Acute Psychosis:
Differential Diagnosis, Evaluation, and Management

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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 about why psychosis develops? Have you been uncertain about how to evaluate whether it is due to a biological (eg, neurologic, medical, psychiatric disorder, or drug-induced), psychological (eg, stress), or sociocultural etiology? Have you been unsure about which aspects of the history, physical examination, and laboratory tests are most likely to yield meaningful information about its etiology and treatment? If you have, the following case vignette and discussion should prove useful.

CASE VIGNETTE

Ms E, a 28-year-old woman, was brought to the emergency department (ED) by her family because of her increasingly erratic behavior over the past several weeks. Her family reported that she appeared well until 4 months ago, when she lost her job. Since then, she became quieter and more withdrawn. Over the past few weeks, she heard her name being called through the walls of her bedroom; however, no one else was in her apartment. She was also convinced that someone had broken into her apartment and poured gasoline into her kitchen, as the smell was overpowering; however, others were unable to detect that characteristic odor. She had called 9-1-1 several times a week to report her concerns, but the police were unable to identify evidence of a break-in. Her building manager became so concerned about the repeated police calls that he notified Ms E's family. In the ED, Ms E was disheveled, confused, and fearful. Her medical and psychiatric history were unremarkable, and she was taking no prescribed medications or illicit drugs. Her family history included a maternal uncle with schizophrenia, and her father had a history of bipolar disorder. A strategy was developed to evaluate her affective, behavioral, and cognitive symptoms so that a timely and effective intervention could be implemented.

DISCUSSION

What Is Meant by the Term *Acute Psychosis*?

The term *psychosis* has been defined differently over the past century in medicine and psychology. Originally, the term was used to emphasize the functional limitations that result from an individual's impaired ability to perceive or "test" reality.[1] This was broad in scope and had a limited focus on specific signs and symptoms. More recently, *psychosis* has come to represent a "clinical syndrome"

Clinical Points

- Broadly speaking, psychotic disorders can be categorized either as primary psychiatric conditions or as psychoses that arise secondary to medical, neurologic, substance-related, or other identifiable causes. However, the underlying "cause" of these conditions often remains uncertain.
- When creating a differential diagnosis, it is important to understand the timeline of symptoms (eg, in relation to other events or changes), the patient's age, their past medical and psychiatric history, concurrent symptoms, and family history.
- A thorough physical and neurologic examination (including a mental status examination/cognitive examination), laboratory testing (eg, a complete blood count, electrolytes, blood urea nitrogen/creatinine, liver function tests, thyroid function tests, erythrocyte sedimentation rate, fluorescent treponemal antibody absorption test for syphilis, antinuclear antibodies, levels of vitamin B_{12} and folate, magnetic resonance imaging scan of the brain, an electroencephalogram, and HIV testing) is critical in patients who are experiencing the acute onset of psychotic symptoms.
- Once a patient's psychotic symptoms have been stabilized (often with use of antipsychotics), positive and negative symptoms of psychosis, cognitive function, and quality of life should be reassessed to ensure recovery from psychosis and better outcomes.

involving hallucinations, delusions, incoherent or disorganized behavior or speech, or some combination of these.[1–3] However, as noted by Gaebel and Zielasek,[2] the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), does not provide a discrete definition for *psychosis*, but instead provides diagnostic criteria for a set of psychotic disorders. To better define the term *acute psychosis*, specific features and disorders need to be considered.

Hallucinations are defined as sensory perceptions in the absence of a corresponding external or somatic stimulus, and in the context of psychosis with a lack of insight (ie, a lack of recognition by the individual that their hallucinations are not associated with actual external stimuli).[1] Examples include a patient who hears voices telling him or her to harm others or sees small animals running across their hospital room. *Delusions* are defined as wildly improbable beliefs that are strongly held despite incontrovertible and obvious counter-evidence and despite what almost everyone else believes.[4] Delusions can be of varied forms, eg, of persecution (ie, believing that one is being targeted or persecuted by others), of grandiosity (ie, believing that one is a very prominent person in some particular and obviously false respect), of erotomania (ie, believing that another individual, often somebody famous, is in love with oneself), or of a religious nature (ie, believing that one is the messiah). *Disorganized thoughts* and *speech* can include illogical content, incomprehensible verbal communication, tangential speech, and other examples of altered cognition and speech.[5] *Disorganized behaviors* can involve psychomotor alterations (eg, odd postures or movements) or catatonia.[5]

Acute psychosis can be described as a clinical syndrome that involves hallucinations, delusions, disorganized thoughts or behaviors, or some combination of these within an acute timeframe (often less than 1 month). Specifically, the *DSM-5* diagnosis of brief psychotic disorder requires the presence of psychotic symptoms for between 1 day and 1 month and that these symptoms not be attributable to other causes.[6] This timeframe differentiates this condition from schizophreniform disorder, which relies on the presence of psychotic symptoms for between 1 and 6 months.[5] In the *International Classification of Diseases, Tenth Revision* (*ICD-10*), the diagnosis most closely corresponding to brief psychotic disorder is acute and transient psychotic disorders (ATPD).[6] In ATPD, onset arises within 2 weeks, "changing and variable" psychotic symptoms are present, and the possibility exists of a recent acute stressor prior to symptom onset.[3]

What Can Cause Psychosis?

Broadly speaking, the differential diagnosis of psychosis can be divided into 3 tiers: psychiatric, medical, and drug induced.

Psychiatric causes include schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, delusional disorder, schizophreniform disorder, brief psychotic disorder, and postpartum psychosis.[5] The underlying "cause" of these conditions, in any deeper neurobiological sense, is uncertain, but each is listed alongside distinguishing factors in a review by Lieberman and First.[5]

Table 1 illustrates medical and neurologic causes of psychosis.[7] Briefly, medical causes include delirium, hypoxia, excessively high or low blood sugar, autoimmune diseases (eg, systemic lupus erythematosus [SLE]), neurologic diseases (eg, Lewy body dementia, Wilson's disease), infection (eg, sepsis, urinary tract infections in older adults), endocrine disorders (eg, Cushing's disease, hyperthyroidism), paraneoplastic syndromes (eg, anti–*N*-methyl-D-aspartate receptor [NMDA] receptor encephalitis in ovarian cancer), vitamin deficiencies (eg, of thiamine, niacin, cobalamin), and a wide range of metabolic and electrolyte derangements (eg, hypercalcemia, hepatic encephalopathy, uremia).[8–10] Griswold et al[8] have provided a comprehensive approach to assessing these causes. Delirium should be emphasized as a major cause of altered mental status in hospitalized patients that can manifest as psychotic symptoms. Delirium is "a syndrome characterized by an acute change in attention, awareness, and cognition" and "is caused by a medical condition that cannot be better explained by a preexisting neurocognitive disorder."[11] In cases of delirium, as in other cases of psychosis secondary to medical causes, the best approach is prevention (eg, proper nutrition and sleep hygiene, avoidance of benzodiazepines and other psychoactive medications if possible) and, if these fail, supportive care alongside treatment of the underlying condition.[12]

Drug-induced psychoses can be grouped along with the medical etiologies of psychosis into one broader category of

Table 1. Medical and Neurologic Conditions Associated With Psychosis[a]

Category/Condition	Examples
Epilepsy	
Head trauma/ traumatic brain injury	
Dementia	Alzheimer's disease, Pick's disease, Lewy body dementia
Stroke	
Space occupying lesions	Primary brain tumors, metastases, abscesses/cysts, tuberous sclerosis, cerebrovascular malformation
Hydrocephalus	
Demyelinating disease	Multiple sclerosis, leukodystrophies
Neuropsychiatric disorders	Huntington's disease, Wilson's disease, Parkinson's dementia
Autoimmune disorders	Systemic lupus erythematosus, paraneoplastic syndromes, autoimmune encephalitis
Infections	Viral encephalitis, neurosyphilis, Lyme disease, HIV, neurocysticercosis, tuberculosis, sarcoidosis, prion diseases
Endocrinopathy	Hypoglycemia, Addison's disease, Cushing's syndrome, hyper-/hypothyroidism, hyper-/hypoparathyroidism
Narcolepsy	
Nutritional deficiencies	Deficiencies of magnesium, vitamin A, vitamin D, zinc, niacin, vitamin B_{12}
Metabolic disorders	Amino acid metabolism (Hartnup disease, homocystinuria, phenylketonuria), acute intermittent porphyria, Fabry's disease, Neimann-Pick type C disease, GM_2 gangliosidosis
Chromosomal abnormalities	Klinefelter's syndrome, fragile X syndrome, 22q11.2 deletion syndrome

[a]Based on Freudenreich et al.[7]
Abbreviation: HIV = human immunodeficiency virus.

Table 2. Substances Associated With Psychosis[a]

Substance/Category	Examples
Alcohol	Numerous forms; may cause psychosis in intoxication or withdrawal
Amphetamine	Methamphetamine, dextroamphetamine
Anabolic steroids	Anadrol, danazol
Cannabis/synthetic cannabinoids	Marijuana, K2, spice
Cocaine	Crack cocaine
Hallucinogens	Phencyclidine, LSD, ecstasy (3,4-methylenedioxymethamphetamine)
Inhalants	Paint thinner, spray paint
Medications	Anesthetics, anticholinergics, antihistamines, antihypertensives (digoxin), antiepileptics, antibiotics, antivirals, antiparasitics
Antiparkinsonian medications	Pramipexole, ropinirole, rotigotine, selegiline
Chemotherapeutic agents	Capecitabine, methotrexate, paclitaxel
Corticosteroids	Prednisone, dexamethasone
Interferon	Interferon α
Muscle relaxants	Baclofen, cyclobenzaprine, tizanidine
Toxins	Heavy metals (arsenic, manganese, mercury), carbon monoxide, organophosphates

[a]Based on Freudenreich et al.[7]
Abbreviation: LSD = lysergic acid diethylamide.

secondary psychoses. However, to emphasize the need to assess for recreational, iatrogenic, and other drug use when evaluating causes of acute psychosis, the categories can be divided. Recreational causes of drug-induced psychosis include cocaine, alcohol, amphetamines, lysergic acid diethylamide (LSD), cannabis, phencyclidine, ketamine, inhalants, and others[7,8,13]; more details are provided in Table 2. Iatrogenic causes include anticholinergics, antiarrhythmics, steroids, antiviral medications, benzodiazepines, barbiturates, dextromethorphan, antihistamines, and antidepressants (eg, in cases of mania triggered by use of selective serotonin reuptake inhibitors in patients with bipolar I disorder).[8,14] Finally, drug withdrawal syndromes (eg, from alcohol and benzodiazepines) can involve psychotic symptoms.[8,15]

The differential diagnosis of acute psychotic symptoms should account for the aforementioned etiologies. With these causes in mind, clinicians may tailor their history, physical examination, and laboratory studies to methodically reach a diagnosis of and management strategy for acute psychosis.

Which Aspects of the Patient's History Are Apt to Influence the Differential Diagnosis and the Workup?

Psychosis can be divided into primary (due to a psychiatric illness) or secondary (due to "organic causes," including delirium, dementia, drugs/toxins, or medical illnesses) categories. Several aspects of the presentation, including the timeline of symptoms, the age of the patient, the prior psychiatric and medical history, the concurrent symptoms, and the family history, are critical to determine if psychosis is primary or secondary, and to clarify the differential diagnosis. Table 3 provides further details.

It is important to understand the timeline of symptoms (eg, acute, or chronic, in relation to other events or changes). Acute-onset psychosis, over hours to a few days, is suggestive of an organic cause, including encephalitis, an endocrinopathy, or a stroke (see Table 1 for a list of medical and neurologic illnesses that can cause psychosis). In further exploring potential organic causes of psychosis, the temporal relationship of symptoms to use of new medications, dose changes, substance use, or withdrawal must also be carefully considered (please see Table 2 for a list of medications and substances that can cause psychosis). Chronic symptoms, those persisting over many months, are more suggestive of a primary psychiatric illness. For example, a prodromal period of nonspecific psychiatric symptoms and functional decline, followed by a gradually developing (ie, over weeks to months) psychosis, is consistent with schizophrenia.

The patient's age also influences the differential diagnosis. Most psychiatric illnesses (including bipolar disorder and schizophrenia) with primary psychotic symptoms develop in adolescence and young adulthood. Primary psychiatric causes for new-onset psychosis should be high on the list of potential causes for patients in these age ranges and much lower on the differential for young children and older adults. In the elderly, delirium, dementia, and other medical or neurologic causes of psychosis should top the list

Table 3. Aspects of the History Important for Differential Diagnosis

Aspect of the History	What to Consider	What It Might Suggest
Timeline of symptoms	Acute	Organic illness
	Waxing/waning	Delirium
	Episodic	Potential association with medications, substance intoxication/withdrawal
	Chronic	Psychiatric illness
Age of the patient	Young (< 10 years old)	Chromosomal or genetic abnormality Infection
	Adolescent, young adult	Psychiatric illness
	Geriatric (> 65 years old)	Dementia Delirium
Prior medical or psychiatric history	History of medical illnesses known to be associated with psychosis	Medical etiology for psychosis
	History of neurologic illnesses known to be associated with psychosis	Neurologic etiology for psychosis
	History of psychiatric illnesses known to be associated with psychosis	Psychiatric etiology for psychosis
	History of substance use	Substance-induced psychosis
	History of taking medications known to be associated with psychosis	Medication-induced psychosis
Co-occurring symptoms	Physical symptoms	Medical etiology for psychosis
	Neurologic symptoms	Neurologic etiology for psychosis
	Psychiatric symptoms	Psychiatric etiology for psychosis
Family history	Family history of medical illnesses known to be associated with psychosis	Medical etiology for psychosis
	Family history of neurologic illnesses known to be associated with psychosis	Neurologic etiology for psychosis
	Family history of psychiatric illnesses known to be associated with psychosis	Psychiatric etiology for psychosis

of possible etiologies. In very young children, one must also consider metabolic disorders and chromosomal or genetic abnormalities.

The patient's prior medical and psychiatric history is crucial to understand. As described in Table 1, numerous medical illnesses can cause psychotic symptoms (eg, autoimmune disorders, thyroid disorders, hypoglycemia). In addition, neuropsychiatric and neurologic disorders, such as dementia, Huntington's disease, and Wilson's disease, can also trigger psychotic symptoms. A history of any of these illnesses known to cause psychosis should elevate them on the differential diagnosis. In addition, many psychiatric illnesses (including schizophrenia, bipolar disorder, and major depressive disorder) can be manifest by psychotic symptoms as a component of their presentation. Finally, a history of substance use, particularly of substances known to trigger psychosis, is important to consider. While a history of an illness does not imply causality for the current presentation, it can influence creation of the differential diagnosis.

Delineating the symptoms that coexist with psychosis is also critical. Physical symptoms (such as weight loss, fever, rash) suggest an underlying organic illness. The constellation of symptoms may indicate a specific illness; for example, the presence of a malar rash, fatigue, and joint pain suggest a diagnosis of SLE. Neurologic symptoms (such as abnormal movements, seizures, focal deficits, or sensory changes) suggest a neurologic illness. Finally, the presence of mood symptoms (eg, depression or mania) or negative symptoms (eg, flat affect, alogia, asociality) often indicates a psychiatric illness.

Understanding the patient's family history also helps to refine the differential diagnosis of psychosis. A family history of psychiatric illnesses known to be associated with psychosis (such as schizophrenia or bipolar disorder) raises these illnesses on the list of differential diagnoses.

Table 4. Physical Examination Findings in Acute Psychosis

Aspect of the Physical Examination	What It Might Suggest (Examples Only)
Vital signs	Alterations may indicate medical illness (eg, fever indicating infection)
Pupils	
Skin	Malar rash (with SLE) Bull's eye rash (with Lyme disease) Dermatitis (with pellagra)
Neurologic examination	Choreiform movements (with Huntington's disease) Pill-rolling tremor and bradykinesia (with Parkinson's disease) Tremor, dysarthria, rigidity, gait disturbance (with Wilson's disease)
Cognitive function	Impaired memory and orientation (with dementia) Impaired attention and alertness (with delirium)

Abbreviation: SLE = systemic lupus erythematosus.

Similarly, a family history of neurologic illnesses associated with psychosis (such as Huntington's disease, Parkinson's disease, or Wilson's disease) also elevates these illnesses on the differential.

Which Aspects of the Physical Examination Should be Assessed in Those With an Acute Psychotic Illness?

A thorough physical and neurologic examination is critical in all patients who are experiencing an acute onset of psychotic symptoms (see Table 4 for more details).

Having a complete set of vital signs (including heart rate, blood pressure, respiratory rate, and oxygen saturation) is important; abnormalities often suggest an underlying medical etiology. The physical examination should be conducted with special attention paid to associated signs or symptoms that might indicate a medical diagnosis. Several areas may be of particularly high yield. For example, pupillary size (dilated or constricted) may indicate substance use or withdrawal. The aberrant pupillary function may indicate

Table 5. Testing in Acute Psychosis[a]

Laboratory Test	Purpose
Complete blood count	Rule out infections, pernicious anemia
Electrolytes, including calcium	Rule out metabolic derangements, Addison's disease, Cushing's disease, hyper-/hypoparathyroidism
Blood urea nitrogen/creatinine	Rule out uremia
Glucose	Rule out hyper-/hypoglycemia
Liver function tests	Rule out liver failure, hepatic encephalopathy, Wilson's disease
Erythrocyte sedimentation rate	Rule out systemic inflammation
Antinuclear antibodies	Rule out systemic lupus erythematosus
Thyroid function tests	Rule out hyper-/hypothyroidism
Vitamin B_{12}	Rule out pernicious anemia
Folate	Rule out folate deficiency
HIV infection	Rule out HIV; recommended for routine care for all patients
FTA-abs test for syphilis	Rule out neurosyphilis
Ceruloplasmin	Rule out Wilson's disease; may be of low yield with many false positives
Serum and/or urine drug screen	Rule out substance-induced psychosis, although many substances do not appear on standard testing and a positive test does not indicate causality
Urinalysis	Rule out urinary tract infection
Neuroimaging	
Magnetic resonance imaging	Rule out demyelinating disease, brain tumor, or stroke
Ancillary Tests, as Clinically Indicated	
Electroencephalogram	Rule out seizures and delirium; may be especially important if there is a history of head injuries or seizures[17]
Chest x-ray	Rule out infection
Lumbar puncture, cerebrospinal fluid (CSF) analysis	Rule out infection or autoimmune encephalitis
Blood cultures	Rule out infection
Autoantibody testing (serum or CSF)	Rule out autoimmune encephalitis
Medication drug levels	Rule out medication toxicity
Toxin levels	Rule out heavy metal (arsenic, manganese, thallium, mercury, carbon monoxide, organophosphate) poisoning

[a]Based on Freudenreich.[16]
Abbreviations: FTA-abs = fluorescent treponemal antibody absorption, HIV = human immunodeficiency virus.

a central nervous system (CNS) lesion, a genetic disorder, or, in the case of an Argyll-Robertson pupil, neurosyphilis. The skin examination is also meaningful, as many medical illnesses that cause psychosis have dermatologic findings, including a malar rash in SLE, dermatitis in pellagra (niacin deficiency), or the bull's eye rash of Lyme disease. In addition, co-occurring findings may suggest other conditions, such as optic neuritis (with eye pain and blurry vision), neuropathy, and muscle weakness that suggests multiple sclerosis.

A neurologic examination is also critical. The complete examination should include an assessment of cranial nerves, sensory and motor function, deep tendon reflexes, cerebellar function, and gait. Focal findings suggest specific etiologies, such as an acute stroke, Parkinson's disease, or Wilson's disease.

A bedside examination of cognitive function is essential. Deficits in orientation, attention, or memory might often indicate delirium or dementia.[7]

Which Laboratory Tests Should Be Administered in the ED When an Individual Presents With an Acute Psychotic Illness?

Laboratory testing must be broad in scope and include an assessment of the major medical causes of psychotic symptoms (see Table 5).[16,17] At a minimum, laboratory testing should include a complete blood count (CBC) with a differential, a chemistry panel (with levels of calcium and glucose), liver function tests (LFTs), thyroid function tests (TFTs), an erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), levels of B_{12} and folate, a human immunodeficiency virus (HIV) test (also recommended as routine care for all patients), a fluorescent treponemal antibody absorption (FTA-abs) test for syphilis, applicable serum drug levels (eg, digoxin, alcohol), a serum and/or urine drug screen, and a urinalysis.[16] Although of interest during the evaluation, ceruloplasmin levels are linked with many false-positive results and, therefore, may be of low yield.[16] Results must be interpreted in the clinical context of the patient's presentation, and positive results do not necessarily imply causality.

Obtaining a magnetic resonance imaging (MRI) scan in the throes of an acute psychotic episode is controversial because incidental findings occur at a similar rate as those of controls.[18] However, given the long-term cost of schizophrenia and its associated morbidity, an MRI scan may be cost-effective, allowing for more definitive exclusion of organic causes of psychosis.[17]

There is no single recommended evidence-based screening examination.[7] Our list of testing is but one example; it is not an exhaustive list. Additional testing is needed if the initial workup is unrevealing or if atypical symptoms exist. For example, a lumbar puncture (LP) should be performed to obtain cerebrospinal fluid (CSF) for analysis if there are concerns for a CNS infection or autoimmune encephalitis. An electroencephalogram (EEG) can be helpful when diagnosing a seizure disorder or confirming a diagnosis of delirium. A chest x-ray and blood cultures are indicated when there is a concern for infection.

Table 6. Key Features That Distinguish Primary and Secondary Psychoses

Feature	Primary Psychosis	Secondary Psychosis
Age at onset	Usually arises during early adolescence or young adulthood	Occur at all ages (mostly 40+ years)
Type of onset	Insidious	Acute or subacute
Hallucinations	Most frequent—auditory; imperative with loss of insight	Most frequent—visual; loss of insight may be present
Delusions	Complex, bizarre, or paranoid	Usually not complex, non-bizarre
Additional physical findings	Typically absent	Usually present
Focal neurologic deficits	Absent	Present
Vital signs and laboratory tests	Usually normal	Abnormal
Appearance	Normal or disheveled	Poor complexion or ungroomed
Consciousness	Intact	Altered
Orientation	Usually normal	May be impaired
Premorbid functioning	Impaired; lower IQ	Usually normal; higher cortical dysfunction develops during the advanced disease stage
Historical information	Family history of psychiatric disorders	History of physical illness
Course of psychosis	Remitting/relapsing	Resolves when the underlying condition is treated

Abbreviation: IQ = intelligence quotient.

How Can the Biological, Psychological, and Sociocultural Etiologies of Acute Psychotic Illness Be Distinguished From One Another?

Acute psychotic illness can be triggered by biological, psychological, or sociocultural factors; however, the exact cause of psychosis is unknown. Regarding biological etiologies, acute psychosis can be caused by a primary psychiatric disorder, such as a psychotic disorder or bipolar disorder, or by a specific medical condition (secondary psychosis), as might occur with anti–NMDA receptor encephalitis or Huntington's disease.[8] Several key features can help primary care physicians (PCPs) to distinguish primary psychiatric disorders from secondary psychoses (Table 6). Briefly, patients with primary psychiatric illnesses are typically young, have an insidious onset of psychosis (eg, with auditory hallucinations), and/or have premorbid signs and symptoms (eg, mood changes, neurocognitive impairments). Psychosis that persists for longer than 6 months and is accompanied by significant deficits in at least 1 functional domain (such as interpersonal withdrawal) are hallmark features of schizophrenia.[19] However, patients with schizophrenia may also experience unusual perceptions or odd thoughts during the prodromal phase; PCPs should recognize these features as those of early-onset schizophrenia.[20] Notably, the presence of a mood disturbance with concomitant psychotic features can distinguish schizoaffective disorder from schizophrenia or a schizophreniform disorder. A diagnosis of delusional disorder can be made if an individual has at least 1 non-bizarre delusion (eg, misinterpretation of perceptions or experiences) that lasts longer than 1 month and does not have other prominent features of schizophrenia.

As described in Table 1, several medical conditions (eg, neurologic, substance-related, autoimmune, drug-induced) have been associated with the onset of psychosis.[8] In general, when acute psychosis is precipitated by a medical condition, the patient often exhibits abnormal vital signs and laboratory tests, an altered level of consciousness or cognition, or visual hallucinations. In emergency care settings, psychosis is the most common feature of delirium in the elderly. Careful attention should be paid to deficits in cognitive domains (eg, orientation, memory, language), the temporal course of psychotic symptoms, signs of systemic disorders, and information gleaned from collateral sources and caregivers, as these components can help to distinguish dementia from other conditions. Importantly, substance-related disorders are the most common cause of acute psychosis in adolescents and young adults; prompt recognition of sudden onset of psychosis with cardinal symptoms of drug abuse or withdrawal can help PCPs to distinguish substance abuse or withdrawal from other causes of secondary psychoses. An accurate medication history (that includes the use of antipsychotics, herbal or over-the-counter drugs, and recreational drugs) should be considered when ruling out drug-induced psychosis from specific medical conditions.

Regarding psychological etiologies, epidemiologic studies have consistently revealed that stress plays a key role in the onset of psychosis.[21] Brief psychotic disorders are often triggered by stressful situations (eg, trauma, loss of a loved one, childbirth).[22] Patients with brief psychotic disorders typically display the hallmark symptoms of acute psychosis for a shorter period and recover within a month. Further, if a brief psychotic episode occurs during pregnancy or within 4 weeks following delivery, it can be classified as postpartum psychosis; women with this condition often have hallucinations (eg, hearing voices that tell them to hurt or kill their baby). In addition, sociocultural factors (eg, poverty, migration, racial discrimination, lack of social support) are linked to the onset of psychosis[23]; prompt recognition of sociocultural etiologies can help PCPs to initiate timely psychiatric interventions to prevent long-term outcomes of psychosis.

Who Is at Risk for Developing an Acute Psychosis, and How Common Are These Conditions?

A combination of biological factors (eg, biological sex, genetic factors, family history of a psychotic disorder) elevates the baseline risk of individuals for developing an acute psychosis. Nearly one-third of children born with 22q11.2 deletion syndrome have a lifetime diagnosis of psychosis, most of them developing it by early adulthood.[24] Importantly, for a person with a biological predisposition to psychosis, various sociodemographic, behavioral, and medical factors can trigger a psychotic episode. Those who are experiencing

Table 7. Treatment Approaches for Patients With Acute Psychosis

Patients with agitation:
- Ensure the safety of the patient and others
- Consider chemical or physical restraint, when needed
- Transfer to the nearest emergency department
- Offer oral haloperidol (with or without oral lorazepam) or a disintegrating tablet of olanzapine or risperidone
- Consider IM medication, including IM haloperidol plus IM diphenhydramine or IM olanzapine, if the patient will not accept oral medications

Patients without agitation:
- Start an antipsychotic considering patient factors as described in Table 8
- Decide on the appropriate clinical setting for the patient and consider inpatient treatment
- Monitor outcomes of treatment closely, including potential adverse medication effects
- Treat underlying causes of psychosis and obtain consultation from experts
- Refer for psychosocial treatments (including family psychotherapy, cognitive remediation therapy, and cognitive-behavioral therapy)

Abbreviation: IM = intramuscular.

Table 8. Patient Factors That Affect the Choice of an Antipsychotic Medication

Characteristic	Recommendations/Considerations
Elderly	Consider use of less anticholinergic agents (eg, aripiprazole)
Cardiovascular risks (eg, diabetes, hypertension, obesity)	Consider medications with fewer metabolic side effects (eg, aripiprazole, lurasidone, ziprasidone, cariprazine, and asenapine)
Risk of QTc prolongation	Avoid haloperidol, ziprasidone, and quetiapine
Insomnia	Consider using sedating medications (eg, quetiapine and olanzapine)
Agitation	Consider sedating medications with a rapid onset of action (eg, olanzapine, haloperidol, orally disintegrating tablets of risperidone or olanzapine, or IM olanzapine or haloperidol)
CNS stimulation intoxication or catatonia	Avoid antipsychotics; instead, consider use of benzodiazepines
Dementia or cognitive impairment	Consider use of antipsychotics as a last resort, as they might increase mortality
Treatment-resistant illness and suicidal ideation	Consider use of clozapine

Abbreviations: CNS = central nervous system, IM = intramuscular, QTc = corrected QT interval.

potential sources of stressors, such as physical stress (eg, binge drinking, having a poor/unhealthy diet, sleep problems), environmental stress (eg, a lack of social support, migration, major life changes), emotional stress (eg, difficulties with social relationships), or acute life events (eg, bereavement, childhood abuse), are more likely to develop an acute psychosis.[25,26] Moreover, evidence suggests that exposure to psychotropic drugs (eg, amphetamines) and cannabis (ie, marijuana) can increase an individual's vulnerability to psychosis and thus potentiate the early onset of a psychotic episode.[25]

In the general population, the overall lifetime prevalence of any psychotic disorder is ~3%, with 0.21% developing a secondary psychosis due to a medical condition.[27] Schizophrenia and related psychotic disorders affect <1% of US adults (prevalence rate: 0.25%–0.64%), and these episodes typically occur during late adolescence and young adulthood.[28] The lifetime prevalence of bipolar disorder is 0.5%–4.3% in primary care patients and 9.3% for those with bipolar spectrum illness.[29] Delusional disorders are less frequent than affective disorders and schizophrenia in the US (*DSM-5* prevalence rate = 0.02%); women are more commonly affected by delusional disorder than are men.[30] Brief psychotic disorder is unusual in the general population, and it occurs twice as often in women as in men.[22] Further, postpartum psychosis affects 1 in 500 to 1,000 women following childbirth; risk factors include a personal or family history of bipolar disorder or a previous psychotic episode.[31] Although psychotic symptoms have been seen frequently among illicit substance users, the prevalence of psychotic symptoms largely depends on the context of use of or withdrawal from these substances. Moreover, evidence suggests a strong dose-response relationship between the prevalence of psychotic symptoms and the severity of illicit drug use.[32]

Which Treatments Can Manage Acute Psychotic Illnesses?

Symptomatic treatment of acute psychosis may be necessary before the etiology of psychosis has been established. Moreover, treatment for acute psychosis varies depending on the severity of the symptoms and the presumptive cause of psychosis. Table 7 illustrates different treatment approaches for patients with acute psychosis. Similarly, multiple patient factors often influence the initial treatment of psychosis (Table 8). In general, pharmacologic interventions, coupled with psychosocial interventions, are the cornerstones of treatment for those presenting with psychosis.

Antipsychotic medications are the mainstay of treatment for acute psychosis.[33] These medications are most helpful for the positive symptoms of psychosis (eg, hallucinations, delusions, and agitation) and are less likely to improve negative symptoms (eg, apathy and amotivation) or cognitive impairment. Atypical antipsychotics, also called second-generation antipsychotics (eg, risperidone, olanzapine, aripiprazole, and lurasidone), and typical antipsychotics, also called first-generation antipsychotics (eg, haloperidol, perphenazine, and chlorpromazine), are the most common pharmacologic options to treat psychotic symptoms. The former is generally preferred over the latter because they are less likely to induce extrapyramidal symptoms (EPS) and tardive dyskinesia (TD).[34]

In general, antipsychotics are chosen based on a patient's experience with antipsychotics and the drugs' side effect

profiles.[35] Aripiprazole and risperidone often are the initial choice because of their favorable side effect profiles. However, patients with agitation might benefit more from the sedating effects of olanzapine, while those with insomnia might benefit more from quetiapine. Patients with a cardiac history or cardiovascular risk factors (eg, diabetes, hypertension, dyslipidemia) should avoid those antipsychotics having frequent metabolic side effects (eg, clozapine, olanzapine, and quetiapine) and those commonly associated with corrected QT interval (QTc) prolongation (eg, ziprasidone, haloperidol, and quetiapine).[36] Similarly, avoiding medications with significant anticholinergic side effects (eg, olanzapine, quetiapine, and clozapine) will be important for the elderly, and avoiding antipsychotic medications may be necessary for those with dementia, psychosis, or catatonia. Clozapine, a second-generation antipsychotic, is reserved for treatment-resistant cases (ie, persistent psychotic symptoms despite 2 adequate treatment trials with 2 different antipsychotics), mainly because of its potential life-threatening side effects.[37] Similarly, augmentation of antipsychotic medications with a mood stabilizer (like lithium or valproic acid) is a reasonable option for the treatment of acute psychotic symptoms. Although the benefits of using 2 or more antipsychotics have not been well established, the practice is common.[38] While antipsychotic medications can help manage psychotic symptoms, they are associated with adverse effects. Short-term adverse effects include involuntary muscle movements, sedation, weight gain, and constipation, while long-term consequences include TD and metabolic side effects, eg, dyslipidemia and diabetes; all side effects should be discussed with patients before starting an antipsychotic. Potential life-threatening adverse effects of antipsychotics include agranulocytosis and myocarditis, especially with clozapine use; fortunately, these complications are rare. In addition to clozapine, electroconvulsive therapy successfully treats treatment-resistant cases of acute psychosis.[39] Because of the potential life-threatening effects of antipsychotics, employing shared decision-making, when deciding upon the appropriate treatment, can improve adherence and treatment outcomes.[40]

Acute psychosis with agitation can reflect a medical emergency; moreover, maintaining the safety of the patient and those around them is the first step in the treatment. If the patient is in the outpatient or community setting, transferring him/her to the nearest ED (to ensure safety) might be necessary. Agitated patients should be managed with behavioral de-escalation techniques and sedating antipsychotics (eg, disintegrating tablets of olanzapine or risperidone, or oral haloperidol). However, if the patient is unable or unwilling to take oral medications, intramuscular (IM) olanzapine alone or IM haloperidol with or without a benzodiazepine (typically lorazepam) can be used.[41] The use of IM haloperidol can result in EPS, and it is often given IM with benztropine or diphenhydramine to mitigate this risk. Physical restraints might be necessary to protect the patient and those around him/her in severe cases of agitation. However, the use of restraints can result in physical and psychological consequences for patients and health care workers.[42]

Once a patient has been stabilized with antipsychotic medications, pharmacotherapy should be coupled with comprehensive psychosocial interventions to help speed recovery from the illness.[43] Psychosocial treatments help individuals cope with positive symptoms of psychosis, and they have the potential to reduce negative and cognitive symptoms of psychosis. Cognitive-behavioral therapy, cognitive remediation therapy, and family therapy have each been effective in improving outcomes of psychosis.[44] Psychosocial skills training and other recovery-oriented community-based services might be even more helpful for those with chronic psychosis.

What Types of Follow-Up May Be Useful Following the Initial Assessment?

After the initial assessment and the initiation of treatment, close follow-up is necessary for effective management of acute psychosis. Depending on the severity, nature, and etiology of psychotic symptoms, a psychiatrist, another mental health professional, a PCP, and specialty providers (including neurologists, rheumatologists, endocrinologists, or infectious disease doctors) might be involved in follow-up care. Multidisciplinary treatment is effective in improving outcomes of psychosis.[45] Unfortunately, it might not be feasible to establish the etiology of psychosis during the initial assessment. Hence, review of the laboratory results and imaging findings from the specialty providers will be important. Similarly, close monitoring of the psychotic symptoms while the patient is still in the acute and maintenance phases of treatment is typically necessary to evaluate the treatment outcomes. Acute safety risks, changes in the presenting symptoms, collateral information, a detailed physical examination (including a mental status examination), consideration of potential withdrawal from substances, and discussions of the risks and benefits of treatment are some of the components of the follow-up evaluations.[46] Once a patient's psychotic symptoms are stabilized, reevaluation of positive and negative symptoms of psychosis, cognitive function, and quality of life is important to ensure recovery from psychosis. As many individuals experience adverse effects from antipsychotics, assessment of the short- and long-term side effects is necessary to improve treatment adherence and ensure better outcomes. Similarly, follow-up with psychosocial skill trainers, rehabilitation practitioners, social workers, and psychotherapists will be necessary to improve a patient's recovery, especially from chronic psychosis.

Case Vignette: What Happened to Ms E?

The ED attending physician formulated a differential diagnosis that included medical, neurologic, and psychiatric illnesses. To rule out medical and neurologic causes of acute psychosis, Ms E's blood was drawn for

testing. Her CBC and differential, electrolytes (including calcium), glucose, LFTs, TFTs, B_{12} and folate levels, ESR, ANA, FTA-abs for syphilis, HIV testing, serum toxicology, urine toxicology, and urinalysis revealed no abnormalities. An MRI revealed no abnormalities. Her vital signs (including temperature, heart rate, blood pressure, respiratory rate, and pulse oxygenation) were within normal limits. A complete physical and neurologic examination also revealed no abnormalities. With all medical and neurologic causes of acute psychosis ruled out, the ED physician requested a psychiatry consultation.

The psychiatric consultant learned that Ms E had lost her job as a waitress because she made too many mistakes with customers' orders and made odd comments about the food being contaminated. Since losing her job 4 months ago, she rarely left her apartment. More recently, she had been worried about someone breaking into her apartment and spilling gasoline in the kitchen. She was also hearing someone call her name and make disparaging comments about her. Ms E's mental status examination revealed she was alert, oriented, and attentive; her short- and long-term memory were intact. There was no evidence of depression or mania; however, she was paranoid and had auditory hallucinations. She denied thoughts of suicide or homicide and lacked insight into her symptoms.

Given that medical and neurologic illnesses had been ruled out, the most likely diagnosis was a schizophreniform disorder. Ms E was admitted to a psychiatric inpatient facility, started on aripiprazole (with subsequent improvement in her symptoms), and discharged to outpatient psychiatric care after a 2-week stay.

CONCLUSION

New-onset psychotic symptoms (often involving hallucinations, delusions, or incoherent or disorganized behavior or speech) are challenging for patients, family members, coworkers, and the health care providers who attempt to evaluate and treat their biological (eg, neurologic, medical, psychiatric disorder, or drug-induced), psychological (eg, stress), and sociocultural underpinnings. Since treatment is largely predicated on the etiology of psychosis, determining the nature, time course, and severity of symptoms and whether symptoms are a consequence of a primary psychiatric condition or a medical/neurologic illness is essential; evaluation involves a broad-based interview and a physical/neurologic examination as well as myriad laboratory testing and brain imaging. A negotiated treatment approach and diligent monitoring of symptoms (and adverse side effects) will help to optimize outcomes.

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REFERENCES

1. Arciniegas DB. Psychosis. *Continuum (Minneap Minn)*. 2015;21(3 Behavioral Neurology and Neuropsychiatry):715–736. PMC4455840.
2. Gaebel W, Zielasek J. Focus on psychosis. *Dialogues Clin Neurosci*. 2015;17(1):9–18.
3. Gelder M, Andreasen N, Lopez-ibor J, et al. Acute and transient psychotic disorders. In: New Oxford Textbook of Psychiatry. 2012;10:1–16.
4. Bell V, Raihani N, Wilkinson S. Derationalizing Delusions. *Clin Psychol Sci*. 2021;9(1):24–37.
5. Lieberman JA, First MB. Psychotic Disorders. *N Engl J Med*. 2018;379(3):270–280.
6. Castagnini A, Galeazzi GM. Acute and transient psychoses: clinical and nosological issues. *Br J Psychiatr Adv*. 2016;22(5):292–300.
7. Freudenreich O, Holt DJ, Goff DC. Psychotic patients. In: Stern TA, Freudenreich O, Smith FA, et al, eds. *Massachusetts General Hospital Handbook of General Hospital Psychiatry*. 7th ed. Edinburgh: Elsevier; 2017.
8. Griswold KS, Del Regno PA, Berger RC. Recognition and differential diagnosis of psychosis in primary care. *Am Fam Physician*. 2015;91(12):856–863.
9. Bojdani E, Zhang T, Shetty S, et al. Hypercalcemia and psychosis: case report, review of the literature, and management considerations. *Prim Care Companion CNS Disord*. 2018;20(6):18nr02356.
10. Keshavan MS, Kaneko Y. Secondary psychoses: an update. *World Psychiatry*. 2013;12(1):4–15.
11. Wilson JE, Mart MF, Cunningham C, et al. Delirium. *Nat Rev Dis Primers*. 2020;6(1):90.
12. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. *Nat Rev Neurol*. 2009;5(4):210–220.
13. Fiorentini A, Cantù F, Crisanti C, et al. Substance-induced psychoses: an updated literature review. *Front Psychiatry*. 2021;12:694863.
14. Marder S. Psychosis in adults: epidemiology, clinical manifestations, and diagnostic evaluation. UpToDate website. 2021. https://www.uptodate.com/contents/psychosis-in-adults-epidemiology-clinical-manifestations-and-diagnostic-evaluation
15. Cosci F, Chouinard G. Acute and persistent withdrawal syndromes following discontinuation of psychotropic medications. *Psychother Psychosom*. 2020;89(5):283–306.
16. Freudenreich O. Secondary schizophrenia. In: *Psychotic Disorders: a Practical Guide*. 2nd ed. Switzerland: Humana; 2020.
17. Freudenreich O, Brown HE, Holt DJ. Psychosis and schizophrenia. In: Stern TA, Fava M, Wilens TE, et al, eds. *Massachusetts General Hospital Comprehensive Clinical Psychiatry*. 2nd ed. Philadelphia, PA: Elsevier; 2016.
18. Sommer IE, de Kort GA, Meijering AL, et al. How frequent are radiological abnormalities in patients with psychosis? A review of 1379 MRI scans. *Schizophr Bull*. 2013;39(4):815–819.
19. Calabrese J, Khalili YA. Psychosis. In: StatPearls. 2022. https://pubmed.ncbi.nlm.nih.gov/31536188/
20. Byrne P. Managing the acute psychotic episode. *BMJ*. 2007;334(7595):686–692.
21. Stilo SA, Murray RM. Non-genetic factors in schizophrenia. *Curr Psychiatry Rep*. 2019;21(10):100.
22. Stephen A, Lui F. Brief psychotic disorder; In: StatPearls. 2021. https://pubmed.ncbi.nlm.nih.gov/30969734/
23. Varchmin L, Montag C, Treusch Y, et al. Traumatic events, social adversity and discrimination as risk factors for psychosis—an umbrella review. *Front Psychiatry*. 2021;12:665957.
24. Weisman O, Guri Y, Gur RE, et al; International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. Subthreshold psychosis in 22q11.2 deletion syndrome: multisite naturalistic study. *Schizophr Bull*. 2017;43(5):1079–1089.
25. Heckers S. Who is at risk for a psychotic disorder? *Schizophr Bull*. 2009;35(5):847–850.
26. Bromley S, Choi M, Faruqui S. *First Episode of Psychosis an Information Guide*. Revised Edition. Center for Addiction and Mental Health; 2015.
27. Perälä J, Suvisaari J, Saarni SI, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry*. 2007;64(1):19–28.
28. National Institute of Mental Health. Schizophrenia. NIMH website. https://www.nimh.nih.gov/health/statistics/schizophrenia
29. Cerimele JM, Chwastiak LA, Dodson S, et al. The prevalence of bipolar disorder in general primary care samples: a systematic review. *Gen Hosp Psychiatry*. 2014;36(1):19–25.
30. Joseph SM, Siddiqui W. Delusional disorder. In: StatPearls. 2021. https://pubmed.ncbi.nlm.nih.gov/30969677/
31. Topiwala A, Hothi G, Ebmeier KP. Identifying patients at risk of perinatal mood disorders. *Practitioner*. 2012;256(1751):15–18, 2.
32. Smith MJ, Thirthalli J, Abdallah AB, et al. Prevalence of psychotic symptoms in substance users: a comparison across substances. *Compr Psychiatry*. 2009;50(3):245–250.
33. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a

systematic review and network meta-analysis. *Lancet*. 2019;394(10202):939–951.
34. Zhang JP, Gallego JA, Robinson DG, et al. Efficacy and safety of individual second-generation vs first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. *Int J Neuropsychopharmacol*. 2013;16(6):1205–1218.
35. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951–962.
36. Foley DL, Morley KI. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. *Arch Gen Psychiatry*. 2011;68(6):609–616.
37. Hasan A, Falkai P, Wobrock T, et al; World Federation of Societies of Biological Psychiatry (WFSBP) Task Force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World J Biol Psychiatry*. 2012;13(5):318–378.
38. Paudel S, Dahal R, Mathias J, et al. Evaluation of risk factors for antipsychotic polypharmacy in inpatient psychiatry units of a community hospital: a retrospective analysis. *Community Ment Health J*. 2019;55(5):750–754.
39. Grover S, Sahoo S, Rabha A, et al. ECT in schizophrenia: a review of the evidence. *Acta Neuropsychiatr*. 2019;31(3):115–127.
40. Paudel S, Sharma N, Joshi A, et al. Development of a shared decision making model in a community mental health center. *Community Ment Health J*. 2018;54(1):1–6.
41. Zimbroff DL. Management of acute psychosis: from emergency to stabilization. *CNS Spectr*. 2003;8(suppl 2):10–15.
42. Wong AH, Ray JM, Rosenberg A, et al. Experiences of individuals who were physically restrained in the emergency department. *JAMA Netw Open*. 2020;3(1):e1919381.
43. Wright A, Browne J, Mueser KT, et al. Evidence-based psychosocial treatment for individuals with early psychosis. *Child Adolesc Psychiatr Clin N Am*. 2020;29(1):211–223.
44. Morrison AP, Pyle M, Maughan D, et al; MAPS group. Antipsychotic medication versus psychological intervention versus a combination of both in adolescents with first-episode psychosis (MAPS): a multicentre, three-arm, randomised controlled pilot and feasibility study. *Lancet Psychiatry*. 2020;7(9):788–800.
45. Dixon LB, Dickerson F, Bellack AS, et al; Schizophrenia Patient Outcomes Research Team (PORT). The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophr Bull*. 2010;36(1):48–70.
46. Addington D, Abidi S, Garcia-Ortega I, et al. Canadian guidelines for the assessment and diagnosis of patients with schizophrenia spectrum and other psychotic disorders. *Can J Psychiatry*. 2017;62(9):594–603.