and 1970 changed psychiatric care forever. In 1948, the federal government established the National Institute of Mental Health; in 1954, chlorpromazine became the first antipsychotic medication to be used in the United States,[7] and in 1963, President John F. Kennedy signed the Community Mental Health Centers Act, which was amended (expanded) in 1968 and again in 1970.[8]

In the years since deinstitutionalization, with the movement of individuals having a serious mental illness (SMI) from psychiatric facilities to the communities, the number of state psychiatric hospital beds decreased from 558,000 in 1955 to 35,000 in 2017. This translated to a loss of beds from 340 per 100,000 people to 11 per 100,000.[9] Transinstitutionalization also explains the movement of people with SMI from state hospital beds to prisons, nursing homes, the streets, and homeless shelters. Although advances in psychopharmacology have ameliorated symptoms for many of those with psychotic disorders, drug treatment has not been a panacea. Moreover, a lack of adequate resources has impeded the provision of comprehensive care (eg, supported housing, transitional employment) that is needed by many of those with SMI.

After the approval of chlorpromazine, several antipsychotics were created and became available; as a class, first-generation antipsychotics (FGAs) block dopamine D_2 receptors and reduce the positive symptoms of psychosis but caused movement side effects. In 1972, clozapine came to the market; however, it was removed in 1975 in many countries due to an alarming rise in the number of cases of neutropenia. However, in 1988, a pivotal study by Kane et al[10] in the United States demonstrated that clozapine manifests superior efficacy in a narrowly defined cohort of those with treatment-resistant schizophrenia; response rates for clozapine in the double-blind, randomized trial were 30% for those in the clozapine arm compared to 4% in the chlorpromazine group.[11] After clozapine, 13 other second-generation antipsychotics (SGAs) received US Food and Drug Administration (FDA) approval. All share 5-hydroxytryptamine (5-HT_{2A}) and D_2 antagonism,

Table 2.

Characteristics of Psychotic Illnesses

Onset type	Incidence	Degree of illness	Condition	Age of Onset	Onset and duration	Unique identifiers	Important tests and clinical clues
Acute	High	Secondary	Substance intoxication	Adolescents/ adults	Acute, brief	+ Urine toxicology, history of substance use	Toxicology screening
Acute	High	Secondary	Substance withdrawal	Adults/elderly	Acute, days-weeks	Withdrawal symptoms, hallucinations (alcohol hallucinosis vs delirium tremens)	Withdrawal scales, electrolytes
Acute	High	Secondary	Delirium (toxic-metabolic encephalopathy)	Elderly	Acute, fluctuating days-weeks	Fluctuating cognition, audiovisual hallucinations, secondary medical cause	Clinical assessment, laboratory tests
Acute	Moderate	Secondary	Epileptic psychosis (ictal, interictal, postictal)	Adolescents/ adults	Acute-episodic	Psychosis associated with epilepsy	EEG, seizure history
Acute	Moderate	Secondary	Autoimmune encephalitis (anti-NMDA)	Young adults	Acute-subacute	Psychosis, seizures, catatonia	CSF antibodies, MRI, EEG
Acute	Moderate	Secondary	Medication-induced psychosis (steroids, levodopa, cefepime, hydroxychloroquine)	Adults/elderly	Acute-subacute	Temporal relationship with medication changes	Medication review
Acute	Low	Primary	Acute and transient brief psychosis	Adolescents/ adults	Acute (<1 month)	Sudden intense psychosis after severe stress	Psychiatric history, stressors
Acute-subacute	Moderate-high	Primary	Bipolar disorder	Young adults	Episodic	Mood swings, pressured speech, insomnia, psychosis	Psychiatric evaluation
Subacute	High	Secondary	Alzheimer dementia	Elderly	Chronic, progressive	Progressive cognitive decline, late psychosis	Cognitive assessment, imaging
Subacute	High	Secondary	Lewy body dementia	Elderly	Chronic, progressive	Early visual hallucinations, parkinsonian symptoms	Neuropsychological tests, neuroimaging
Subacute	Moderate-high	Secondary	Parkinson disease	Elderly	Chronic	Parkinsonian symptoms first, cognitive impairment and visual hallucinations later	Neurological examination, medication review
Subacute	Moderate	Secondary	Frontotemporal dementia	Elderly	Chronic	Behavioral/language changes, insidious onset	Neuropsychological tests, neuroimaging
Subacute	Moderate	Secondary	Vascular dementia (poststroke psychosis)	Elderly	Subacute-chronic	History of stroke, persecutory delusions	MRI/CT imaging
Subacute	Moderate	Secondary	Brain tumor	Adults/elderly	Progressive	Neurological deficits, insidious psychosis	MRI/CT imaging
Subacute	Moderate	Secondary	SLE (lupus cerebritis)	Young adults	Episodic-subacute	Autoimmune symptoms, cognitive/psychiatric changes	ANA, autoimmune panel
Subacute	Moderate	Primary	Major depressive disorder with psychosis	Adults	Episodic	Depression, mood-congruent psychosis	Depression screening
Subacute-chronic	Moderate-high	Primary	Schizophrenia	Adolescents/ young adults	Chronic, months-years prodrome	Social withdrawal, cognitive impairment, audiovisual hallucinations	Psychiatric evaluation
Subacute-chronic	Moderate-high	Primary	Schizoaffective disorder	Adolescents/ adults	Episodic-chronic	Psychosis with mood episodes	Psychiatric history

Abbreviations: ANA = antinuclear antibody, CSF = cerebrospinal fluid, CT = computed tomography, EEG = electroencephalogram, MRI = magnetic resonance imaging, NMDA = *N*-methyl-D-aspartate, SLE = systemic lupus erythematosus.

leading to metabolic side effects.[12] LAI antipsychotics (eg, depot formulations for haloperidol and fluphenazine decanoates, and later other SGA options) expanded treatment flexibility. In September 2024, a novel treatment for schizophrenia was approved by the FDA, xanomeline-trospium, a muscarinic agonist, which avoids the blockade of postsynaptic D_2 receptors and thus prevents the associated movement and metabolic side effects.[13,14] This medication will be discussed further in a subsequent section.

How Do Antipsychotic Agents Work, and What Symptoms Do They Mitigate Most?

Schizophrenia has a complex neurobiology, for which our collective understanding remains limited.[15] While monoamines (eg, dopamine, serotonin, norepinephrine)

are highly implicated in the disorder, other neurotransmitters (eg, glutamate, acetylcholine) are also involved. Further, each symptom cluster (eg, positive, negative, cognitive) has a unique neurobiology, and there is heterogeneity within each symptom cluster among individuals with schizophrenia. For instance, many patients who meet criteria for treatment-resistant schizophrenia are thought to have aberrancies that are unrelated to dopamine signaling, hence their poor response to conventional treatments.[16] Given these complexities, antipsychotics remain relatively blunt tools that often modulate biology downstream of a poorly understood underlying pathophysiology. Nonetheless, they offer substantial benefits for many individuals with psychotic disorders, and their use remains the standard of care in psychiatry.

Broadly speaking, the unifying mechanism of action among antipsychotics in schizophrenia has been based on dopamine D_2 receptor blockade.[17] Specifically, reduction of dopaminergic activity along the mesolimbic circuit at the striatum is thought to be the mechanism by which antipsychotics treat positive symptoms (ie, delusions, hallucinations, disorganization).[17] However, dopamine dysregulation does not occur in isolation; rather, multiple other neurotransmitter systems, including serotonin, glutamate, and acetylcholine, also modulate dopamine signaling. Serotonin receptor overactivity, particularly at 5-HT_{2A} receptors, and glutamatergic NMDA receptor hypofunction can both increase mesolimbic dopamine firing and suppress mesocortical dopamine activity, contributing to positive and negative symptoms, respectively. Similarly, cholinergic pathways influence dopaminergic tone; for example, muscarinic receptor agonists can decrease mesolimbic dopamine activity, thereby reducing positive symptoms. Off-target dopamine blockade, however, is also responsible for side effects (eg, extrapyramidal symptoms [EPS]) and worsening negative symptoms. Antipsychotic activity at other neurotransmitter receptors (such as those for serotonin, histamine, and acetylcholine) is often responsible for side effects.

Currently, there are 3 antipsychotics (aripiprazole, brexpiprazole, and cariprazine) that act as partial agonists of the D_2 receptor; each contains the letters "pipra" or "ripra," and they are sometimes referred to as "third-generation" antipsychotics.[17] Two antipsychotics have little to no activity at the D_2 receptor: clozapine and xanomeline-trospium.[17] Interestingly, clozapine is the only antipsychotic medication currently approved by the FDA for treatment-resistant schizophrenia despite causing minimal D_2 blockade. The mechanism of clozapine's unique benefits remains somewhat unclear, although imaging studies have demonstrated a decreased glutamate signal in the caudate in response to clozapine administration.[18] Xanomeline-trospium works as a muscarinic agonist at M_1 and M_4 receptors, and it lacks direct dopamine activity. This muscarinic agonism is thought to decrease acetylcholine in the midbrain where dopamine release is facilitated[18]; therefore, in the presence of xanomeline-trospium, dopamine release is reduced, but through a more selective, upstream fashion that spares motor areas, thereby avoiding EPS.

Regarding negative and cognitive symptoms, despite their consequences on real-life functioning,[19] no antipsychotics have consistently been shown to be beneficial (Table 3). Moreover, antipsychotics can worsen negative and cognitive symptoms if there is an excess of off-target dopamine blockade (ie, secondary negative symptoms).[17] Beyond antipsychotic medications, there are no FDA-approved treatments for negative or cognitive symptoms of schizophrenia. Often, the benefits of antipsychotics or other psychotropics on negative or cognitive symptoms are related to other factors (eg, treatment of the positive symptoms or comorbid depression). Nonetheless, pharmacologic treatment and incorporation of psychosocial treatments have been beneficial.[19] Cariprazine may be a preferred antipsychotic for those with prominent negative symptoms, as it has compared favorably with risperidone[20] in a manufacturer-sponsored trial, although it is unclear whether this was an epiphenomenon of cariprazine's therapeutic benefits for depression[21] or a lower risk of inducing secondary negative symptoms.[22]

Are Antipsychotic Agents Equally Efficacious for the Treatment of Psychotic Illnesses?

Assessment of efficacy is important when selecting an antipsychotic medication. Compared to all other antipsychotics, clozapine has superior efficacy. Clozapine is the only antipsychotic that is FDA approved for treatment-resistant schizophrenia. However, a recent meta-analysis revealed that amisulpride, olanzapine, zotepine, and risperidone also had increased efficacy for overall symptom improvement, while the oral formulations of all other FGAs and SGAs have similar efficacy. LAIs have improved efficacy compared to oral formulations, an observation that is likely related to their enhanced treatment adherence.[24] LAIs are also correlated with significant improvements in morbidity and mortality rates.[25] The newest antipsychotic agent, xanomeline-trospium (Cobenfy, Kar-XT), acts upstream from the dopamine receptor targeted by the FGAs and SGAs. Its efficacy compared to placebo has been demonstrated in several time-limited clinical trials.[13,26] However, no head-to-head clinical trials have compared xanomeline-trospium to FGAs and SGAs; thus, their relative efficacy is still unknown. Nevertheless, a meta-analysis reported that xanomeline-trospium had similar efficacy to aripiprazole, risperidone, and olanzapine.[27]

Table 3.

Efficacy of Antipsychotics on Changes in Functioning and Symptoms in Schizophrenia[23]

Class of antipsychotics	Overall change in symptoms	Positive symptoms	Negative symptoms	Cognitive symptoms
First generation				
Chlorpromazine	++	+++	++	++
Fluphenazine	?	?	?	?
Haloperidol	++	+++	+	+
Loxapine	++	?	?	?
Molindone	?	?	?	?
Perphenazine	+++	++	+++	+++
Pimozide	?	?	?	?
Thioridazine	?	?	?	?
Thiothixene	?	?	?	?
Trifluoperazine	+	?	?	?
Second generation				
Clozapine	+++	+++	+++	+++
Asenapine	++	++	+++	+++
Iloperidone	+	+	+	+
Lumateperone	?	?	?	?
Lurasidone	++	+	+	+
Olanzapine	+++	+++	+++	+++
Paliperidone	++	+++	++	++
Pimavanserin	?	?	?	?
Quetiapine	++	++	++	++
Risperidone	+++	+++	++	++
Ziprasidone	++	++	++	++
Third generation				
Aripiprazole	++	+	++	++
Brexpiprazole	+	+	+	+
Cariprazine	+	+	++	++
New generation				
Xanomeline-trospium	?	?	?	?

Symbols: +++ = relatively high efficacy, ++ = relatively moderate efficacy, + = relatively low efficacy, - = unknown, insufficient data, or very low confidence data.

Which Treatment-Related Side Effects Interfere With Tolerability of Antipsychotics and Can Precipitate Life-Threatening Conditions?

Antipsychotic medications have myriad side effects (Table 4), including several that are potentially lethal (eg, neuroleptic malignant syndrome [NMS], QTc prolongation, and constipation). NMS (characterized by the classic tetrad of fever, rigidity, mental status changes, and autonomic instability) necessitates cessation of all antipsychotic medications and rapid treatment. QTc prolongation is common among antipsychotic agents, particularly FGAs, as well as ziprasidone and iloperidone; it increases the risk of torsades de pointes ("twisting of points") that can be lethal. Antipsychotics also cause gastrointestinal (GI) hypomotility that can lead to constipation, ileus, and ischemic bowels and progress to obstruction, toxic megacolon, sepsis, and death. The agents most likely to induce these adverse effects are clozapine and quetiapine.[28] In addition, clozapine has several rare but life-threatening side effects (eg, agranulocytosis, myocarditis, seizures, and orthostatic hypotension). Moreover, all FGAs and SGAs have an FDA "black box warning" regarding the increased risk of death when used in elderly individuals with dementia.

Dopamine-blocking antipsychotics also have a bevy of other adverse effects that interfere with their tolerability (including metabolic changes and weight gain, after extended use).[29] The agents most likely to induce these effects are clozapine and olanzapine, while those with lowest risk include lurasidone,[29] ziprasidone,[29] lumateperone,[30] and xanomeline-trospium.[26] FGAs and SGAs can also cause abnormal movements (ie, EPS, including dystonia, akathisia, and parkinsonism), which typically develop early in treatment, especially with use of high-potency FGAs. A late-developing motoric side effect is tardive dyskinesia, which is characterized by irregular but typically irreversible choreiform movements even after the antipsychotic medication has

Table 4.

Common Side Effects of Antipsychotic Agents

Antipsychotic Class or Agent	Life-threatening side effects	Non–life-threatening side effects
First-generation antipsychotics	• Neuroleptic malignant syndrome • QTc prolongation • Gastrointestinal hypomotility • Black box warning: increased mortality in elderly patients with dementia	• Motor side effects (extrapyramidal symptoms) • Hyperprolactinemia • Sedation (some) • Sexual side effects
Second- and third-generation antipsychotics	• Neuroleptic malignant syndrome • QTc prolongation • Gastrointestinal hypomotility • Black box warning: increased mortality in elderly patients with dementia	• Metabolic side effects (most) • Hyperprolactinemia (some) • Sedation (some) • Sexual side effects
Clozapine	• Agranulocytosis • Myocarditis • Seizures • Orthostatic hypotension • Gastrointestinal hypomotility • Neuroleptic malignant syndrome • QTc prolongation • Black box warning: increased mortality in elderly patients with dementia	• Metabolic side effects • Sedation • Sexual side effects
Xanomeline-trospium	• None reported	• Gastrointestinal (nausea, vomiting, dyspepsia, diarrhea, constipation) • Hypertension

been discontinued. Hyperprolactinemia is also common with use of high-affinity dopamine receptor antagonists, such as the FGAs, risperidone, and paliperidone.[23] Low-affinity medications (eg, aripiprazole, clozapine, and quetiapine) are considered prolactin sparing.[23] FGAs and SGAs can also cause sexual side effects[31] (eg, decreased libido, anorgasmia, and erectile dysfunction), through hyperprolactinemia and D_2, α-1, 5-HT_{2a}, and muscarinic receptor antagonism. Many antipsychotics (especially clozapine, olanzapine, and quetiapine) also cause sedation, which can be severe. Finally, some antipsychotics (eg, chlorpromazine) are potent anticholinergics and can induce cognitive dulling.

Xanomeline-trospium, with central muscarinic agonism and peripheral muscarinic antagonism, has a different side effect profile than FGAs and SGAs. Its most common side effects are GI (eg, nausea, vomiting, dyspepsia, diarrhea, and constipation).[13,26] It can also cause hypertension.[13,26] It is less apt to induce sedation, motor side effects, and weight gain than placebo.[13,26] Prolongation of the QTc interval has not been observed with its use.[26]

What Other Factors Should Be Considered When Selecting an Antipsychotic Agent?

In addition to considering medication efficacy and their side effect profiles, other factors (eg, patient health factors, medical comorbidities, and logistical concerns that affect adherence and access) should be considered when selecting an antipsychotic agent.

Patient health factors include age, race, and family history of treatment response. Regarding age, older adults (especially those with dementia) are at an elevated risk of adverse effects (eg, TD, aspiration events, and mortality in the setting of antipsychotic administration).[32] Nonetheless, they remain first-line treatment options for schizophrenia, although lower doses are often necessary, and closer monitoring is warranted. Moreover, race/ethnicity is associated with a variability in drug response, in part due to polymorphisms of the cytochrome P450 (CYP450) system, which is responsible for much of the metabolism of antipsychotic medications.[33] For instance, 5%–10% of Caucasians are CYP450-2D6 poor metabolizers, compared to 1%–2% of Asians and 2%–5% of African Americans.[34] While antipsychotic selection should not be based solely on these factors, treatment responses differ among certain demographic groups, which merits dose monitoring and adjustment. Because of this metabolic heterogeneity and therefore the clinical response, a family history of effective treatment with an antipsychotic may guide drug selection.

Medical comorbidities (eg, benign prostatic hypertrophy [BPH], a cardiac history, or liver disease) should also be considered when selecting an antipsychotic. For example, highly anticholinergic antipsychotics should be used cautiously in those with medical problems that increase the risk of urinary retention.[35] In individuals with BPH or pelvic organ prolapse, the addition of chlorpromazine, clozapine, olanzapine, or xanomeline-trospium increases the risk of

urinary retention. A cardiac history should also be considered during antipsychotic selection due to the propensity of several cardiac conditions to induce orthostatic hypotension, hypertension, reflex tachycardia, QTc prolongation, torsades de pointes, and myocarditis.[36] For instance, among patients with baseline conduction abnormalities, ziprasidone (the most QTc-prolonging SGA) may not be preferred over an antipsychotic such as aripiprazole (among the least QTc-prolonging of antipsychotics). Lastly, antipsychotic use poses varying risks of hepatotoxicity and to differing degrees hepatic metabolism.[37] Paliperidone, for example, undergoes minimal hepatic metabolism, and reports of liver failure have not been associated with its use, which makes it a potentially preferred antipsychotic agent for those with liver disease.[37]

Logistical factors around dosing should also be considered due to their impact on treatment adherence. For instance, antipsychotics dosed once daily lead to improved adherence.[38] Ziprasidone and xanomeline-trospium are antipsychotics administered twice daily, which may increase the potential for missing doses. Moreover, lurasidone and ziprasidone are the 2 antipsychotics that must be taken with meals (having 350 and 500 calories, respectively); if not taken properly, absorption may be hindered, thus diminishing efficacy.[39,40]

The potential for weight gain varies across antipsychotics and should inform medication selection, particularly in patients at risk for metabolic syndrome. Agents such as olanzapine and clozapine carry the highest risk for weight gain and metabolic disturbances, whereas aripiprazole, ziprasidone, and lurasidone typically have lower risks. In addition, the availability of LAI formulations (eg, risperidone, paliperidone, aripiprazole, and olanzapine) can enhance medication adherence, especially in patients who struggle with maintaining consistent oral medication schedules.

Lastly, many newer antipsychotics (eg, brexpiprazole, cariprazine, lumateperone, pimavanserin, and xanomeline-trospium) tend to be costly or require prior authorization for insurance coverage.[41] By way of contrast, several generic antipsychotics (eg, risperidone, olanzapine, and quetiapine) can be made affordable through programs such as the Walmart $4 List (Table 5).[42]

How Should Dosing Be Initiated, Titrated, Maintained, Tapered, and Discontinued?

In general, it is best to "start low and go slow" when initiating any antipsychotic agent. However, starting at a higher dose should be considered when managing an acute psychotic episode, when lower doses of certain medications are activating (eg, aripiprazole), and when patients are unlikely to accept gradual dose titrations. Patient age and the site of administration (inpatient or outpatient setting) also inform initial dosing decisions. Older adults and individuals treated in outpatient settings may require lower initial doses and more gradual titration, while inpatient settings often allow for closer monitoring and more aggressive dosing when clinically indicated. After establishing that an agent is tolerable (eg, anaphylaxis or dystonia has not developed), the dose should be titrated gradually (while monitoring for adverse effects) until an effective dose has been reached. Throughout the treatment course, symptoms should be assessed while partaking in therapeutic drug monitoring (TDM). TDM is especially helpful when clozapine is being prescribed, as there is a threshold above which clozapine is effective (350 mcg/L) for most people and an upper limit (1,000 mcg/L) above which the risk of seizures may outweigh the drug's antipsychotic benefits.[43] Of note, clozapine blood levels are significantly reduced by cigarette smoking by virtue of its effect on the CYP1A2 pathway, while clozapine doses should be reduced during periods of smoking cessation.

After achieving symptom remission, or at least symptom reduction, the American Psychiatric Association recommends ongoing treatment with antipsychotic medication.[44] The goal of maintenance treatment is to prevent relapse (by using the lowest effective medication dose). Moreover, treatment failure should not be declared until a patient has been taking the medication for an adequate duration. When nonadherence arises in those with schizophrenia-spectrum illnesses, use of LAI antipsychotics can ensure medication adherence, thereby reducing the risk of relapse and rehospitalization. Using LAI antipsychotics should be presented early in the treatment course as a viable and potentially preferred option; moreover, some patients prefer to avoid taking a daily pill.[45]

Tapering of medication doses, whether it is at the patient's insistence or while changing medications, should be done gradually to minimize withdrawal symptoms. The tapering schedule should consider the medication's half-life and receptor affinity. Medications with shorter half-lives (eg, quetiapine) require slower tapering to avoid withdrawal symptoms, while those with long half-lives (eg, aripiprazole) can typically be tapered more rapidly. In addition, slow and gradual tapering is especially important for strong D_2-blocking medications (eg, haloperidol or risperidone), particularly when lowering from low dosages, to prevent withdrawal dyskinesia and psychotic decompensation. Abrupt reduction of clozapine dosing can precipitate a cholinergic crisis, as well as rebound psychosis or catatonia.[46] Close monitoring for symptom re-emergence and manifestations of drug withdrawal is essential; therefore, having a relapse prevention plan or a wellness recovery action plan can help a team to mitigate risks. Unfortunately, some patients are unable to recognize their

Table 5.
Other Considerations for Antipsychotic Selection

Categories	Considerations	Details
Patient health factors	Age	• Older age and dementia confer increased rates of adverse effects • Lower doses and closer monitoring are indicated
	Race/ethnicity	• Variability in cytochrome P450 enzyme metabolism due to polymorphisms occurs across racial/ethnic groups
	Family history of treatment response	• Positive response in family member may confer an increased likelihood of a response
Medical comorbidities	Genitourinary issues	• More potent anticholinergic antipsychotics may confer an increased risk of urinary retention • Consideration should be given to benign prostatic hyperplasia, neurogenic bladder, and pelvic organ prolapse
	Cardiac disease	• Risks of orthostatic hypotension, hypertension, reflex tachycardia, QTc prolongation, torsades de pointes, and myocarditis should be considered
	Liver disease	• Risk of hepatotoxicity is highest with chlorpromazine, clozapine, and olanzapine • Paliperidone undergoes minimal hepatic metabolism and has a low risk of hepatotoxicity
Administration logistics	Dosing schedule	• Twice-daily administration is recommended for ziprasidone and xanomeline-trospium
	Food absorption	• Lurasidone absorption requires co-administration with >350 calories • Ziprasidone absorption requires co-administration with >500 calories
Cost and access	High cost and/or prior authorization is often needed	• Brexpiprazole • Cariprazine • Lumateperone • Pimavanserin • Xanomeline-trospium
	Options included on $4 Walmart List	• Risperidone • Olanzapine • Quetiapine

early warning signs and symptoms of relapse during a psychotic decompensation.[9] Therefore, clinicians should discuss this concept with patients and their family members or support systems early in treatment and prepare a monitoring plan (Table 6).

What Type of Monitoring Is Needed for Antipsychotic Agents?

Table 7[44] summarizes recommended guidelines for monitoring patients on antipsychotic medications, underscoring the importance of integrated psychiatric and medical care in managing schizophrenia and reducing associated health risks. Routine and systematic monitoring is critical for identifying and managing medical complications associated with antipsychotic use. Approximately 40% of patients with schizophrenia develop a metabolic syndrome, which significantly increases their cardiovascular risk compared to those in the general population. Thus, regular surveillance of modifiable cardiovascular risk factors (eg, smoking status, dyslipidemia, diabetes, and weight gain) is essential.[48]

Baseline evaluations (before starting an antipsychotic) should include a complete blood count, a basic metabolic panel (with electrolyte levels, renal and hepatic function), thyroid-stimulating hormone level, and a pregnancy test for women of childbearing potential. Metabolic assessments (eg, weight, BMI, waist circumference, fasting glucose, hemoglobin A1C (HbA1c), lipid panels, and blood pressure) must be performed routinely.

BMI should be assessed at every clinical visit during the initial 6 months of antipsychotic treatment, followed by quarterly checks. Patients with a BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least 1 weight-related comorbidity should be considered for GLP-1 agonist therapy (eg, tirzepatide, semaglutide) for weight management. Waist circumference, fasting glucose, HbA1c, and lipid panels should be measured initially and 4 months after treatment initiation, thereafter at least annually. More frequent monitoring is advised for patients started on high-risk antipsychotics (eg, clozapine and olanzapine).[44]

Metabolic syndrome—defined by the presence of at least 3 of the following: increased waist circumference, triglycerides greater or equal to 150 mg/dL, reduced high-density lipoprotein cholesterol (less than 40 mg/mL in men and less than 50 mg/dL in women), elevated blood pressure (greater or equal to 130/85 mm Hg), and a fasting glucose (greater or equal to 100 mg/dL)—should be checked at baseline, 4 months after initiation, and annually thereafter.[44]

EPS require monitoring via the Abnormal Involuntary Movement Scale at least annually, at a higher

Table 6.

Strategies for Initiating, Maintaining, and Tapering Antipsychotic Agents[9,11,44,47–53]

	Initiation (mg/d)	Maintenance (mg/d)	Maximum (mg/d)	Discontinuation taper	Long-acting injectable options	Comments
First generation						
Chlorpromazine	25–100	200–800	1,000–2000	Slow taper over 6–8 weeks to minimize rebound psychosis	n/a	IM, liquid, and suppository formulations available
Fluphenazine	2.5–10	6–20	40	Recommended for oral	25 mg/1 mL 12.5–50 IM q 2–3 wk	Short-acting injectable formulation available
Haloperidol	1–15	5–20	100	Recommended for oral	50 mg/1 mL 100 mg/1 mL ≥300 IM q 2–4 wk	
Loxapine	20	60–100	250	Recommended	n/a	Liquid and injectable formulations available
Molindone	50–75	30–100	225	Recommended	n/a	Liquid formulation available
Perphenazine	8–16	8–32	64	Recommended	n/a	Injectable formulation available
Pimozide	0.5–2	2–4	10	Recommended	n/a	
Thioridazine	150–300	300–800	800	Recommended	n/a	Liquid formulation available
Thiothixene	6–10	15–30	60	Recommended	n/a	
Trifluoperazine	4–10	15–20	50	Recommended	n/a	
Second generation						
Asenapine	10 3.8 (transdermal)	10–20 3.8–7.6 (transdermal)	20 7.6 (transdermal)	Recommended	n/a	ODT and transdermal patch available
Clozapine	12.5–25	250–450	900	Slow taper to avoid anticholinergic rebound, although discontinuation may need to be abrupt in the setting of neutropenia or myocarditis	n/a	ODT and liquid available Therapeutic drug monitoring is essential for dosing. Target clozapine level should be ~350 mcg/L
Iloperidone	2	12–24	24	Recommended	n/a	
Lumateperone	42	42	42	Not necessary	n/a	10.5 or 21 for strong or moderately potent CYP 3A4 inhibitors or hepatic impairment
Lurasidone	40	40–120	160	Recommended	n/a	Should be taken with >350 kcal
Olanzapine	5	15–20	20 per insert 40 per CATIE trial	Recommended	210–405 mg IM q 2–4 wk *Not in use in most places due to post-injection monitoring requirements*	ODT available
Olanzapine-Samidorphen	5–10	10-10 – 20-10	20–10	Recommended		More metabolically neutral
Paliperidone	3	3–12	12	Recommended for oral	39–236 mg IM q 4 wk 273–819 mg IM q 12 wk 1,092–1,560 mg IM q 26 wk	
Quetiapine	50 IR 300 ER	400–800	800	Recommended	n/a	
Risperidone	2	2–8	8	Recommended for oral	12.5 mg–50 mg IM q 2 wk 50–250 mg SC q 4 or 8 wk	ODT available
Ziprasidone	40	80–160	320	Recommended	n/a	Should be taken with >500 kcal
Third generation						
Aripiprazole	10–15	10–15	30	Recommended for oral, but long half-life and dual agonist/antagonist properties make withdrawal side effects less likely	675 mg IM ×1 loading 441–1,064 mg IM q 4–8 wk 160–400 mg IM q 4 wk 720–960 mg IM q 8 wk	10 mg starting dose for schizophrenia to avoid risk of activation at lower doses; ODT available
Brexpiprazole	1	1–4	4	Not necessary	n/a	
Cariprazine	1.5	1.5–6	6	Not necessary	n/a	
New generation						
Xanomeline-trospium	100/40 (50/20 BID)	200/40	150/60	Recommended	n/a	Take 1 h before or 2 h after eating

Abbreviations: BID = twice a day, CYP = cytochrome P450 isoenzyme, ER = extended release, IM = intramuscular, IR = immediate release, n/a = not applicable, ODT = orally disintegrating tablet, SC = subcutaneous.

Table 7.

Antipsychotic Monitoring Guidelines for Prevention of Medical Morbidity[44]

Medical Monitoring During Antipsychotic Treatment
Establish baseline measures before treatment
• Complete blood cell count
• Chemistry panel (electrolytes, renal function, liver function)
• Thyroid-stimulating hormone
• Pregnancy test for women of childbearing age
Metabolic measures
• Weight, BMI
– BMI at every visit for the first 6 mo, then at least quarterly
• Waist circumference, fasting glucose, HbA1c, and lipid panel
– 4 mo after treatment initiation then at least annually*
• Blood pressure, pulse
– As clinically indicated
Metabolic syndrome
• Establish if the patient meets criteria for a metabolic syndrome at baseline, 4 mo after treatment initiation, and then at least annually
• Three of the following 5 risk factors must be present:
– Elevated waist circumference (>102 cm [40.2 inches] for men and >88 cm [34.6 inches] for women);
– Elevated triglycerides (≥150 mg/dL);
– Reduced HDL-C (<40 mg/dL in men or <50 mg/dL in women);
– Elevated BP (systolic BP ≥130 mm Hg and/or diastolic BP ≥85 mm Hg);
– Elevated fasting glucose (≥100 mg/dL)
Extrapyramidal symptoms
• Abnormal Involuntary Movement Scale
– Assessed at least every 12 mo**
Cardiac monitoring
• Baseline and annual electrocardiogram if the patient is on a high QT-risk antipsychotic (eg, thioridazine, ziprasidone, iloperidone, chlorpromazine) or with cardiac risk factors (eg, history of arrhythmia, recent myocardial infarction, congenital long QT syndrome)
• Prolonged QTc: >500 ms should raise concern
Prolactin monitoring
• Clinical evaluation at every visit
• If symptomatic (eg, menstrual irregularities, galactorrhea, gynecomastia, sexual dysfunction, changes in libido), obtain a serum prolactin level to confirm hyperprolactinemia

*More frequent monitoring may be needed (eg, patients on clozapine or olanzapine).
**More frequent (at least every 6 mo) monitoring in high-risk patients (eg older than 55 y, on first-generation antipsychotics, history of EPS).
Abbreviations: BMI = body mass index, BP = blood pressure, EPS = extrapyramidal symptoms, HDL-C = high-density lipoprotein cholesterol.

frequency (every 6 months) for high-risk patients, including those over the age of 55 years, those receiving FGAs, or those with prior EPS.[44] Patients prescribed antipsychotics that are known to prolong the QT interval (eg, thioridazine, ziprasidone, iloperidone, and chlorpromazine) or those with existing cardiac risk factors should have an electrocardiogram performed at baseline and annually thereafter. QTc intervals that exceed 500 ms are generally considered as clinically significant, although no absolute QTc threshold mandates the discontinuation of an antipsychotic.[44] Individualized clinical decisions should be guided by a comprehensive risk-benefit assessment, particularly considering patient-specific risk factors.

Finally, prolactin-related symptoms should be evaluated at each visit. Serum prolactin levels should be measured when symptoms that suggest hyperprolactinemia (eg, menstrual disturbances, galactorrhea, gynecomastia, sexual dysfunction, or alteration of libido) are present. When elevated, switching to a prolactin-sparing antipsychotic should be considered via shared decision-making.[44]

What Happened to Mr A?

Upon Mr A's inpatient admission, he underwent a comprehensive psychiatric evaluation and was started on xanomeline-trospium at a dose of 50-20 mg twice daily. Laboratory results (including a comprehensive metabolic panel, liver function test, and tests of renal function) were within normal limits, as were his vital signs. He experienced mild nausea and diarrhea, which resolved after 7 days. After tolerating the initial dosage well and showing partial improvement of his psychotic symptoms over the next 2 weeks, his dosage was increased to 100-20 mg twice daily. At this dose, his psychotic symptoms abated without inducing significant adverse effects. After 4 weeks of hospitalization, Mr A was discharged home.

Following discharge, Mr A continued to receive xanomeline-trospium, and he was monitored closely. After about 5 months, he was substantially improved, and his prolactin level (10 ng/mL) normalized, with resolution of gynecomastia and associated distress. He also reported that his cognition and attention improved, which allowed him to engage in cognitively demanding activities (eg, reading and watching movies). He denied having EPS, including akathisia. In addition, he gradually lost weight, which alleviated his metabolic issues. Mr A remains stable on xanomeline-trospium, with regular outpatient monitoring.

CONCLUSION

Although antipsychotics remain relatively blunt tools that often modulate biology downstream of a poorly understood underlying pathophysiology, they offer substantial benefits for many individuals with psychotic disorders, and their use remains the standard of care in psychiatry. In addition, antipsychotics are commonly used off-label for managing acute behavioral issues and psychosis associated with dementia, delirium, substance use, and developmental disorders across inpatient, long-term care, and outpatient settings. The unifying mechanism of action among antipsychotics has been based on dopamine D_2 receptor blockade (ie, reduction of dopaminergic activity along the mesolimbic circuit at the striatum is likely the mechanism by which antipsychotics treat delusions, hallucinations, and disorganization). Two antipsychotics have little to no activity at the D_2 receptor: clozapine and xanomeline-trospium. Off-target dopamine blockade, however, is also

responsible for side effects (eg, EPS) and worsening negative symptoms.

Antipsychotic medications have myriad side effects, including several that are potentially lethal (eg, NMS, QTc prolongation, and GI hypomotility [that can lead to ileus, ischemic bowels, and sepsis], agranulocytosis, myocarditis, and seizures). FGAs and SGAs can also cause abnormal movements (ie, EPS, including dystonia, akathisia, parkinsonism), which typically develop early in treatment, especially with use of high-potency FGAs, as well as TD (a late-developing motoric side effect). Although many newer antipsychotics (eg, brexpiprazole, cariprazine, lumateperone, pimavanserin, and xanomeline-trospium) tend to be costly or require prior authorization for insurance coverage, they may be preferred after undergoing a personalized cost-benefit analysis.

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