PSYCHOSIS CARE IN PRIMARY CARE:

A primary care clinician's guide to psychosis

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PREFACE

I host a weekly online education and consultation service based on the ECHO® model for clinician support. The model revolves around the concept of moving clinically useful information out of ivory towers and into the hands of the many frontline clinicians who could use it.

I've learned from my work in this area that many primary care clinicians are asked to solve clinical problems involving psychosis.

The primary care clinician may be the first medical professional that a person with psychosis sees. And in many cases, the primary care clinician may be the only medical professional available to the patient for the foreseeable future. The primary care clinician may be the one asked to determine the cause of psychosis and to treat it.

This guide aims to help primary care clinicians screen for psychosis, determine underlying causes, and initiate treatment, if necessary, while patients wait for specialist care. To provide straightforward guidance and clear, actionable steps, I've simplified a complicated topic, but I hope that learning these key points will build the foundation for you to feel comfortable discussing and assessing psychosis in your patients.

This guide can help primary care clinicians:

- Understand and recognize psychosis
- Effectively search for medical or pharmacological causes of psychosis
- Initiate treatment for psychosis, if needed
- Prevent and mitigate side effects of psychiatric medications

This guide is also a work in progress. Please do consider sending me your feedback and suggestions for making this a more useful guide for primary care clinicians engaged this important, compassionate work.

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2. PSYCHOSIS IN PRIMARY CARE

A primary care clinician is likely to be the first contact a person with psychosis has with the health care system. Nearly two-thirds of young people with early psychosis make help-seeking attempts in primary care in the six months before first diagnosis (Anderson *et al*., 2013).

Primary care clinicians are well-positioned to help people with psychosis:

- They know their patients' medical histories and can note unusual changes from prior behavior that might otherwise go unnoticed.
- They already have long-term trusting relationships with their patients. That trust is crucial when dealing with a highly stigmatized, often frightening condition.
- They can use their broad medical expertise to evaluate medical causes of psychosis.
- Help from a primary care clinician reduces the need for psychiatric hospitalization and aversive experiences with police and emergency medical services.

In one survey, family physicians estimated that they saw between one and two patients per year with signs and symptoms of first-episode psychosis (Simon *et al.,* 2009). However, a study that interviewed a low-income patient population in the waiting room of a large urban practice found that as many as one in five patients (21%) reported one or more psychotic symptoms (Olfson *et al.,* 2002). The prevalence of psychosis varies in different populations, with higher rates seen in low-income populations experiencing more socioeconomic stressors. The Olfson study also suggests that psychosis in primary care settings may be more common than we realize.

3. WHAT IS PSYCHOSIS?

3.1 Psychosis is a misperception syndrome

Psychosis is best understood as a **misperception syndrome**. It arises when the thinking parts of the brain try to make sense of clusters of misperceptions from the perceiving parts of the brain.

3.2 Mental status findings in psychosis

Psychosis is defined by the presence of hallucinations or delusions. People experiencing psychosis may have hallucinations *or* delusions, although they commonly have both. Psychosis may also be accompanied by severely disorganized thoughts, speech or behavior.

3.2.a Hallucinations

A hallucination is a perception that has the qualities of a genuine perception but occurs without a corresponding external stimulus.

- Auditory hallucinations are the most common type, commonly manifesting as:
  - A distinct voice that seems to be coming from a separate person
  - Unintelligible whispers
  - Running commentary that narrates someone's life
  - Derogatory or unpleasant statements
- Visual hallucinations are the second most common type, typically patterns, shapes or distortions of visual stimuli.
- Olfactory, gustatory and tactile hallucinations are also possible.

3.2.b Delusions

- The DSM-5 defines a delusion as a "fixed belief that is not amenable to change in light of conflicting evidence" (American Psychiatric Association, 2013).
- Delusional beliefs probably develop as the reasoning parts of the brain attempt to make sense of clusters of misperceptions. Ideas of persecution or supernatural forces, for example, may feel true if they can explain odd experiences such as unusual (hallucinated) voices or (misperceived) sense of special significance from ordinarily irrelevant events.
- Delusional ideas are reinforced because they reduce psychological distress that can arise from perplexing misperception events. They are further reinforced by providing a framework for interpreting future misperception events.

There are several common categories of delusional belief. Familiarity with common types of delusional beliefs can help clinicians better explore the nature of their patients' symptoms.

- **Paranoid or persecutory delusions:** This is the most common type of delusion. Being somewhat suspicious may be evolutionarily advantageous to avoid danger. When confronted with clusters of anomalous experiences or perceptions, suspicious beliefs are a common default.

- Delusions involving spirituality, supernatural beings, religion or grandiosity: Beliefs involving special powers or supernatural forces can make sense of the odd experiences that can arise from clusters of misperceptions.
- Referential delusions: These involve seeing or inferring special meaning in ordinary events. Affected people might think that a nod from someone on TV or certain words in a newspaper contain a special message just for them.
- Somatic delusions: These involve unusual, improbable, or impossible beliefs about the body.
- Erotomanic delusions: These involve beliefs that other people, often of higher status, are in love with them.
- Nihilistic delusions: These involve a belief in impending catastrophe or doom.
- Thought insertion: This is the belief that one's own thoughts are being put there by someone else.
- Thought broadcasting: This is the belief that one's thoughts can be heard by others.

3.2.c Disorganized or bizarre thoughts and behaviors

Psychosis may sometimes be accompanied by disorganization.
Ideas conveyed in speech may become tangential, difficult to follow or frankly illogical. Speech may progress to a state of fluent aphasia (sometimes termed "word salad").
Behaviors may appear disorganized, haphazard or purposeless.

3.3 Psychosis is a nonspecific symptom with many possible causes

In many respects, psychosis is very much like fever. It is relatively easy to recognize, yet it has a wide variety of possible underlying causes.
Psychosis can arise as a medication side effect, a symptom of medical illness, or in association with a psychiatric syndrome.

4. SCREENING FOR PSYCHOSIS

Although psychosis is a relatively common condition with better treatment outcomes when detected early, there is currently no validated screening tool for use in primary care settings (Kennedy *et al.,* 2020).

On the other hand, studies have shown that individuals who seek treatment in a primary care setting for nonspecific mental health concerns such as depression, suicidal ideation, obsessive-compulsive symptoms or social isolation are at greater risk of developing psychosis (Sullivan *et al*., 2018).

Although universal screening for psychosis in primary care settings has not been recommended, clinicians should look for signs of psychosis whenever patients:

- Have a positive mental health screen (for depression, anxiety, suicidality, etc.) or
- Show functional decline in school, work or relationships (e.g., lower grades or poor work performance)

Screening for psychosis triggered by nonspecific psychiatric or functional symptoms is especially important when there is a family history of bipolar disorder or psychosis.

4.1 Opening the discussion

I have found the following approach to be helpful when opening a discussion about psychosis:

- Be curious, calm and matter of fact. If you are comfortable, patients are also likely to feel more comfortable talking about their hallucinations and delusions.
- Normalize the experience of misperceptions.
- Start by acknowledging the stress in someone's life. If you are already discussing a positive depression screen, this can naturally lead into talking about how stress and emotional distress can trigger misperceptions.
- Sample scripts:
    - Sometimes when we are under periods of high stress, our thoughts get really intense, and sometimes it can feel like those thoughts are not our own or are coming from somewhere else. Has anything like that been happening for you?
    - Sometimes during periods of intense stress, we can start to see, hear, smell or feel unusual things that don't seem obvious to others. Has anything like that been happening to you?
    - Sometimes it can seem that things aren't really as they seem. Sometimes they can even feel unreal. Has anything like that been happening in your life?
    - Sometimes when people are very stressed, they get a feeling like people are working against them, or that there are people watching them. Has that ever happened to you?
    - Sometimes people feel like they have special powers to deal with difficult situations. Has that ever happened to you?

4.2 The Psychosis Screening Information Tool

A psychosis screening information tool has been developed by the Center for Early Detection, Assessment and Response to Risk (CEDAR) in conjunction with Boston Children's Hospital (BCH) Psychiatry and Adolescent Medicine, the Massachusetts Child Psychiatry Access Project (MCPAP) and the Prevention Collaborative.
It is available online at PsychosisScreening.org.

Their FACTS mnemonic can help recall the symptoms worth asking about:

Functional decline
Atypical perceptual experiences
Cognitive difficulties
Thought disturbance or unusual beliefs
Speech or behavior that is disorganized

They suggest the following screening questions:

- Have you started to wonder if your mind was trying to trick you or was not working right?
- Have you felt confused whether an experience was real or imaginary?
- Have you thought that some person, force or creature was around you, even though you couldn't see anyone?
- Have your thoughts been so strong that you felt like you heard them or worried other people could hear them?
- Have you seen objects, people or animals that no one else could see?
- Have you heard voices or sounds that no one else could hear?
- Have you thought that the world may not be real or that you may not be real?
- Have you thought that people were following or spying on you?

5. THE DIFFERENTIAL DIAGNOSIS OF PSYCHOSIS

Psychosis is a nonspecific symptom. It has a variety of possible causes.
Causes of psychosis can be grouped into three broad categories:

- Adverse effect of therapeutic medications or recreational drugs (chemical psychosis)
- Symptom of physical (organic) disease (medical psychosis)
- Symptom of a psychiatric syndrome (psychiatric psychosis)

5.1 Chemical psychosis

Psychosis can occur as a side effect of a medication, an herbal supplement or a recreational drug.

The table below (adapted from Ambizas, 2014) illustrates that a wide range of medications with varied mechanisms of action may cause psychosis in some individuals.

Analgesics	NSAIDs, Opioids, Tramadol
Antibiotics	Cephalosporins, Chloramphenicol, Clarithromycin, Cycloserine, Dapsone, Erythromycin, Fluoroquinolones, Isoniazid, Metronidazole, Streptomycin, Trimethoprim/Sulfamethoxazole
Antimalarials	Chloroquine, Mefloquine
Antivirals	Acyclovir, Didanosine, Efavirenz, Ganciclovir, Oseltamivir, Valganciclovir, Zidovudine
Cardiovascular	ACE inhibitors, Alpha-2 agonists, Anti-arrhythmics, Beta-blockers, Calcium channel blockers, Digoxin
Endocrine	Anabolic steroids, Corticosteroids
Gastrointestinal	H2 receptor antagonists, Proton pump inhibitors
Muscle relaxants	Baclofen, Cyclobenzaprine, Tizanidine
Neurological	Amantadine, Anticholinergics, Anticonvulsants, L-DOPA, Dopamine receptor agonists (e.g., bromocriptine, pramipexole, ropinirole), Modafinil
Miscellaneous	Antihistamines, Barbiturates, Dextromethorphan, Disulfiram, Erythropoietin, Pseudoephedrine, Sildenafil

Drug-induced psychosis can usually be recognized by temporal associations. It is most common when a drug is started, but it can also occur when a drug is withdrawn. Creating a timeline of symptoms, life events, and drug prescription and consumption is extremely helpful.

Two classes of drugs – ADHD medications and cannabis – deserve additional discussion based on their popularity and frequent underestimation of psychosis risk.

5.1.a Psychosis risk from stimulants

ADHD is commonly treated with stimulants such as amphetamine, amphetamine derivatives or methylphenidate. These drugs augment dopamine signaling by promoting dopamine release and inhibiting its reuptake. Drugs that augment dopamine signaling are always associated with increased psychosis risk.

Clinical trials that supported FDA approval estimated a 0.1% risk of stimulant-induced psychosis (Adderall XR prescribing information). But these short-term studies of patients without significant comorbid illness or family histories of mental illness may underestimate the risk of psychosis from therapeutic doses of stimulants in clinical settings. 6.1% of children being treated with stimulants for ADHD developed psychosis in a naturalistic observational study, for example (Cherland & Fitzpatrick, 1999).

5.1.b Psychosis risk from cannabis

User-experience surveys reveal the ability of cannabis to cause psychosis. Between 6% to 51% of cannabis consumers have experienced paranoia from their use, while 2% to 20% have experienced hallucinations (Green *et al.*, 2003).

Human laboratory studies repeatedly show that cannabis, cannabis extracts or THC produce symptoms of psychosis in healthy volunteers (Sherif *et al.*, 2016). And double-blind, placebo-controlled clinical trials of THC elicited paranoia or hallucinations in a subset of volunteers (Marinol prescribing information, 2017).

Glutamate is the brain's most widely used neurotransmitter molecule, and glutamate signaling distortion probably explains THC-induced psychosis. A recent magnetic resonance spectroscopy study found that healthy volunteers who experienced psychosis from THC had abnormal baseline levels of glutamate metabolites and greater glutamate perturbation compared to volunteers who did not develop psychosis (Colizzi *et al.*, 2020).

5.1.c Substance-induced psychosis may predict increased risk of severe mental illness

Substance-induced psychosis is associated with subsequent development of bipolar disorder or schizophrenia. Rates vary according to the substance. A meta-analysis of 50 different studies involving 34,244 people diagnosed with an episode of substance-induced psychosis (Murrie *et al.*, 2020) found the following degrees of risk:

SUBSTANCE THAT CAUSED AN EPISODE OF SUBSTANCE-INDUCED PSYCHOSIS	RISK OF LATER DEVELOPING SCHIZOPHRENIA
Cannabis	34% likelihood
Hallucinogens	26% likelihood
Amphetamines	22% likelihood
Opioids	12% likelihood
Alcohol	10% likelihood
Sedatives	9% likelihood

5.2 Medical psychosis

The differential diagnosis of psychosis includes a wide range of nonpsychiatric medical illnesses, including:

- Autoimmune: lupus, celiac disease, Hashimoto's encephalopathy, anti-NMDA receptor encephalitis, other autoimmune encephalitides
- Endocrine: thyroid disease, parathyroid disease, Addison's disease, Cushing's disease
- Genetic: Wilson's disease, Fabry's disease, homocystinuria, porphyria, Huntington's disease, Klinefelter's syndrome, tuberous sclerosis, velocardiofacial syndrome
- Infectious: encephalitis, neurosyphilis, cerebral malaria, HIV
- Neoplastic: brain tumors, paraneoplastic syndrome
- Neurologic: cerebrovascular lesions, cranial trauma, hydrocephalus, meningioma, multiple sclerosis
- Nutritional: vitamin D deficiency, zinc deficiency, pernicious anemia, pellagra
- Toxins: heavy metal toxicity

5.2.a Medical causes of psychosis can be easily missed

- Psychosis may be the first sign of a medical illness, appearing before other symptoms have developed.
- Psychosis may be part of an atypical presentation of a common illness.
- Psychosis may so grab the attention of patients, families and clinicians that more subtle physical signs or symptoms may be missed, or mistakenly attributed to psychosis.
- Regrettably, cognitive biases may lead to premature conclusions that a patient's psychosis has a psychiatric origin.
- Also regrettably, physical exams, neurological exams and comprehensive laboratory testing is often minimized or neglected at specialized mental health care centers.

5.2.b Frequency of medical causes of psychosis

The true frequency of medical causes of psychosis is unknown. However, the following studies suggest that medical causes of psychosis are common enough to always justify meticulous medical evaluation.

- One of every eight patients admitted to a hospital psychiatric ward had medical illness that either caused or exacerbated psychiatric symptoms. 80% of those medical diagnoses were initially missed (Johnson, 1968).
- After undergoing a standardized battery of medical tests, 60% of psychiatric inpatients had a previously undetected medical disease that caused or worsened their psychosis (Hall *et al.,* 1980).
- Consistently applying a standardized testing panel detected underlying medical disease as the cause of first-episode psychiatric symptoms in 60% of 100 consecutively screened individuals (Henneman *et al.*, 1994).
- In an emergency department patient sample, medical disease was the cause of psychosis in over one-third of studied cases (Etlouba *et al.*, 2018).

- One of every 18 patients in a first-episode psychosis program had a medical cause of their psychosis (Johnstone *et al.,* 1987).
- 6% to 10% of patients with schizophrenia had clinically unsuspected brain lesions deemed probably relevant to psychiatric symptoms (Falkai, 1996).

"Medical psychosis" cannot be distinguished from "psychiatric psychosis" based on the type or nature of psychotic symptoms.

5.3 Psychiatric psychosis

Psychosis is associated with several distinct psychiatric syndromes. It should not be assumed that someone experiencing psychosis has schizophrenia. Identifying the particular psychiatric condition that may be present can better inform treatment planning and prognostic expectations. The following psychiatric conditions are associated with the possibility of psychosis:

5.3.a Schizophrenia

- Defined by the presence of psychosis accompanied by functional decline that has persisted for at least six months and cannot be better explained by the effects of drugs, medical illness or other psychiatric condition.

5.3.b Schizophreniform disorder

- Similar to the diagnostic criteria for schizophrenia, but with symptom duration of less than six months.

5.3.c Brief psychotic disorder

- Psychosis, lasting between one day and one month, that is not explained by the effects of drugs or medical illness.

5.3.d Delusional disorder

- Delusional disorder is defined by at least one month of one or more delusions without any other prominent symptoms of psychosis.

5.3.e Major depressive disorder

- Major depressive episodes are characterized by at least two weeks of persistent sad or low mood, along with: decreased energy; changes in appetite, sleep or activity level; thoughts of guilt, worthlessness, hopelessness, death or suicide.
- Up to 18% of individuals with major depressive disorder report delusions or hallucinations (Ohayon & Schatzberg, 2002)

5.3.f Bipolar disorder

- Bipolar disorder is defined by the presence of manic episodes. Episodes of mania may alternate with episodes of depression.
- A manic episode is defined by at least one week of persistently elevated mood along with an unusually high level of energy and activity. Manic episodes are typically accompanied by decreased need for sleep, increased talkativeness, grandiosity, impulsivity or irritability.
- Psychosis occurs in 20% to 50% of patients with acute bipolar mania (Keck *et al.*, 2003)

5.3.g Borderline personality disorder

- A central feature of borderline personality disorder is the experience of intense emotions and a high degree of emotional reactivity.
- Borderline personality may also involve: poor sense of identity, chronic feelings of emptiness, frantic efforts to avoid real or imagined abandonment, inappropriate or intense anger, patterns of intense yet unstable interpersonal relationships, impulsive or reckless behavior, or recurrent suicidal threats, gestures or self-injurious behavior.
- Diagnostic criteria for borderline personality disorder acknowledge that transient, stress-related paranoid ideation may occur (American Psychiatric Association, 2013).
- A recent study (Slotema *et al.*, 2018) found psychotic disorders in 38% of people with borderline personality disorder.

5.3.h Post-traumatic stress disorder (PTSD)

- Although psychotic symptoms are not part of the diagnostic criteria for PTSD, studies have shown that a portion of people with PTSD will experience hallucinations or delusions (usually persecutory) independently of flashbacks or dissociative episodes.
- PTSD with secondary psychotic features (PTSD-SP) is emerging as a diagnostic entity (Hamner, 2011).
- Psychotic symptoms may occur in 15% to 64% of people with PTSD (Gaudiano & Zimmerman, 2010).

6. MEDICAL WORKUP OF PSYCHOSIS

Medical causes of psychosis need to be ruled out before psychiatric causes may be considered.

6.1 History and physical exam

In addition to details about the onset and nature of psychosis symptoms, the history should include details about sleep, appetite, mood and level of subjective energy or activity. Ask about thoughts of death or suicide. Inquire about factors that may aggravate or alleviate symptoms. It is extremely helpful to construct a timeline with best-estimate dates of symptom onset or offset.

A detailed history of medication use, supplement use and recreational substance use is important because it may reveal associations with onset or offset of psychiatric symptoms. Making a medication/supplement/drug use timeline is the most effective way to determine if psychosis has been externally induced.

Family history should include not only psychiatric symptoms or diagnoses among relatives, but also a history of medical diseases.

Patients should receive a complete physical exam. Because psychosis can arise from dysfunction in a broad range of physiological systems, there is no such thing as a focused exam when looking for a medical explanation for psychosis.

Patients should receive a complete neurological exam. It is worthwhile to look for cortical release signs (primitive reflexes) such as the palmomental reflex, grasp reflex, snout reflex and glabellar tap sign. These are nonspecific signs, but if a person has them or other focal neurological deficits, it suggests that there may be intracranial pathology that merits further workup, including a brain MRI.

6.2 Lab tests and imaging

There is universal agreement that laboratory testing and imaging should be included in the medical workup of psychosis. There is no consensus, however, about what constitutes an adequate laboratory or imaging panel for detecting or ruling out medical causes.

The following table lists the tests recommended in four different published guidelines.

CATEGORY	TEST	COLEMAN AND GILLBERG, 1997	FREUDENREICH ET AL., 2009	ROYAL AUSTRALIA AND NEW ZEALAND COLLEGE OF PSYCHIATRISTS (GALLETLY ET AL., 2016)	AMERICAN PSYCHIATRIC ASSOCIATION (KEEPERS ET AL., 2020)
Standard blood	Complete blood count	✔	✔	✔	✔
	Electrolytes	✔	✔	✔	✔
	Calcium	✔	✔		
	Phosphorus	✔			
	Kidney function tests	✔	✔		✔
	Liver function tests	✔	✔	✔	✔
	Lipid panel	✔	✔		✔
	Fasting blood glucose	✔	✔		✔
Hormone-related	Thyroid stimulating hormone (TSH)	✔	✔		✔
	Prolactin level		Consider		If indicated on the basis of clinical history
	Pregnancy test		In women of childbearing age		For women of childbearing potential
Inflammation-related	Erythrocyte sedimentation rate		✔	✔	
	Antinuclear antibody	✔	✔		
	Anti-NMDA receptor antibodies			✔	
	Anti-voltage-gated potassium channel antibodies			✔	
	Anti-glutamic acid decarboxylase antibodies			✔	

CATEGORY	TEST	COLEMAN AND GILLBERG, 1997	FREUDENREICH ET AL., 2009	ROYAL AUSTRALIA AND NEW ZEALAND COLLEGE OF PSYCHIATRISTS (GALLETLY ET AL., 2016)	AMERICAN PSYCHIATRIC ASSOCIATION (KEEPERS ET AL., 2020)
Infection-related	Hepatitis C		Consider	Hepatitis screen, if indicated	
	HIV test		✔	If indicated	
	Syphilis screen (FTA)	✔	✔ (Specifies that the fluorescent treponema antibody (FTA) test is to be used)	Screening for sexually transmitted diseases, if indicated	
Metabolic, deficiency	Ceruloplasmin	✔	✔		
	Copper	✔			
	Zinc	✔			
	Vitamin B12	✔	✔		
	Vitamin A	✔			
	Vitamin D (1,25-dihydroxy)	✔			
	Methionine	✔			
	Phenylalanine	✔			
	Heavy metals testing		If indicated		
	Mature RBC porphobilinogen deaminase				
	Saturated very long chain fatty acids (males only)	✔			
	Lymphoblast alpha-galactosidase (males only)	✔			
Urine	Drug test	✔	✔	✔	If clinically indicated
	24-hour copper	✔			
	24-hour amino acids	✔			
	24-hour vitamin B3 end-products	✔			
	24-hour adrenal steroids	✔			

CATEGORY	TEST	COLEMAN AND GILLBERG, 1997	FREUDENREICH ET AL., 2009	ROYAL AUSTRALIA AND NEW ZEALAND COLLEGE OF PSYCHIATRISTS (GALLETLY ET AL., 2016)	AMERICAN PSYCHIATRIC ASSOCIATION (KEEPERS ET AL., 2020)
Imaging	Brain imaging	✔	✔ MRI preferred over CT	✔	If indicated on the basis of neurological examination or history (MRI preferred over CT)
	Chest X-ray	✔	If indicated		
Other tests	Electroencephalogram (EEG)	✔			
	Lumbar puncture		If indicated		
	Chromosomal testing		If indicated		If indicated on the basis of physical examination or history, including developmental history
	Electrocardiogram		Recommended for anyone thought to have cardiac risk factors		If cardiac risk factors are present, or before treatment with chlorpromazine, droperidol, iloperidone, pimozide, thioridazine or ziprasidone
	Psychometric testing			If possible	

6.3 When is imaging indicated?

The American Psychiatric Association (APA) does not recommend brain imaging unless indicated on the basis of neurological examination or history (Keepers *et al*., 2020). However, the APA does not specify the kinds of neurological findings that would indicate imaging.

The APA position seems to imply that psychosis is not a neurological symptom. Yet psychosis can indicate dysfunction in brain regions such as the frontal lobe, cingulate gyrus or temporal lobe, and that these brain regions often do not produce sensory, motor or coordination deficits when damaged.

I share the views of Coleman and Gillberg (1997), Freudenreich *et al.* (2009), and the Royal Australia and New Zealand College of Psychiatrists that psychosis itself is an indication for brain imaging.

6.4 The tests I recommend

I recommend the following tests to search for medical causes of psychosis:

- Complete blood count with differential
- Electrolytes panel
- Calcium
- Renal function tests
- Liver function tests
- Lipid panel
- Fasting blood glucose
- Thyroid stimulating hormone (TSH)
- Thyroid peroxidase antibody
- C-reactive protein
- Erythrocyte sedimentation rate
- Antinuclear antibody
- Autoimmune encephalitis panel, serum
  (this includes: anti-NMDA receptor antibodies; anti-voltage-gated potassium channel antibodies; and anti-glutamic acid decarboxylase antibodies)
- Tissue transglutaminase IgA and total IgA level
- Gliadin antibodies (IgA and IgG)
- HIV screen
- Syphilis screen using fluorescent treponemal antibody (FTA) method
- Ceruloplasmin
- Drug test (urine or serum)
- Brain imaging (MRI with contrast is preferred)

My list contains two tests (thyroid peroxidase antibody and tissue transglutaminase antibody) that don't appear in other published guidelines.

Thyroid peroxidase antibody is elevated in over 90% of cases of Hashimoto's thyroiditis. While the test has a false positive rate of up to 20%, a positive result may indicate steroid responsive encephalopathy with autoimmune thyroiditis, which can be treated with a brief course of steroids to reverse psychosis (Laurent *et al.*, 2016). A positive thyroid peroxidase screen should prompt a thorough search for neurological symptoms that might support a diagnosis of encephalopathy.

My rationale for tissue transglutaminase and gliadin antibodies is to screen for early celiac disease or non-celiac gluten sensitivity. Case reports have described individuals who experienced schizophrenia-like psychosis for many years before gastrointestinal manifestations of celiac disease (Jansson *et al.*, 1984; De Santis *et al.*, 1997). Seropositivity to these antibodies is about seven-fold higher in people with schizophrenia compared to the general population (Cascella *et al.*, 2011). Several small studies

and case reports have shown that gluten-free diets, grain and dairy-free diets, and ketogenic diets may reduce symptoms of psychosis in some individuals (Severance *et al.*, 2016)

It's important that a thorough medical workup be completed for everyone with psychosis before diagnosing a psychiatric condition. Missing a medical cause of psychosis may prolong psychiatric symptoms and needlessly expose people to medications that can cause significant side effects.

7. MEDICATIONS, GENERAL CONSIDERATIONS

If timely access to psychiatric specialty care is unavailable, primary care clinicians may opt to prescribe antipsychotic medications. This section will focus on a few of the most widely prescribed antipsychotic medications. Because there are not any significant differences in the effectiveness of the various first-line antipsychotic medications, primary care clinicians familiar with just a handful of the available options can effectively treat psychosis.

7.1 Typical versus atypical antipsychotic medications

Following the dopamine hypothesis of psychosis, the first generation of antipsychotic drug development produced a variety of drugs that had dopamine receptor antagonism as a common mechanism of action. Because they all blocked dopamine receptors, they possessed a similar set of neurological side effects that were "typical" of dopamine receptor blockade.

The serendipitous discovery of clozapine revealed that it was possible to reduce or eliminate psychosis with minimal risk of neurological side effects. This "atypical" side effect profile is based on combining dopamine receptor antagonism with serotonin receptor antagonism. Although they have lower risks of neurological side effects, this advantage may disappear when atypical antipsychotic drugs are used at higher doses.

Broadly speaking, "typical" (first-generation) antipsychotic drugs are based on dopamine receptor antagonism. "Atypical" (second-generation) drugs are based on combined dopamine and serotonin receptor antagonism." With the exceptions of clozapine and, to a lesser extent, olanzapine, there are not significant differences in efficacy between typical and atypical drugs. There are, however, significant differences in side effect profile between the two subcategories. Neurological side effects are more likely from typical antipsychotics.

7.2 Dosing considerations

Many people with a first episode of psychosis who have not taken antipsychotics before respond to relatively low medication doses. They also tend to be more sensitive to side effects.

Pharmacotherapy guidance from the NIH's NAVIGATE study of first-episode psychosis recommended starting antipsychotic medication dose at 50% of the lower range of the recommended on-label dose. Starting at lower doses minimizes the risk of side effects.

Within approved dosing ranges, higher doses generally do not improve response rates or accelerate recovery.

7.3 Relative risk comparisons

Although the various antipsychotic drugs have similar efficacy at reducing psychosis, there is considerable variability in their side-effect risk. The following table is a summary of relative risk of important side effects from several commonly prescribed antipsychotic medications.

	WEIGHT GAIN	DYSLIPIDEMIA	ELEVATED PROLACTIN	NEUROLOGICAL SIDE EFFECTS	SEDATION	QTC PROLONGATION	ORTHOSTATIC HYPOTENSION
Aripiprazole	+	+	-	+	+	+	-
Risperidone	+++	+	+++	+++	++	++	+
Paliperidone	+++	+	+++	+++	+	++	++
Ziprasidone	+	+	+	++	+	+++	+
Lurasidone	+	+	+	++	+	+	+
Olanzapine	++++	++++	+	++	++	++	+
Quetiapine	+++	+++	+	+	++	+++	++

8. SPECIFIC MEDICATION INFORMATION

There may be clinical situations in which primary care clinicians will want to prescribe medications to relieve symptoms of psychosis. The following brief summaries highlight important clinical features of a select number of medications commonly used in the treatment of psychosis. Clinicians should review the complete prescribing information before prescribing.

8.1 Antipsychotic medications

8.1.a Aripiprazole

Aripiprazole (Abilify) is a high-affinity partial agonist at the dopamine D2 receptor. This means that aripiprazole, at relatively low concentrations, can attach itself to the D2 receptor and partly activate the receptor rather than fully block it. Aripiprazole limits the receptor to about 30% of its full signal-transducing potential. Thus, in high-dopamine environments, aripiprazole reduces the overall dopamine signal strength. Meanwhile, in low-dopamine environments, aripiprazole may augment dopamine signaling.

Aripiprazole offers the following potential benefits:

- Aripiprazole efficacy is similar to other first-line antipsychotic medications
- Long-acting injectable formulations are available. Patients who respond well to aripiprazole and wish to continue it can transition to once-a-month or once-every-two-month injections.
- Compared to other antipsychotic drugs, aripiprazole's weight gain risk is in the lower third of relative risk.
- Aripiprazole's hyperprolactinemia risk is negligible.
- With a very long half-life (approximately 72 hours), the impact of a missed dose is diminished.
- Its long half-life allows for once-daily dosing.
- It is not necessary to take with food.
- Compared to quetiapine (Seroquel) and ziprasidone (Geodon), aripiprazole had higher rates of long-term adherence, suggesting a better combination of efficacy and side-effect experience (Gómez-Revuelta *et al.*, 2018).

Aripiprazole dosing

- Many psychiatrists initiate aripiprazole treatment at 2 mg or 5 mg daily and work up to 10 to 15 mg daily as needed, waiting one to two weeks between dose adjustments.
- 30 mg/day is the maximum FDA-approved dose.

Common adverse reactions to aripiprazole in short-term clinical trials of aripiprazole in adults with schizophrenia or bipolar disorder were:

- Akathisia (8% to 13%)
- Sedation (8%)
- Restlessness (6%)
- Tremor (6%)
- Extrapyramidal disorder (5%)

8.1.b Risperidone

Risperidone (brand name Risperdal) is an atypical antipsychotic drug. It is a high-affinity dopamine D2 receptor antagonist and serotonin 2A receptor antagonist.

A long-acting injection formulation is available. Patients who respond well to risperidone and wish to continue it can transition to a once-every-two-weeks injection.

Risperidone dosing

The manufacturer's recommended initial dose for adults with schizophrenia is 2 mg/day; and 2 mg/day to 3 mg/day for adults with bipolar disorder. The manufacturer-recommended starting dose of adolescents is 0.5 mg/day.

Risperidone's effective dose range is between 1 mg/day to 6 mg/day.

Common adverse reactions to risperidone in short-term clinical trials in adults with schizophrenia or bipolar disorder were:

- Parkinsonism (12% to 20%)
- Anxiety (16%)
- Somnolence (12% to 14%)
- Somnolence (12%)
- Dystonia (5% to 11%)
- Dizziness (10%)
- Dyspepsia (10%)
- Akathisia (5% to 9%)
- Nausea (5% to 9%)
- Tremor (6%)

Risperidone's weight gain risk is in the middle third of relative risk.

8.1.c Paliperidone

Paliperidone (brand name Invega) is an atypical antipsychotic drug. It is a high-affinity dopamine D2 receptor antagonist and serotonin 2A receptor antagonist. Its chemical name is 9-hydroxyrisperidone. It is the major active metabolite of risperidone.

A long-acting injection formulation is available. Patients who respond well to paliperidone and wish to continue it can transition to a monthly injection, or a once-every-three-months injection, or a once-every-six-months injection.

Paliperidone dosing

The manufacturer's recommended initial dose for adults with schizophrenia is 6 mg/day. The manufacturer-recommended starting dose of adolescents with schizophrenia is 3 mg/day. The recommended maintenance dose if 3 mg to 6 mg/day.

Common adverse reactions to paliperidone in clinical trials in adults with schizophrenia or schizoaffective disorder were:

- Extrapyramidal symptoms (7% to 20%)
- Tachycardia (14%)
- Somnolence (6% to 12%)
- Akathisia (4% to 10%)

Paliperidone's weight gain risk is in the middle third of relative risk.

8.1.d Ziprasidone

Ziprasidone (brand name Geodon) is an atypical antipsychotic drug.
Compared to other options, ziprasidone has relatively lower risks of weight gain or neurological side effects.

Ziprasidone dosing

The manufacturer's recommended initial dose for adults with schizophrenia is 20 mg every 12 hours with food. The dose may be increased to a maximum of 80 mg every 12 hours with food.
It is very important that ziprasidone be taken with food. Bioavailability is decreased by about 50% if ziprasidone is taken on an empty stomach.

Common adverse reactions to ziprasidone in short-term clinical trials in adults with schizophrenia or bipolar disorder were:

- Somnolence (14% to 31%)
- Extrapyramidal symptoms (14% to 31%)
- Dizziness (16%)
- Akathisia (8% to 10%)
- Nausea (10%)
- Asthenia (5% to 6%)
- Abnormal vision (3% to 6%)

Ziprasidone can prolong the QT interval in dose-dependent fashion. Less than 1% of people taking ziprasidone experience significant QT prolongation (Camm *et al.*, 2012). Ziprasidone should be avoided in patients with long QT intervals, or in those taking other drugs with the potential to prolong the QT interval.

Ziprasidone's weight gain risk is in the lower third of relative risk.

8.1.e Lurasidone

Lurasidone (brand name Latuda) is an atypical antipsychotic drug. It is structurally similar to ziprasidone but does not require BID dosing and does not significantly affect the QT interval.

Lurasidone dosing

Lurasidone's recommended starting dose is 40 mg daily. The maximum recommended dose is 160 mg/day.

Lurasidone should be taken with food. Its bioavailability is reduced by approximately 50% if lurasidone is taken on an empty stomach.

Common adverse reactions to lurasidone in short-term clinical trials in adults with schizophrenia or bipolar disorder were:

- Somnolence (7% to 26%)
- Akathisia (6% to 22%)
- Extrapyramidal symptoms (5% to 22%)
- Nausea (7% to 17%)

Lurasidone's weight gain risk is in the lower third of relative risk.

8.1.f Olanzapine

Olanzapine (brand name Zyprexa) is an atypical antipsychotic drug. Olanzapine appears to have slightly higher efficacy than other first-line antipsychotic drugs, but also carries significantly higher risk for weight gain.

Olanzapine dosing

The manufacturer's recommended initial dose for adults with schizophrenia is five to 10 mg/day, with a target dose of 10 mg/day within several days. The manufacturer states that the effective dose range for schizophrenia is 10 mg to 15 mg/day. The manufacturer also states that doses above 10 mg/day are not likely to be more effective than the 10 mg/day dose.

Common adverse reactions to olanzapine in short-term clinical trials in adults with schizophrenia or bipolar disorder were:

- Somnolence (35%)
- Extrapyramidal symptoms (8% to 32%)
- Dry mouth (22%)
- Asthenia (lack of energy, strength) (15%)
- Dizziness (11% - 18%)
- Constipation (9% - 11%)
- Dyspepsia (11%)

- Non-aggressive objectionable behavior (8%)
- Increased appetite (6%)
- Weight gain (6%)
- Postural hypotension (5%)
- Akathisia (5%)

Olanzapine's weight gain risk is in the upper third of relative risk.

8.2 Psychosis associated with bipolar mania

Psychosis is present in approximately 50% of cases of mania. The presence of mania indicates a diagnosis of bipolar disorder. Except for lurasidone (which is not approved for bipolar mania), any of the antipsychotic medications described above can effectively treat bipolar mania.

8.3 Psychosis associated with major depressive episode

Antidepressants are strongly recommended for anyone with severe major depressive disorder that is associated with psychosis. Psychosis associated with depression often improves once the depression improves. An SSRI or SNRI antidepressant combined with aripiprazole work well together for treating psychotic depression or treatment-resistant depression.

8.4 Trazodone

Sleep disruption is relatively common in people experiencing psychosis. Trazodone is commonly used, both in primary care practice and psychiatric practice, to promote sleep. Although trazodone is usually well-tolerated and successful, one of its metabolites is m-chlorophenylpiperazine (mCPP), which can occasionally worsen psychiatric symptoms. Patients offered trazodone should be monitored for unexpected worsening of mental status.

8.5 Benzodiazepines

The experience of psychosis can be intensely distressing and anxiety-provoking. (Imagine, for example, how you might feel if you perceive a snake moving within your abdomen and moving toward your heart). Benzodiazepines can alleviate anxiety effectively and rapidly. They can also promote sleep. And benzodiazepines have been used for decades to treat antipsychotic-induced restlessness (akathisia).

8.6 Medications to manage side effects

8.6.a Benztropine

Benztropine (brand name Cogentin) is a CNS-permeable antagonist at the muscarinic subtype of the acetylcholine receptor. It belongs to a drug category commonly termed "anticholinergic" though it would more precisely be termed "antimuscarinic."

Benztropine is FDA-approved for treating symptoms of Parkinson's disease. It is also approved for treating drug-induced extrapyramidal symptoms. In practice, benztropine is useful for reducing or eliminating drug-induced parkinsonism (tremor, rigidity, bradykinesia) or acute dystonic reactions to antipsychotic medications.

It is effective at doses of 0.5 mg or 1 mg, once or twice daily.

Typical of any centrally acting antimuscarinic agent, primary side effects of benztropine include: dry mouth, urinary retention, constipation, tachycardia, and short-term memory impairment. It should be avoided in patients with closed-angle glaucoma.

8.6.b Diphenhydramine

Diphenhydramine (brand name Benadryl) is a first-generation antihistamine. Diphenhydramine is also a competitive antagonist at the muscarinic acetylcholine receptor. Because of its antimuscarinic activity, diphenhydramine can alleviate, eliminate or prevent the extrapyramidal side effects of antipsychotic medication.

Diphenhydramine doses of 25 mg to 50 mg once or twice daily may be effective. It may be given as frequently as every 4 to 6 hours.

In addition to its potential for sedation, the side-effect risks of diphenhydramine are similar to those of benztropine.

8.6.c Amantadine

Amantadine was developed as an antiviral drug. Its pharmacological effects are complex. Amantadine is a weak non-competitive antagonist of the NMDA subtype glutamate receptor. Amantadine can also increase extracellular dopamine levels. Its mildly pro-dopamine effects make amantadine a useful treatment for Parkinson's disease and for drug-induced extrapyramidal effects.

Amantadine can reduce, eliminate or prevent drug-induced parkinsonism or dystonia. It is typically dosed at 100 mg twice daily for this purpose.

The most common side effects of amantadine are: orthostatic hypotension, syncope, dizziness, dry mouth, constipation and peripheral edema. Though uncommon, amantadine can produce livedo reticularis, which is reversible upon discontinuation. Amantadine may also produce delusions or hallucinations in a small number of cases.

Adverse effects from amantadine are nonetheless uncommon, and amantadine appears to have a more favorable tolerability profile than antimuscarinic medications (Caroff *et al.*, 2020).

9. MINIMIZING SIDE EFFECTS

The antipsychotic medications have a relatively complex side-effect profile that includes some potentially serious outcomes. However, it is possible to prescribe these medications in ways that minimize risk.

9.1 Categories of common side effects: Neurological, metabolic, endocrine

The common side effects of antipsychotic medications can be grouped into three categories: neurological, metabolic or endocrine.

The **neurological side effects** are also called extrapyramidal side effects. They are caused by dopamine receptor antagonism. The neurological (extrapyramidal) side effects include:

- Drug-induced parkinsonism
- Dystonic reaction
- Akathisia
- Tardive dyskinesia

The metabolic side effects of antipsychotic medications revolve around dysregulation of glucose metabolism. They are partly related to the blockade of histamine or serotonin receptors. The metabolic side effects of antipsychotic medication include:

- Increased appetite
- Weight gain
- Hyperglycemia
- Dyslipidemia

The endocrine side effects of antipsychotic medications include hyperprolactinemia and insulin dysregulated insulin signaling. Hyperprolactinemia risk is a consequence of dopamine receptor antagonism. The mechanism(s) underlying insulin signaling disturbance is not understood.

9.2 General strategies to minimize side effects

Broadly speaking, there are four possible methods for reducing side-effect risk:

1) Choosing lower-risk medications
2) Minimizing dose
3) Switching to a different medication
4) Adding a medication to reduce the side effect

9.2.a Choosing lower-risk medications

The likelihood of a particular side effect often differs between medications. The risk of weight gain from olanzapine, for example, is much greater than from lurasidone. Clinicians can reduce risk of undesirable side effects by prioritizing medications with lower risk for the side effect in question.

9.2.b Minimizing dose

As the dose of medication increases so does the risk for side effects. Clinicians can minimize the risk that a side effect develops by initiating medications at the lowest feasible dose. In cases where a side effect develops during treatment, reducing the dose is one of the possible options to reduce side-effect intensity or eliminate the side effect.

Since many side effects are dose-related, many clinicians will respond to side effects by reducing the dose of antipsychotic medication. This strategy is common in clinical practice, and clinical experience suggests that it is often effective. The approach is rarely the subject of clinical studies, however

9.2.c Switching to a different medication

Changing the medication is another option. Different medications have different affinities for neurotransmitter receptors. Drugs with lower dopamine-receptor affinity may be chosen as alternatives for side effects related to excessive dopamine antagonism. Drugs with lower histamine-receptor affinity may be chosen for side effects thought to arise from excessive histamine antagonism, and so forth. Like the dose-reduction strategy, the efficacy or risk of medication switching has not been widely addressed in clinical studies.

9.2.d Adding a medication to target the side effect

In many cases, the intensity of discomfort or the medical risk of a side effect may demand immediate, effective intervention. In these cases, the addition of "side effect" medication is highly desirable.

Alternately, there are cases where the person with psychosis has gotten good results with their psychiatric symptoms and wishes to continue the medication that works for them or would prefer not to risk changes to an otherwise effective treatment. Adding an additional medication to reduce or eliminate unwanted side effect makes sense in this case.

9.3 Neurological side effects

The neurological side effects of antipsychotic medications are commonly called "extrapyramidal side effects." They were called "extrapyramidal" because their neurological pathways originate in the basal ganglia and – unlike voluntary motor signals – do not pass through the pyramids of the medulla on their way to the spinal cord.

The extrapyramidal side effects involve changes in muscle tone, posture, initiation of movement, desire for movement or impaired suppression of unnecessary movement. The extrapyramidal symptoms include: drug-induced parkinsonism, dystonic reaction, akathisia and tardive dyskinesia.

9.3.a Drug-induced parkinsonism

Description

Drug-induced parkinsonism appears nearly identical to Parkinson's disease. Both conditions involve reduced dopamine signaling in the basal ganglia. (In drug-induced parkinsonism, it's because

dopamine receptors are blocked; in Parkinson's disease, it's because dopamine-producing cells are dying).
Signs of drug-induced parkinsonism include:

- Muscular rigidity
- Tremor
- Bradykinesia (slowed movements)
- Reduced facial expression
- Stooped posture
- Reduced arm swing when walking
- Short-stepped gait

Risk factors and prevention

The risk of drug-induced parkinsonism is related to the extent of dopamine receptor occupancy. Positron emission tomography studies suggest that drug-induced parkinsonism is unlikely to develop unless dopamine receptor occupancy exceeds 80%. In contrast, psychosis reduction can occur with 40% to 70% receptor occupancy.
Although drug-induced parkinsonism risk is reduced with atypical antipsychotic drugs, their advantage may disappear at higher doses.

Treatment of drug-induced parkinsonism

Since drug-induced parkinsonism is probably due to excessive blockade of dopamine receptors, reducing the dose of the offending medication is a logical intervention.
Drug-induced parkinsonism can be treated pharmacologically by co-prescribing an anticholinergic medication such as benztropine (Cogentin) or by co-prescribing amantadine.

9.3.b Dystonia

Description

Dystonia is a sustained muscle contraction.
Dystonic reactions to antipsychotic medications commonly involve the trunk or extremities and can result in abnormal posture.
Dystonic reactions can occur in any almost any skeletal muscle, including:

- Tongue
- Eye (extrinsic muscles)
- Neck
- Larynx
- Pharynx
- Intercostal muscles

Medical urgency of dystonic reactions

Dystonic reactions can be frightening and may be painful.

Dystonic reactions involving the pharynx, larynx or intercostal muscles can result in dysphagia, choking, aspiration or airway restriction.

Risk factors and prevention

Dystonic reactions occur in 3% to 10% of individuals treated with antipsychotic medications.
Risk factors for dystonic reactions include: younger age, male sex or history of cocaine use.
The risk of dystonic reaction is higher in first-generation antipsychotic medications with high affinity for the dopamine receptor.
In the first-generation antipsychotic era, patients at high risk of dystonic reaction (young men, or people with prior history of dystonic reaction) were pre-treated with, or co-prescribed, benztropine or diphenhydramine prophylactically.
The risk of acute dystonia is lower with atypical antipsychotic drugs. Dystonia prophylaxis is no longer widely practiced.

Treatment of acute dystonic reaction

Dystonic reactions respond quickly and usually completely to benztropine or to diphenhydramine.
Individuals who experience dystonia are usually transitioned to a different antipsychotic drug, with lower dopamine receptor affinity.

9.3.c Akathisia

Description

Akathisia is essentially a state of restlessness. The term akathisia was coined from Greek root words meaning "unable to be still."

Akathisia may present either motoric restlessness or it may be primarily or entirely subjective, an inner experience.

Motor signs of akathisia may include:

- Being unable to sit still
- Being unable to stand still
- Crossing and uncrossing arms or legs
- Shifting weight back and forth from one leg to the other while standing
- Walking in place
- Fidgeting
- Pacing

The subjective experience of akathisia is often difficult for affected people to describe. Patients often endorse feeling as if they could crawl out of their skin.

Akathisia is a frequently missed diagnosis. Clinicians or family members may interpret motoric signs of akathisia as agitation and ascribe it to the psychosis instead of the medication. Akathisia is frequently mistaken for anxiety.

Risk factors and prevention

People with mood disorders appear to be more vulnerable to akathisia from antipsychotic medications.

Increased akathisia risk has also been linked to: iron deficiency, type 2 diabetes or rapid dose increases.

Akathisia is more common with first-generation antipsychotic medications. Among patients given standard doses of first-generation antipsychotic medications, mild akathisia may develop in 40% of patients and moderate to severe akathisia may occur in 20% (Sachdev and Kruk, 1994).

Among the atypical antipsychotic drugs, aripiprazole and brexpiprazole appear to have the highest akathisia risk. However, the majority of people experiencing akathisia from aripiprazole describe it as moderate and temporary. Olanzapine, quetiapine and iloperidone are the antipsychotic medications with the lowest risk.

The risk of akathisia may be reduced using second-generation medications at the lowest reasonable doses.

Treatment of akathisia

Because akathisia can be intensely uncomfortable, co-prescription of an akathisia-reducing medication is often indicated. Several options exist.

Propranolol

Doses of 40 to 80 mg per day are typically used to relieve akathisia. Owing to short half-life (three to six hours), propranolol is usually dosed twice daily. An extended-release formulation is available for patients who use it regularly.

Avoid propranolol in patients with asthma or low blood pressure.

Benzodiazepines

Clonazepam in doses of 0.5 to 2.5 mg per day is supported by placebo-controlled trials as a treatment for antipsychotic-induced akathisia.

Clonazepam and other benzodiazepines should be avoided in patients with substance use disorder.

Mirtazapine

Mirtazapine, 15 mg per day, appears better than placebo and equivalent to propranolol at relieving antipsychotic-induced akathisia.

Mirtazapine is relatively sedating and can stimulate appetite. As an antidepressant medication, mirtazapine might have the potential to cause or exacerbate mania.

Cyproheptadine

Cyproheptadine was introduced in 1961 as a treatment for allergic rhinitis or urticaria.
Cyproheptadine antagonizes the histamine H1 receptor and the serotonin (2A, 2B, and 2C) receptors.
Cyproheptadine (8 mg BID) produced marked relief of antipsychotic-induced akathisia is an open clinical study (Weiss *et al.,* 1995) and was equivalent to propranolol at reducing antipsychotic-induced akathisia in a double-blind study (Fischel *et al.*, 2001).

Trazodone

Though developed as an antidepressant, trazodone is commonly used in psychiatric practice and in primary care as a sleep aid. A single placebo-controlled study suggested that trazodone (100 mg/day) may reduce antipsychotic-induced akathisia (Stryjer *et al.*, 2010).
Since it possesses antidepressant properties, trazodone might provoke or worsen mania.

9.3.d Tardive dyskinesia

Description

Tardive dyskinesia is characterized by involuntary movements. It is caused by long-term use of antipsychotic medications or other dopamine receptor-blocking drugs.
Multi-year time frames of medication use are typically required before tardive dyskinesia develops. However, there have been reports of tardive dyskinesia developing after just a few months of treatment.
The dyskinetic movements of tardive dyskinesia may be jerk-like (choreiform) or slow, convoluted or writhing (athetoid). Choreiform and athetoid movements often happen together in tardive dyskinesia, with initial jerky movements followed by longer, slower writhing movements.
The most common site of onset of tardive dyskinesia is the muscles of the tongue, jaw or lower face. Lip-smacking, tongue thrusting or grimacing are common manifestations of orofacial involvement. Although orofacial movements are common, the dyskinetic movements can affect any muscle or muscle group including the digits, extremities, trunk, pharynx or diaphragm.
The jerky, writhing and irregular dyskinetic movements of tardive dyskinesia are easily distinguished from the rhythmic 3-to-5 cycles per second oscillating tremor of drug-induced parkinsonism.

Risk factors and prevention

The risk of tardive dyskinesia is most strongly associated with the degree of exposure to dopamine receptor antagonist drugs. Degree of exposure is based on both dose and duration of use.
Other risk factors for tardive dyskinesia include:

- Advanced age
- Female sex
- African ethnicity
- Pre-existing mood disorder
- Diabetes

- HIV-positive status
- High sensitivity to acute extrapyramidal side effects

Because degree of exposure to antipsychotic drugs is the strongest risk factor for tardive dyskinesia, the strongest preventive strategy is therefore to limit exposure to antipsychotic medications. Where possible, they should be avoided. When necessary, they should be used at the lowest effective dose.

Tardive dyskinesia may be irreversible

Tardive dyskinesia is especially concerning because the abnormal involuntary movements might become permanent. Between 33% and 50% of cases of tardive dyskinesia will never entirely abate.

Treatment of tardive dyskinesia

If tardive dyskinesia develops while taking an antipsychotic medication, and if clinical circumstances suggest that the antipsychotic medication should continue, the following treatment options exist:

- Transition to a second-generation medication if tardive dyskinesia develops while taking a first-generation antipsychotic medication.
- If tardive dyskinesia develops while taking a second-generation medication, consider transitioning to a medication with lower affinity for the dopamine receptor.
- Prescribe one of the medications with FDA approval for tardive dyskinesia (valbenazine or deutetrabenazine).
- Amantadine 100 mg BID has been helpful in some cases.
- Benzodiazepines can be helpful in some cases.

9.4 Prevention and treatment of weight gain from antipsychotic medications

Many antipsychotic medications can significantly increase weight and create additional metabolic adverse effects such as dyslipidemia and hyperglycemia. These metabolic side effects can be disfiguring and can lead to increased risks for additional morbid outcomes and shorten lifespan. Cases of severe hyperglycemia with ketoacidosis have been reported.

9.4.a Risk factors

Antipsychotic medications that block histamine H1 receptors or serotonin 2A or 2A receptors have the highest risk of provoking weight gain. Both histamine and serotonin antagonism can stimulate appetite and lead to increased calorie consumption. Additionally, histamine and serotonin receptors are located throughout the body and are situated in organs and tissue that regulate energy balance. For reasons not understood, the weight gain risk of antipsychotic drugs is substantially higher in children and adolescents. Up to 80% of children prescribed antipsychotic medications will experience significant weight gain (Ratzoni *et al.*, 2002).

9.4.b Prioritizing lower-risk medications

Antipsychotic medications vary in their risk of weight gain. Based on several meta-analyses, the following risk hierarchy has been suggested (Dayabandara *et al.*, 2017)

Highest risk	Clozapine Olanzapine
Moderate risk	Quetiapine Risperidone Paliperidone
Lower risk	Aripiprazole Brexpiprazole
Lowest risk	Molindone Haloperidol Ziprasidone Lurasidone

9.4.c Diet and exercise

Numerous studies have shown that diet and exercise interventions can reduce antipsychotic-induced weight gain. Although a logical first-line strategy, clinicians should consider:

- The clinical studies showing effectiveness of diet/exercise strategies were conducted in patients capable of providing informed consent and interested in participating in the diet/exercise intervention. Thus, results from diet/exercise studies may overestimate effectiveness compared to real-world clinical scenarios.
- Successful adherence to diet/exercise strategies is challenging for well-resourced people without significant mental health concerns. The presence of mental illness, pharmacologically stimulated appetite, and medication-induced disruption of insulin signaling are significant additional barriers.

9.4.d Metformin

Antipsychotic-induced weight gain is associated with elevated glucose levels and reduced insulin sensitivity. Metformin lowers glucose levels and improves insulin sensitivity.

Meta-analyses of metformin studies consistently find that metformin significantly reduces the pace of antipsychotic-induced weight gain and reduces weight that has already been gained from antipsychotic medications (Zheng *et al.*, 2015).

Dosing of metformin for antipsychotic-induced weight gain is similar to dosing for type 2 diabetes.

9.4.e GLP-1 agonists

Glucagon-like peptide-1 is a peptide hormone that is primarily produced and released by specialized cells within the small intestine. It reduces blood glucose levels by enhancing glucose-dependent insulin secretion and inhibiting glucagon release.

GLP-1 also suppresses appetite by delaying gastric emptying and stimulating GLP-1 receptors in the hypothalamus.

GLP-1 agonist drugs were developed for the treatment of diabetes but are also FDA-approved for chronic weight management.

Compared with metformin, the number of clinical trials of GLP-1 agonists in the treatment of antipsychotic-related weight gain is much smaller. However, the estimated effect size is much larger (e.g., Whicher *et al.,* 2021).

9.4.f Melatonin

A small number of small studies suggest the potential for melatonin to mitigate antipsychotic-induced weight gain (reviewed by Wang *et al.*, 2016). Although the evidence base addressing melatonin's utility in weight loss is quite small, the side effect profile of melatonin is favorable. And its status as a natural compound is appealing to many consumers and clinicians.

9.4.g Topiramate

Topiramate treats seizure disorders and prevents migraines. Appetite reduction with subsequent weight loss is a common side effect.

Several studies have shown that topiramate can prevent or reduce weight gain from antipsychotic drugs. A meta-analysis found an average weight loss of 3.8 kg during topiramate use (Goh *et al.*, 2019). Adding topiramate to antipsychotic medications might further reduce psychosis. A meta-analysis found that adding topiramate to antipsychotic drugs reduced psychosis rating scores with an effect size of 0.58 (Zheng *et al.*, 2016).

On the other hand, there are numerous case reports of topiramate worsening psychosis symptoms. Further, topiramate may cause significant side effects, including paresthesia and cognitive slowing. Topiramate studies have a relatively high discontinuation rate.

9.4.h Opioid receptor antagonists

Opioid receptor antagonists have been proposed as weight-loss-assistance tools based on the role of the endogenous opioid system in mediating the rewarding aspects of food consumption. Recently, the opioid receptor antagonist samidorphan has been combined with olanzapine. The combination drug (Lybelvi) has been approved for the treatment of schizophrenia or bipolar disorder. Initial clinical trials suggested that the pace of weight gain was reduced with this combination drug. However, a recent meta-analysis did not find a significant overall advantage with respect to weight gain. Meanwhile, the combination drug did not prevent the elevations of blood glucose or triglyceride levels typical of olanzapine (Srisurapanont *et al.*, 2021).

9.5 Hyperprolactinemia

Description

Dopamine inhibits the activity of prolactin-making cells in the pituitary gland. Because they are dopamine receptor antagonists, most antipsychotic medications can block this baseline prolactin inhibition and thus cause hyperprolactinemia.

Prolactin levels vary with age, gender, stress level and physical activity. Hyperprolactinemia can be defined as prolactin levels greater than 28.3 ng/ml for women and 16.5 ng/ml for men (Soto-Pedre *et al.*, 2017).

Hyperprolactinemia can negatively impact health and life quality by contributing to:

- Breast enlargement
- Galactorrhea
- Gynecomastia
- Hirsutism
- Sexual dysfunction
- Erectile dysfunction
- Irregular periods or amenorrhea
- Infertility
- Erectile dysfunction
- Reduced testosterone levels
- Reduced bone mineral density
- Weight gain
- Autoimmune thyroiditis

Risk factors and prevention strategies

The risk for hyperprolactinemia is related to the intensity of dopamine receptor antagonism. The extent of dopamine receptor antagonism is related to the affinity of the medication (higher-affinity drugs pose greater risk) and the dose of medication employed. (Even lower-affinity drugs can cause hyperprolactinemia at sufficiently high doses.)

Because of its partial agonist activity, aripiprazole does not elevate prolactin levels.

Treatment

There are several options for treating antipsychotic-induced hyperprolactinemia.

- Adding low doses of aripiprazole (2 to 5 mg/day) often reduces elevated prolactin levels.
- The dose of the offending medication can be reduced.
- The offending medication can be switched to one with lower dopamine receptor affinity.
- Adding metformin has been reported to reduce elevated prolactin levels in antipsychotic-induced hyperprolactinemia (Zheng *et al.*, 2017).
- Adding topiramate has been reported to reduce elevated prolactin levels in antipsychotic-induced hyperprolactinemia (Huang *et al.*, 2017).

9.6 Neuroleptic Malignant Syndrome (NMS)

Description

Neuroleptic malignant syndrome (NMS) is a rare but potentially life-threatening complication of antipsychotic medication treatment. Recent estimates suggest a frequency of 0.02% (Spivak *et al.*, 2000). It is defined by the occurrence of fever and muscle rigidity in people taking antipsychotic medications and in people who have abruptly discontinued them.

Confusion, altered level of consciousness, or other mental status changes precede the onset of fever and rigidity in about 70% of cases. NMS is often accompanied by signs of "autonomic instability" which may include: tachycardia, hypertension or labile blood pressure, dysrhythmias or diaphoresis. Though not required for diagnosis, NMS is commonly associated with elevated levels of creatine kinase and elevated white blood cell count.

Medical urgency of NMS

Although NMS itself is a rare occurrence, once underway it can be medically serious. A recent population-based study of 1,346 cases in the United States found a 5.6% mortality rate (Modi *et al.*, 2016). Medical complications from NMS are numerous and include: rhabdomyolysis, acute kidney injury, hepatic failure, respiratory failure and cardiac events.

Risk factors and prevention

NMS can develop at any point in treatment and from any type of dopamine receptor antagonist exposure.

However, NMS risk appears higher with:

- The use of first-generation antipsychotic medications
- High doses of antipsychotic medications
- Recent initiation of antipsychotic therapy (approximately 80% of NMS cases develop within the first month of treatment)
- Recent or rapid dose increase
- Recent switching from one medication to another
- Parenteral administration of antipsychotic medication
- Recent discontinuation of antipsychotic medication

The risk of NMS may be reduced by:

- Selecting atypical antipsychotic medications instead of first-generation agents
- Avoiding the use of short-acting injectable medication
- Avoiding rapid dose escalation
- Avoiding abrupt discontinuation of antipsychotic medication

Treatment

Antipsychotic medication should be discontinued as soon as NMS is reasonably suspected. The strongest predictor of survival from an episode of NMS is time to discontinuation of antipsychotic

medication. Patients whose medications were discontinued soon after the onset of NMS symptoms had better outcomes and survival rates than those who continued using them for longer times.
In the less common scenario that NMS symptoms arise because someone who had been taking antipsychotic medication chronically suddenly stopped them, then the medications should be resumed.
In any case, a person with suspected NMS should be closely monitored, and should probably be admitted to the hospital to allow prompt administration of supportive care when indicated.

10. ADDITIONAL RESOURCES

There are several options for primary care clinicians to get additional information, support or consultation when working with people with psychosis.

The SAMHSA Early Serious Mental Illness Treatment Locator

The United States Substance Abuse and Mental Health Services Administration (SAMHSA) maintains a searchable nationwide directory of clinics that work with individuals experiencing the recent onset of serious mental illness.
The directory address is: https://www.samhsa.gov/esmi-treatment-locator

Project ECHO

Initiated at the University of New Mexico, the ECHO project was designed to bridge health gaps in rural communities by connecting specialists at academic centers with front-line clinicians. ECHO sessions are held online and are offered at no cost. Clinicians can present cases and receive expert guidance.

Northeast Ohio Medical University offers two ECHO groups that can support primary care clinicians who are caring for people with psychosis. SZconsult meets every Tuesday at noon, eastern time. Integrated Care at NEOMED (IC@N) meets every Friday at noon, eastern time. Additional information about these programs can be found at: neomed.edu/projectecho/

SMI Adviser

SMI Adviser is an information and consultation service sponsored by the American Psychiatric Association and SAMHSA. SMI Adviser provides clinicians with education, data and consultations to make evidence-based decisions.
Clinicians can request consultation at: smiadviser.org/clinicians

Psychiatry for All Physicians Facebook Group

Founded by Dr. Christina Girgis, the Facebook group "Psychiatry for All Physicians" is an education-focused group for physicians of any specialty who care for people with psychiatric symptoms. The group can be found at: facebook.com/groups/psychiatryforallphysicians

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