WHEN PSYCHOSIS IS NOT SCHIZOPHRENIA

Definition • Medical causes • Substances • Psychiatric context

TOP 3 THINGS EVERY PHYSICIAN SHOULD KNOW

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Disclosures

- None
- No relationship with any organization that involves direct financial payments, membership on advisory boards or speakers' bureau, funded grants or clinical trials, patents on a drug, product or device
- No other investments or relationships that could be seen as having the potential to influence the content of the educational activity

Objectives

- By the end of the presentation, participants will be able to:
- Recognize medical causes of psychosis
- Identify substance-related psychosis
- Differentiate psychosis in other psychiatric disorders

DSM-5-TR FRAMEWORK

Psychosis - A syndrome, not a diagnosis

- A common symptom of many psychiatric, neurodevelopmental, neurologic, and medical conditions
- *Early APA and DSM* broadly defined it as “gross impairment in reality testing” or “loss of ego boundaries” that interferes with the capacity to meet the ordinary demands of life
- Described in 5 domains
- Severity is defined by the significance, number, and duration of psychotic signs and symptoms.
- Describe the syndrome and then determine its cause

Clinical implication

The presence of psychosis identifies what the patient is experiencing—not why it is occurring.

Etiology requires context, examination and longitudinal course.

American Psychiatric Association. DSM-5-TR. Schizophrenia Spectrum and Other Psychotic Disorders. 2022.

DESCRIBE BEFORE DIAGNOSING

DSM-5-TR describes psychosis across five domains

1	**Delusions**	Fixed beliefs resistant to conflicting evidence
2	**Hallucinations**	Perception-like experiences without an external stimulus
3	**Disorganized thinking**	Usually inferred from disorganized speech, severe enough to impact communication
4	**Abnormal motor behaviour**	Gross disorganization or catatonia
5	**Negative symptoms**	Reduced emotional expression, speech or motivation

No single domain establishes schizophrenia.

American Psychiatric Association. DSM-5-TR. 2022; pp. 101–138.

CLINICAL SCENARIO

The same symptom can arise from very different illnesses

A 29-year-old presents with paranoia, voices and three nights without sleep.

1. **Is attention and cognition intact?**
2. **What changed—illness, medication or substance?**
3. **Does psychosis track a mood episode?**

Medical causes

MEDICAL DIFFERENTIAL

Think in etiologic groups

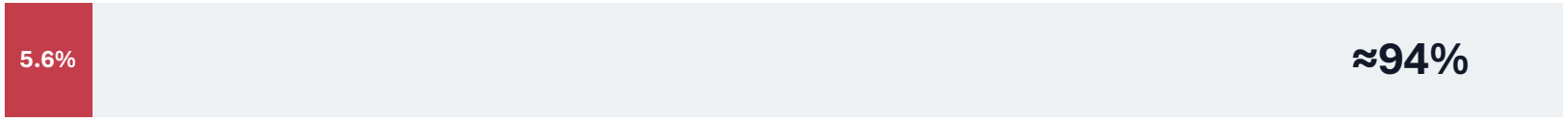
Category	Conditions	Clues
Delirium / metabolic	Hypoglycemia; electrolytes; hepatic/renal failure; hypoxia	**Inattention;** altered arousal; fluctuation; **disorientation**
Endocrine / nutritional	Thyroid; Cushing; calcium; B12/folate	Systemic signs; weight/skin change; weakness; cognitive change
Infectious / inflammatory	HIV; neurosyphilis; encephalitis; SLE/vasculitis	Fever; headache; immunosuppression; seizures
Neurological	Epilepsy; tumour; stroke; MS; TBI; Huntington disease	Focal signs; headache; movements; personality/cognitive change
Neurodegenerative	Lewy body; Alzheimer; FTD; Parkinson disease	Late onset; progressive decline; visual hallucinations; parkinsonism

Skikic & Arriola. First Episode Psychosis Medical Workup. Psychiatr Clin North Am. 2020.

MEDICAL AND NEUROLOGICAL

Medical causes are the minority—but missing them matters

Identified organic cause in younger first-episode cohorts



identified organic cause

no identified organic cause

MRI

5.9%

changed management
NNS 18
Blackman et al

The remaining presentations are not all schizophrenia: mood disorders, substance-related and other primary psychoses remain in the differential.

Low prevalence does not justify low vigilance when the cause is **urgent, treatable** and potentially **reversible.**

Tesnières et al. L'Encéphale. 2026. Blackman et al. JAMA Psychiatry. 2023;80:1047–1054.

MEDICAL DIFFERENTIAL

Red flags

- **Atypical age at onset**
- **Hours-to-days onset or rapid progression**
- **Fluctuating attention or consciousness**
- Fever or autonomic instability
- New focal neurological findings
- **Seizure or new severe headache**
- **Abnormal movements or catatonia**
- Marked cognitive/language deterioration
- **Postpartum or immunosuppressed state**
- Extreme antipsychotic sensitivity

NEUROLOGICAL EMERGENCY

Autoimmune encephalitis is a “cannot-miss” psychosis mimic

Psychosis / behaviour

↓

Language or cognition

↓

Catatonia / movements

↓

Seizures / autonomic change

Escalate

Neurology
EEG + MRI
CSF studies
Paired serum/CSF antibodies

Broad serum screening in uncomplicated psychosis is not supported.

Pollak et al. Lancet Psychiatry. 2020;7:93–108.

Substance-related causes

HISTORY AND DSM-5-TR ANCHOR

The substance history is a diagnostic test

WHAT	Substances, prescriptions, OTC agents, supplements
WHEN	**First use, last use, escalation, cessation and symptom onset**
HOW MUCH	Quantity, frequency, route, cannabis potency and binge pattern
WITHDRAWAL	Tremor, sweating, insomnia, seizures or autonomic change
BEFORE	Psychosis predating exposure or occurring during abstinence
VERIFY	Collateral, pharmacy record and targeted toxicology

DSM-5-TR: substance/medication-induced psychotic disorder

1. **Delusions and/or hallucinations**
2. **Develop during or soon after exposure, intoxication or withdrawal**
3. Agent is capable of producing the syndrome
4. Not better explained by an independent psychotic disorder
5. Not exclusively during delirium

Persistence during sustained abstinence raises concern for a primary disorder.

American Psychiatric Association. DSM-5-TR. 2022.

SUBSTANCE- AND MEDICATION-INDUCED

A plausible exposure timeline is necessary—but not sufficient

Exposure	Characteristic context or clues
Stimulants	Paranoia; agitation; insomnia; sympathetic activation; tactile phenomena
Cannabis / high-potency THC	Paranoia; perceptual change; anxiety; disorganization
Alcohol or sedative withdrawal	Tremor; diaphoresis; hypertension; seizures; delirium risk
Corticosteroids	Mania often coexists with psychosis; dose increases risk
Dopaminergic / anticholinergic drugs	Hallucinations; cognitive change or delirium—especially in older adults

Ask specifically

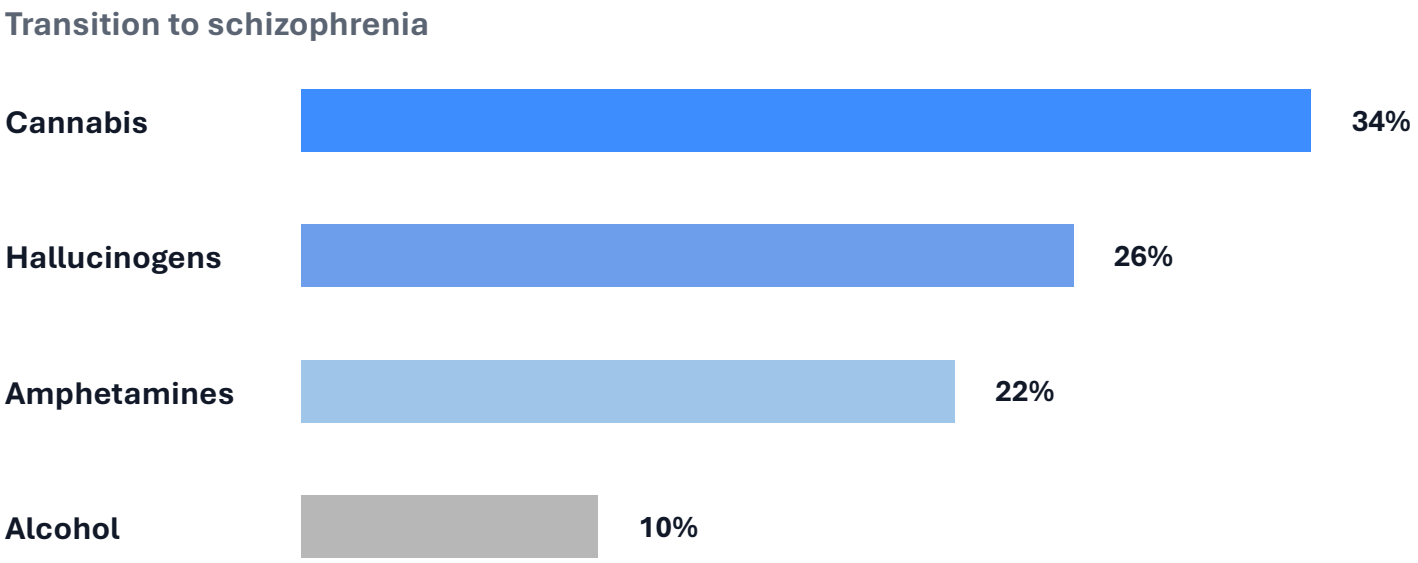
- **Prescription changes***
- OTC + supplements
- Cannabis potency/frequency
- Binges and last use
- Collateral + toxicology

*Medications; Muscle relaxants, Antihistamines, Antidepressants, Cardiovascular medications, Antihypertensive medications, Anticonvulsants, Antiparkinson medications, Chemotherapy agents,

APA Practice Guideline for Schizophrenia, 3rd ed.; Front Pharmacol. 2025;16:1628765.

LONGITUDINAL RISK

“Substance-induced” does not mean benign or finished



≈25%

overall pooled transition after substance-induced psychosis

Follow cannabis- and stimulant-associated psychosis like other first episodes.

Murrie et al. Schizophrenia Bulletin. 2020;46:505–516. 40,783 participants.

Psychiatric Context

PSYCHIATRIC CONTEXT

Psychiatric diagnosis depends on when psychosis occurs

MOOD

PSYCHOSIS

TIME

Psychosis outside major mood episodes

Schizophrenia-spectrum more likely

Psychosis confined to mania/depression

Affective psychosis more likely

Unclear at first episode

Keep diagnosis provisional

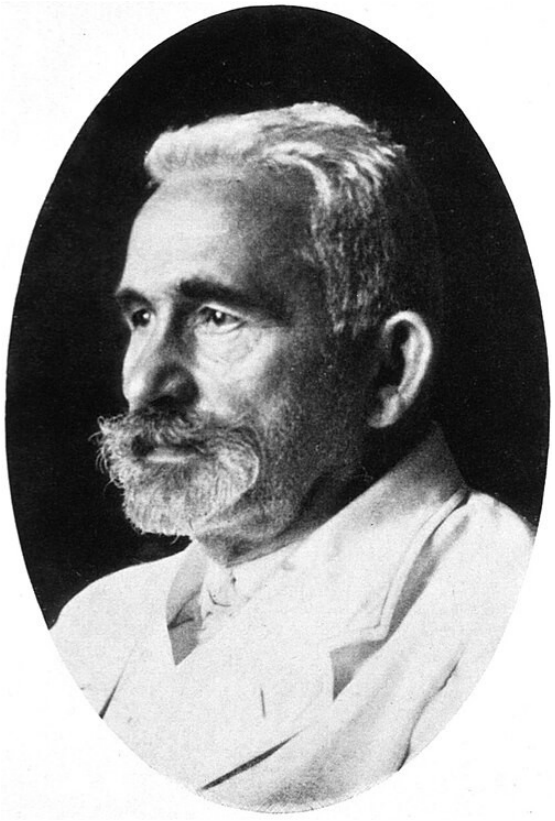
Schizophrenia vs Bipolar Disorder

- Emil Kraepelin (1856–1926). Dementia praecox vs Manic-depressive psychosis based on course and outcome;

- Disordered intellectual functioning, constant deterioration, virtually no recoveries and a poor outcome vs exacerbations and remission, and many complete recoveries.

- Response to medication not helpful.

- GWAS uncover shared genomic loci and overlapping risk genes tied to synaptic function, calcium channel activity, and neuronal development, e.g *DISC-1* is associated with increased risk for schizophrenia, bipolar illness, major depression, and other conditions.



SCHIZOPHRENIA VS BIPOLAR I DISORDER

Longitudinal course provides the strongest distinction

Feature	Schizophrenia	Bipolar I disorder
Typical age of onset	Late adolescence to early adulthood; commonly early-to-mid 20s	Often adolescence or early adulthood, but a wider age distribution
Gender pattern	Modestly more common and earlier onset in males	Overall prevalence approximately equal between males and females
Psychosis outside mood episodes	Psychosis is not confined to major mood episodes	Persistent psychosis during euthymia argues against bipolar psychosis
Course of illness	Often chronic or relapsing, with residual symptoms between episodes	Episodic mania and depression, with greater tendency toward recovery
Premorbid trajectory	Social, academic, occupational or cognitive decline may precede psychosis	Premorbid functioning often relatively preserved until a mood episode
Interepisode functioning	Negative, cognitive or psychotic symptoms may persist	Often returns substantially toward baseline, especially earlier in illness
Prognosis	On average, greater persistent cognitive and functional impairment	Generally better interepisode recovery, but recurrence and suicide risk remain
Strongest diagnostic anchor	Persistent non-affective psychosis + functional decline + ≥6-month course	Syndromal mania + episodicity + psychosis confined to mood episodes

No single feature is pathognomonic; diagnose from the complete longitudinal pattern.

DSM-5-TR criteria summarized

DIAGNOSTIC ANCHORS—NOT SHORTCUTS

DSM-5-TR criteria turn phenomenology into diagnosis

SCHIZOPHRENIA

1. **≥2 Criterion A symptoms for ≥1 month**
2. **At least 1: delusions, hallucinations or disorganized speech**
3. Functional decline
4. Continuous disturbance ≥6 months
5. Mood, substance and medical causes excluded

BIPOLAR I

1. **At least 1 manic episode**
2. **Mood change + increased energy/activity**
3. ≥1 week—or any duration if hospitalized
4. Marked impairment, hospitalization or psychosis
5. Exclude substance or medical cause

MDD + PSYCHOSIS

1. **Major depressive episode: ≥5 symptoms over ≥2 weeks**
2. **Depressed mood or anhedonia required**
3. Delusions and/or hallucinations occur during the episode
4. No manic or hypomanic episode
5. Psychosis outside depression redirects the diagnosis

American Psychiatric Association. DSM-5-TR. 2022. Criteria summarized

DISTINGUISHING FEATURES AND PSYCHIATRIC MANIFESTATIONS

Dementias differ in cognition, behaviour and psychosis

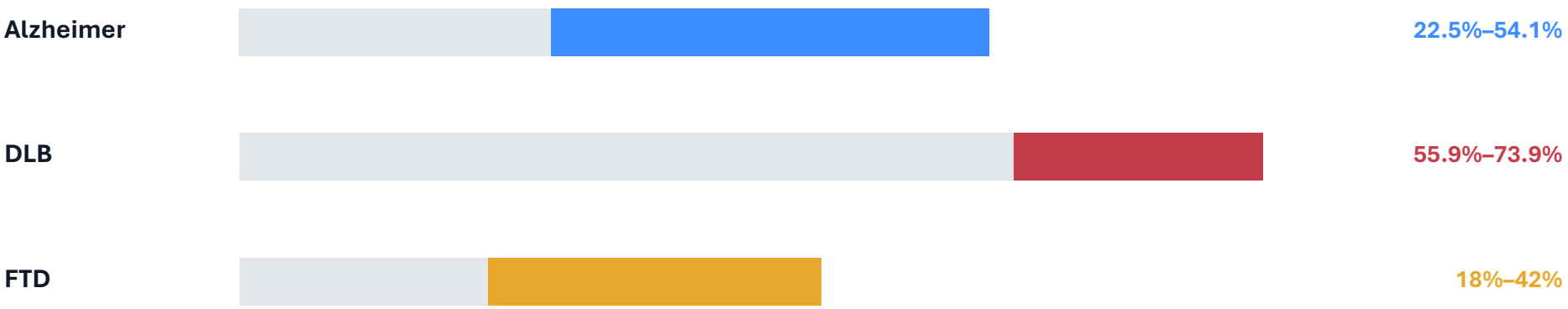
Dementia	Cognitive / neurological pattern	Psychiatric manifestations	Psychosis pattern / discriminator
Alzheimer	Progressive episodic-memory loss; later language and executive decline	Apathy, depression, anxiety, agitation	Delusions > hallucinations: theft, abandonment, infidelity; misidentification. Hallucinations often later
Lewy body dementia	Attention, executive and visuospatial deficits; fluctuations; parkinsonism; REM sleep behaviour disorder	Depression, anxiety, apathy, sleep disturbance; medication-related impulse-control symptoms	Early formed visual hallucinations, illusions. DLB: cognition before/within 1 year of motor onset; PDD: dementia later
Behavioural FTD	**Early personality, social-conduct and executive change;** memory may initially be preserved	Disinhibition, apathy, loss of empathy, compulsions, hyperorality	Classic delusions/hallucinations less prominent; consider genetic FTD when present
Vascular dementia	Executive slowing; stepwise or variable course; focal signs and gait change	Apathy, depression, irritability and emotional lability	Psychosis less characteristic; hallucinations require assessment for delirium or additional neurodegenerative pathology

Early recurrent visual hallucinations + fluctuations + parkinsonism strongly favour Lewy body disease.

COMPARATIVE EVIDENCE

Psychosis is most prevalent—and most visually distinctive—in DLB

Psychosis prevalence reported across 98 studies



DLB signature Visual hallucinations 50%–69.6% • misidentification delusions 16.6%–78.3%

Antipsychotics may worsen parkinsonism and cause severe sensitivity reactions in Lewy body dementia.

Dementia and delirium reinforce one another

Delirium superimposed on dementia - acute change from baseline, fluctuation, and impaired attention
Visual hallucinations and paranoid ideas can occur, particularly in hyperactive or mixed delirium.

VULNERABILITY

Pre-existing dementia
Reduced cerebral reserve increases susceptibility to delirium.

ACUTE INSULT

Delirium
Acute onset, fluctuating course and impaired attention or awareness.

AFTERMATH

Cognitive decline
May accelerate decline or unmask previously unrecognized neurodegeneration.

Possible mechanisms include neuronal injury, shared vascular or inflammatory factors, frailty, unmasking of preclinical neurodegeneration, and delirium acting as an acute stress test of limited cognitive reserve.

The relationship is clinically large—and bidirectional

PRACTICE IMPLICATION

After delirium, document cognition and arrange follow-up. In dementia, actively prevent and screen for delirium during acute illness or hospitalization.

3–7×

Higher delirium risk with dementia

≈3×

Higher subsequent dementia risk after delirium

31%

Diagnosed with dementia within 5 years*

TAKE-HOME FRAMEWORK

Three questions prevent premature schizophrenia diagnoses

1	ATTENTION?	Is this delirium or a rapidly evolving neurological syndrome?
2	TIMELINE?	What changed—and does the timing make pharmacological sense?
3	MOOD?	Does psychosis occur outside a syndromal mood episode?

Psychosis is a syndrome. The safest diagnosis is sometimes provisional.

References

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