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Misdiagnosis of Psychosis: Differential Diagnosis, Medical Causes, and Diagnostic Safety

Narrative Literature Review

Abstract—Psychosis is a syndrome rather than a single disease entity, and its causes range from primary psychotic disorders to mood, substance-related, neurological, autoimmune, endocrine, developmental, trauma-related, and culturally mediated presentations. Diagnostic error occurs in both directions: a schizophrenia-spectrum diagnosis may be assigned prematurely, or clinically important psychotic phenomena may be minimized, attributed too narrowly, or mistaken for culturally normative experience. This narrative review examines diagnostic safety in first and atypical presentations, emphasizing collateral chronology, physical and neurological examination, hypothesis-led investigation, toxicology when indicated, medication and substance timelines, and longitudinal reassessment. Abrupt onset, fluctuating attention or consciousness, autonomic instability, seizures, focal neurological signs, abnormal movements, catatonia, or unexpected cognitive change should heighten concern for a secondary medical or neurological cause. Because first-episode diagnoses vary in stability, early formulations should remain provisional when evidence is incomplete. Racial disparities in schizophrenia diagnosis also support systematic assessment of mood, trauma, culture, language, and service context. Communication should validate distress without either aggressively disputing a belief or affirming unverified content. The review proposes that diagnostic safety is a longitudinal process with four linked tasks: precise description of psychotic phenomena, proportionate investigation of high-consequence alternatives, treatment of immediate risk without overstating etiological certainty, and scheduled revision against the observed course. Diagnostic uncertainty becomes clinically useful only when it is explicit and tied to investigation, treatment, and review.

Index Terms—psychosis, differential diagnosis, first-episode psychosis, misdiagnosis, delirium, autoimmune encephalitis, substance-induced psychosis, provisional diagnosis, diagnostic safety

I. INTRODUCTION

Hearing a voice, expressing an unusual belief, or speaking incoherently can arise through different clinical pathways. Initial assessment must address immediate safety and medical urgency while describing the presentation precisely enough to avoid adopting an earlier label without scrutiny. Psychosis may require rapid treatment, but urgency does not confer diagnostic certainty.

Earlier JPPC articles examined a case of psychosis, treatment-resistant schizophrenia and psychosis, and Communication-Focused Therapy for psychosis (Haverkampf, 2012, 2016, 2017), with emphasis on meaning and therapeutic communication. The present review turns to differential diagnosis and diagnostic safety across medical, neurological, autoimmune, substance-related, mood, trauma-related, developmental, cultural, and structural considerations. Here, diagnostic safety refers to practices that reduce both missed secondary causes and premature closure on a chronic primary diagnosis. Its central premise is that urgent care, etiological inquiry, explicit provisionality, and scheduled revision should proceed together.

II. SCOPE AND REVIEW METHOD

This narrative review includes sources available through 30 May 2025. Searches covered first-episode psychosis, diagnostic stability, medical and neurological assessment, autoimmune psychosis and encephalitis, substance-induced psychosis, racial disparity, cultural formulation, and dimensional models of psychosis. Priority was given to professional guidance, systematic and umbrella reviews, meta-analyses, longitudinal and diagnostic studies, and clinically informative original research. Bibliographic details were checked against PubMed, Crossref, or the issuing organization. Earlier JPPC articles were included when directly relevant.

The aim is to support recognition, differential formulation, and safe clinical decision-making, not to produce a pooled effect estimate or prescribe a universal investigation panel.

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Group-level findings must be interpreted in the individual clinical context, and current guidance should be checked for updates.

Unless otherwise stated, all tables and boxed frameworks in this article are author-developed clinical syntheses intended to organize assessment and discussion; they are not validated instruments or substitutes for clinical judgment.

Core propositions

- Psychosis is a syndrome; the immediate tasks are to identify risk, level of care, and plausible cause.
- First or atypical presentations require medical, neurological, medication, and substance assessment.
- Delirium, catatonia, seizures, and autoimmune or other neurological disorders are high-consequence differentials.
- Mood course, trauma, culture, development, and structural bias shape interpretation.
- Diagnostic uncertainty is useful only when evidence, alternatives, investigation, treatment, review, and revision triggers are explicit.

III. DEFINING PSYCHOTIC PHENOMENA

Delusions cannot be defined solely by whether a clinician regards an idea as implausible. Assessment should address content, conviction, preoccupation, evidential basis, flexibility, cultural context, and consequences. Hallucination-like experiences vary by modality, perceived location, controllability, context, relation to sleep, trauma, substances, and insight. Disorganization is best documented through concrete examples of speech or behavior rather than a global impression. Negative symptoms may overlap with depression, medication effects, cognitive impairment, trauma, and social deprivation.

The American Psychiatric Association's diagnostic manual distinguishes primary psychotic disorders from mood disorders with psychotic features, substance/medication-induced conditions, and psychotic disorder due to another medical condition (American Psychiatric Association, 2013). Diagnostic categories support communication and research but do not substitute for an individual formulation. van Os and Reininghaus (2016) describe psychosis as a transdiagnostic and extended phenotype, emphasizing that psychotic-like experiences also occur outside categorical psychotic disorders.

Language can narrow diagnostic reasoning before evidence has been gathered. Terms such as "paranoid" may refer to realistic fear, trauma-related hypervigilance, personality traits, intoxication, delirium, or a delusional belief. "Responding to internal stimuli" is an inference from behavior, not a description of the person's experience. Before translating an observation into a diagnosis, clinicians should ask what the person experiences, when it began, how certain they feel, and what meaning they give it. Developmental, linguistic, sensory, and cognitive factors should be distinguished from a new psychotic process by comparison with the person's baseline and a collateral chronology.

Premature labeling can produce circular reasoning: an experience is called psychotic because a psychosis diagnosis is already recorded, and the diagnosis is then defended by that same interpretation. No single unusual experience is diagnostically specific; its form, associated signs, course, distress, impairment, and context must be considered together.

Describing psychotic phenomena precisely

Domain	Questions
Belief	Content, conviction, evidence, flexibility, preoccupation, cultural context, consequences?
Perception	Modality, perceived internal/external location, controllability, command content, relation to sleep, insight?
Thought/speech	Derailment, incoherence, latency, language, developmental baseline?
Behavior	Disorganization, catatonia, apparent goal, context, immediate danger?
Negative symptoms	Expression, speech, motivation, pleasure, social opportunity, medication effects?
Cognition/attention	Fluctuation, orientation, memory, level of consciousness?

IV. FIRST-EPISODE MEDICAL AND NEUROLOGICAL SAFETY

A first episode of psychosis requires medical as well as psychiatric assessment; schizophrenia should not be assumed at presentation. The history should reconstruct tempo of onset and recent infection or fever, seizures, head injury, endocrine symptoms, pregnancy or postpartum status, prescribed and nonprescribed medication, supplements, substance exposure, sleep, and neurological change. Examination should include vital signs, physical and neurological findings, cognition, attention, movement, and catatonic features. Investigations should follow the presentation and local protocols.

Skikic and Arriola (2020) review evidence-informed medical assessment in first-episode psychosis. The American College of Radiology provides guidance on neuroimaging in altered mental status, including new-onset delirium and new-onset psychosis (Expert Panel on Neurological Imaging et al., 2024). A systematic review catalogued a wide range of somatic causes and found no universally accepted comprehensive workup (Dissaux et al., 2023). These sources converge on a clinically guided approach: basic medical assessment should not be omitted, whereas additional tests should answer questions raised by the history, examination, or atypical features rather than constitute indiscriminate screening.

Features that heighten concern for a secondary cause include abrupt or rapidly progressive onset, fluctuating

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attention or consciousness, fever, autonomic instability, seizures, focal neurological signs, abnormal movements, catatonia, severe headache, new cognitive decline, late or otherwise atypical onset, and a close temporal relationship to medication or substance exposure. A psychiatric history does not reduce the possibility of concurrent medical illness and should not lower clinical vigilance. Severe sleep disruption belongs on the same timeline because it may contribute to the presentation or signal an evolving mood, substance-related, or medical condition.

Selected red flags for secondary psychosis

Finding	Concern raised
Fluctuating attention or consciousness	Delirium, intoxication, neurological or systemic illness
Seizure or focal neurological sign	Neurological disease, encephalitis, structural lesion
Fever or autonomic instability	Infection, toxic state, malignant syndrome, encephalitis
Abnormal movements or catatonia	Neurological or autoimmune disorder, medication effect, severe psychiatric illness
Abrupt or atypical onset	Substance or medication effect, medical illness, mood disorder, brief psychosis
Postpartum onset	Mood or psychotic emergency with medical and safeguarding needs
New exposure or withdrawal	Prescription, over-the-counter, recreational substance, toxin, withdrawal

V. AUTOIMMUNE AND OTHER MEDICAL CAUSES

Autoimmune encephalitis may present with psychiatric symptoms, seizures, cognitive change, movement disorder, autonomic instability, and altered consciousness. Graus et al. (2016) proposed a clinical approach that permits early syndrome recognition before antibody results are available. The criteria do not justify routine screening of every person with chronic psychosis; they support escalation when the temporal pattern, neurological findings, and associated features are compatible.

Pollak et al. (2020) proposed an international consensus approach to suspected autoimmune psychosis and warning signs for neurological investigation. The proposed construct remains under development and should be applied in collaboration with neurology and other relevant specialties. Over-recognition may expose patients to invasive investigations or inappropriate immunotherapy, whereas under-recognition may delay treatment of a serious disorder.

Other medical contributors include endocrine and metabolic disturbance, infection, epilepsy, neurodegenerative or structural disease, nutritional deficiency, and medication toxicity. Each test should answer a defined clinical question. Normal screening results do not prove a primary psychotic disorder, just as an incidental abnormality does not prove causation. Findings must be interpreted against timing, examination, and course.

VI. SUBSTANCES, MEDICATIONS, AND WITHDRAWAL

Cannabis, stimulants, hallucinogens, corticosteroids, dopaminergic agents, anticholinergic burden, and other substances or medications can produce or exacerbate psychotic symptoms. Alcohol or sedative withdrawal may cause severe perceptual disturbance and delirium. Inquiry should be nonjudgmental and specific about amount, potency, route, frequency, timing, last use, prescribed and nonprescribed products, and withdrawal.

Substance-induced psychosis is not necessarily brief or benign. Murrie et al. (2020) found substantial but variable rates of later transition to schizophrenia after substance-induced and other brief psychoses. These findings support follow-up and risk reduction; they neither invalidate an initial substance-related formulation nor make transition inevitable.

Timing informs but does not settle causation. Substance use may precede symptoms, follow them as an attempt to cope, or arise from shared vulnerability. Toxicology has limited detection windows and raises questions of consent and interpretation. Acute medical risk, psychosis, and substance use should be addressed together rather than divided between services. When the reported exposure and clinical course diverge, the next step may include a repeated history, collateral information, targeted toxicology, medical or specialist substance-use review, or observation as intoxication resolves or abstinence continues.

Constructing a substance and medication timeline

Point	Record
Baseline	Mental state and function before exposure
Exposure	Substance or medicine, dose, potency, route, combinations
Latency	Time from use, dose change, or withdrawal to symptoms
Course	Change during clearance, abstinence, sleep, and treatment
Recurrence	Episodes without exposure; vulnerability and family history
Risk	Withdrawal, overdose, contamination, driving, safeguarding

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VII. MOOD, TRAUMA, DISSOCIATION, DEVELOPMENT, AND CULTURE

Mania and severe depression may include psychotic features. Assessment should establish whether psychotic symptoms occur only during mood episodes, whether mood symptoms occupy most of the illness course, and whether there are periods of reduced need for sleep, increased activity, psychomotor change, guilt, or nihilistic thinking. The early course may not permit a stable distinction; the working diagnosis should therefore remain provisional until the longitudinal relationship between mood and psychosis becomes clearer.

Trauma-related intrusions, dissociation, hypervigilance, voice-hearing, and beliefs about danger may resemble psychosis or coexist with it. Trauma inquiry should be paced, clinically relevant, and safe. Trauma should not become a default explanation that obscures disorganization, negative symptoms, functional decline, or medical risk. Developmental social-communication differences, intellectual disability, linguistic or sensory impairment, and cognitive limitations may also shape the presentation and should be assessed against the person's established baseline.

Culture shapes which beliefs and experiences are shared, sanctioned, or spiritually meaningful. Qualified interpreters and cultural consultation can reduce misinterpretation, but culture should not be used to dismiss distress, coercion, or impairment. A cultural framework and clinically significant symptoms may coexist; assessment should determine how each contributes to the presentation. Longitudinal assessment of depressive and bipolar symptoms is important because the distinction has direct treatment implications (Malhi et al., 2018; Singh et al., 2017; Daveney et al., 2019). Population data on trauma and posttraumatic stress disorder support sensitive inquiry into exposure, but exposure alone does not establish a trauma-based explanation for psychosis (Koenen et al., 2017).

VIII. BIAS, EQUITY, AND DIAGNOSTIC CONTEXT

Research in the United States has repeatedly identified Black–White disparities in schizophrenia diagnosis. Olbert et al. (2018) found a persistent disparity that was not fully explained by measured factors. Schwartz and Blankenship (2014) discuss possible contributors, including clinician bias, cultural misunderstanding, service pathways, and differences in the assessment of mood symptoms.

Reducing bias requires structured practice; good intentions alone are insufficient. Clinicians should describe observed speech and behavior precisely, obtain comparable mood and trauma histories, seek cultural and linguistic context, distinguish observation from inference, and review collateral accounts critically. A useful counterfactual question is whether the same evidence would be interpreted differently in a patient from another racial, cultural, or social group. Coercive pathways, prior treatment, and justified mistrust can all shape communication during assessment.

Structural racism and social adversity are not competing diagnoses, but they influence exposure, help-seeking, service contact, and the information available to the assessor. Diagnostic review should consider the consequences of an earlier label for coercion, medication, access to services, and life opportunities. When apparent disorganization may reflect linguistic difference, developmental context, or unfamiliar cultural norms, an appropriately qualified interpreter or cultural consultation should be used and the basis for interpretation documented.

Police or emergency involvement may heighten guardedness, fear, and perceived threat. Behavior should therefore be interpreted within the circumstances of the encounter, not detached from them. The formulation should identify each collateral source's relationship to the person, opportunity to observe, and possible bias, and should record barriers to participation or treatment.

Equity does not mean applying less rigorous diagnostic criteria. It requires more complete contextual evidence and greater care not to mistake structural constraint for individual pathology. Records should distinguish observed behavior from inference, describe how referral or coercive pathways shaped the encounter, and identify missing assessment or intervention that limits diagnostic confidence.

Access and participation also affect the interpretation of outcomes. A person should not be described as treatment resistant when the recommended intervention was unavailable, inaccessible, or not delivered with sufficient continuity. Attendance is not a proxy for recovery. Diagnostic review should consider the care actually offered and received, treatment burden and adverse effects, and the person's opportunity to exercise meaningful choice.

Bias-resistant diagnostic practices

Risk	Practice
Vague inference	Record exact speech, behavior, and context
Underassessment of mood	Use the same structured lifetime mood inquiry across patients
Cultural or linguistic misinterpretation	Use qualified interpretation or cultural consultation; ask about community meaning
Stereotyped threat appraisal	Separate clinician discomfort from evidence of violence risk
Inherited diagnosis	Reconstruct supporting evidence rather than copying the prior label

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Risk	Practice
Single-source account	Seek consented collateral information and document the source's opportunity to observe and possible bias

IX. DIAGNOSTIC STABILITY, SECOND OPINION, AND REVISION

First-episode diagnoses vary in stability. Fusar-Poli et al. (2016) found relatively high stability for some categories and substantial diagnostic change for others across longitudinal studies. Such change may reflect evolution of the illness, better information, treatment effects, or an initial error. A provisional diagnosis should therefore be revisited as evidence accumulates; it should not be treated as fixed.

Longitudinal review should track specified psychotic phenomena, mood, cognition, negative symptoms, function, substance exposure, medication response and adverse effects, physical health, and recovery. Persistent symptoms may reflect incomplete adherence or treatment, ongoing substance exposure, trauma-related or mood symptoms, medical illness, psychosocial adversity, or treatment-resistant primary psychosis (Haverkampf, 2016). The observed course refines the formulation but does not by itself establish etiology.

Response to antipsychotic treatment is not etiologically specific; improvement can occur in primary psychotic, mood-related, substance-related, and some medical presentations. Apparent nonresponse may reflect adherence, dose, pharmacokinetics, ongoing exposure, an inaccurate treatment target, or an incorrect formulation. Akathisia, sedation, metabolic effects, and emotional blunting may themselves alter presentation and engagement. Target symptoms, expected functional benefit, and potential harm should therefore be defined before treatment and reviewed over time.

Brief, atypical, and substance-induced psychoses have heterogeneous outcomes. Group-level transition rates cannot predict an individual's course and should not be presented as deterministic. Active follow-up remains appropriate, including review of symptom persistence, abstinence where relevant, mood, cognition, function, treatment effects, and disengagement. Early improvement is encouraging but does not remove the need for proportionate longitudinal review.

A second opinion is particularly appropriate when onset was abrupt and medical assessment was incomplete, the course is atypical, the diagnosis carries major treatment or legal consequences, adverse effects are substantial, or there is persistent disagreement about what was observed. The second clinician should reconstruct the chronology independently and examine the original evidence rather than simply endorse or reject the existing diagnosis.

Diagnostic revision should be explained clearly: what new evidence changed confidence, what remains uncertain, and what treatment implications follow. A change in diagnosis does not make the person's earlier experiences or their consequences unreal. If a schizophrenia-spectrum diagnosis is no longer supported, ongoing voice-hearing, trauma, mood symptoms, substance-related needs, or disability still require appropriate care. Removing a label must not remove treatment.

A provisional diagnosis should state the evidence supporting the current formulation, the alternatives that remain active, what is being investigated, which treatment is required despite uncertainty, and when formal review will occur. The record should also identify the findings or course that would increase or reduce confidence. Operationalized uncertainty is a clinical plan, not an indefinite label.

Minimum documentation for a provisional diagnosis

Element	Document
Current formulation	Diagnosis or syndrome and the evidence supporting it
Active alternatives	Plausible differentials and why they remain open
Immediate care	Treatment and risk management required despite uncertainty
Investigation	Tests, observations, or consultations linked to clinical questions
Review plan	Interval, responsible clinician or team, and information to obtain
Revision triggers	Findings or course that would alter confidence or level of care

X. COMMUNICATION DURING PSYCHOSIS ASSESSMENT

Confrontation may intensify mistrust, whereas affirming an unverified explanation may reinforce harmful conclusions. A safer approach validates the person's distress and experience, remains neutral about disputed explanations, and explores evidence, impact, alternatives, and risk. For example: "That sounds frightening. I cannot verify that your neighbor is controlling the radio, but I want to understand what you have noticed." This preserves the therapeutic relationship while maintaining reality-based boundaries.

Command hallucinations require direct questions about content, perceived authority, intent, past compliance, ability to resist, and protective factors. Beliefs involving other people require assessment of planned contact, surveillance, access to weapons or other means, and intended action, without assuming violence on the basis of diagnosis alone. Risk formulation must remain individualized.

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Communication-Focused Therapy is an author-developed supplementary formulation that emphasizes meaningful information exchange and a stable therapeutic setting (Haverkampf, 2017); it is not efficacy evidence and should not replace diagnostic assessment. This perspective may complement medical assessment, antipsychotic treatment when indicated, family intervention, and evidence-based psychosocial care. NICE guidance supports multidisciplinary treatment and physical-health monitoring in psychosis and schizophrenia (National Institute for Health and Care Excellence, 2014).

Questions should be brief and transparent, especially when the person is frightened, confused, or overstimulated. Clinicians should explain why information is being sought, distinguish validation of distress from agreement with an unverified belief, and adapt the pace to capacity, consent, and setting. The goal is not immediate agreement but enough trust for safe assessment and collaborative reality testing.

When a belief is disputed, communication has three distinct tasks: acknowledge the distress and consequences, state the limits of the available evidence, and assess actions the person may take because of the belief. Keeping these tasks separate permits empathy without endorsement and creates a basis for shared safety planning.

Collateral information can improve temporal reconstruction when its source, relationship to the person, opportunity to observe, and possible interests are recorded. Explain why collateral information is sought, seek consent where appropriate, observe confidentiality and safeguarding duties, and distinguish a report from an independently established fact. Apparent disagreement between accounts is information to investigate rather than a reason to treat one source as automatically authoritative.

Communication over time can also provide longitudinal evidence. Changes in coherence, responsiveness, threat interpretation, social withdrawal, or ability to consider alternatives may help identify deterioration or recovery, but no single conversational feature is pathognomonic. Interpretation should remain linked to chronology, culture, language, neurodevelopment, medication and substance exposure, medical findings, and function.

XI. MEASUREMENT, INTERVIEW, FOLLOW-UP, AND REVISION

At the outset of care, define what will be reviewed, at what interval, and by whom. Symptom measures may be useful, but they should be interpreted alongside function, safety, adverse effects, physical health, and the person's priorities. Establish a practical baseline where possible and specify what degree of change would be clinically meaningful. An unexpected course is diagnostic evidence and should trigger reconsideration before automatic treatment intensification.

Symptom and course. Record the psychotic phenomena being followed, including form, frequency, conviction, distress, and functional effect. Review whether they resolve, persist, or change in character. Short-term fluctuations should be interpreted cautiously rather than treated as a new diagnosis or definitive treatment response.

Behavior and function. Follow attention, cognition, neurological signs, physical health, self-care, and the ability to carry out ordinary roles. A person may report fewer symptoms while remaining substantially impaired, or function may improve before subjective experiences change. Both patterns should inform subsequent assessment and the level of care.

Health and exposure. Place mood course, sleep, substance exposure, withdrawal, medication changes, and relevant medical findings on the same timeline. New fever, movement change, confusion, seizure, autonomic symptoms, or other neurological developments should reopen medical assessment rather than be attributed automatically to an established psychiatric diagnosis.

Relationships and participation. Review social withdrawal, negative symptoms, family and service contact, treatment benefit, and adverse effects without assuming that attendance is equivalent to recovery. Ask which activities and relationships have become possible, which remain constrained, and whether treatment burden or mistrust is reducing participation.

Formulation and treatment. State which diagnosis and alternatives are currently most plausible, what evidence would increase or reduce confidence, and when formal review will occur. If the expected response or course does not occur, reconsider the diagnosis, treatment delivery, context, and level of care before adding further intervention.

Balanced domains for follow-up

Domain	Outcome to monitor
Symptom and course	Resolution or evolution of the specified psychotic phenomena
Behavior and function	Attention, cognition, neurological signs, physical health, and daily function
Health and exposure	Mood course, substance exposure, withdrawal, medication, and sleep
Relationships and participation	Social function, negative symptoms, treatment benefit, and adverse effects
Formulation and treatment	Diagnostic stability and timely revision across follow-up

Assessment begins with safety and medical urgency, followed by precise description of the phenomena. Inquiry should cover beliefs, perceptions, thought and speech, behavior, negative and cognitive symptoms, attention, and consciousness. Onset should be reconstructed alongside sleep, mood, infection, neurological change, substances, withdrawal,

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medication, trauma, culture, language, and development. Brief questions, transparent explanations, and a nonconfrontational stance help preserve both information and trust. Collateral history may be essential when capacity, memory, or communication is impaired, but the source, relationship, opportunity to observe, consent basis, and possible bias should be documented.

These domains should be used flexibly, not as a script to be completed in one sitting. Begin with a recent episode, compare it with the person's usual baseline, and ask when the feature is absent as well as present. When collateral information is needed, explain its purpose and limits, obtain it with consent or another appropriate legal basis, and record how directly the source observed the events.

Urgency. Ask about medical instability, fluctuating attention or consciousness, catatonia, command experiences, self-harm or violence, severe self-neglect, and the ability to meet basic needs. Reconstruct what occurred before, during, and after the most concerning episode, including onset, duration, change over hours or days, and immediate consequences for safety or care.

A symptom's apparent absence may reflect limited recall, shame, language, fear, or the way the question was asked. Record the source of information and degree of confidence. When the account suggests delirium, neurological change, intoxication, withdrawal, or rapidly increasing risk, specify whether urgent medical review, collateral history, observation, or a change in setting is required.

Phenomenology. Ask about beliefs, perceptions, thought and speech, behavior, negative symptoms, cognition, insight, conviction, flexibility, context, and impact. Use the person's own words and at least one concrete example rather than inherited terms such as "paranoid," "disorganized," or "responding to internal stimuli." Note what changes with sleep, company, language, stress, or environment.

A single experience may support several hypotheses, and apparent absence may reflect limited opportunity or disclosure. Separate observation from inference and identify whose account is being used. When the phenomenology does not fit the working diagnosis, clarify terminology, compare earlier records, obtain consented collateral information where appropriate, or continue observation rather than force the finding into the current diagnosis.

Timeline. Establish whether onset was abrupt or gradual and place changes in sleep, mood, infection, cognition, neurological function, pregnancy or postpartum status, medication, and social circumstances on the same chronology. Ask about earlier episodes, whether the person returned to baseline, and symptoms occurring under different conditions.

Chronology is often incomplete early in illness. Record dates and confidence rather than forcing precision. Differences among accounts from the patient, family, records, and services should be described rather than merged into a single narrative. Conflicting timelines may require clarification, additional records, targeted medical assessment, or longitudinal review without compromising immediate safety.

Exposure. Assessment should cover prescribed and nonprescribed medication, supplements, alcohol, cannabis, stimulants, hallucinogens, sedatives, toxins, intoxication, and withdrawal. Ask about dose, potency, route, combinations, last use, changes from baseline, sleep, and the interval between exposure and symptoms. A nonjudgmental manner improves the likelihood of obtaining clinically useful detail.

Context. Include trauma, dissociation, culture, language, development, social adversity, sensory or intellectual disability, and the legal or coercive setting. Ask what the experience means to the person and whether it is shared or sanctioned within a community. Guardedness in an emergency or police pathway may not have the same meaning as similar behavior in a trusted setting. If context changes the formulation, document whether an interpreter, cultural consultation, developmental history, trauma assessment, collateral information, or longitudinal review is required.

Diagnostic assessment is a sequence, not a one-time labeling event. Risk management, phenomenology, chronology, examination, exposures, context, investigation, and follow-up proceed in parallel and should be revisited as evidence changes. Questionnaires can structure inquiry and establish a baseline, but no score determines diagnosis or treatment independently of course, function, risk, and context. New evidence that conflicts with the working formulation should prompt revision rather than reinterpretation designed to preserve the existing category.

Structured assessment domains

Domain	Questions to address
Urgency	Medical instability, delirium, catatonia, command experiences, self-harm or violence, basic care needs?
Phenomenology	Beliefs, perceptions, thought, behavior, negative and cognitive symptoms?
Timeline	Abrupt or gradual onset, sleep, mood, infection, neurological change, postpartum status?
Exposure	Substances, withdrawal, medication, supplements, toxins?
Context	Trauma, culture, language, development, social adversity, legal setting?
Investigation	Which history or examination finding justifies which test or consultation?

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Domain	Questions to address
Follow-up	Which diagnostic alternatives and observations will be reviewed, and when?

XII. APPRAISING AND APPLYING THE EVIDENCE

Evidence relevant to the differential diagnosis of psychosis is methodologically heterogeneous. Professional guidance combines research and expert judgment within a particular service context and date. Systematic reviews reduce selective citation but inherit the definitions and biases of their source studies; original studies provide chronology and detail but remain more vulnerable to sampling, measurement, confounding, and chance.

Diagnostic labels, structured interviews, symptom scales, single items, observed behavior, and administrative outcomes are not interchangeable measures. Studies of first-episode psychosis, diagnostic stability, medical workup, autoimmune presentations, substance-related psychosis, culture, and racial disparity may therefore answer different clinical questions. Reports should name the measure when it affects interpretation and distinguish a statistically reliable group difference from a clinically meaningful change for an individual.

Causal language should match study design. Cross-sectional associations cannot establish temporal order; longitudinal associations improve temporal ordering but remain vulnerable to confounding and measurement error. Random allocation supports causal inference for the intervention tested under trial conditions, not for every proposed explanation of an individual's presentation. Proposed mechanisms should guide questions, examination, and observation rather than be presented as established causes without case-specific evidence.

Group averages may conceal people who improve, do not respond, deteriorate, or cannot access an intervention. Trials may exclude medical complexity, active substance problems, acute risk, unstable housing, language barriers, or multiple diagnoses. Before applying a finding, compare the study population, clinician expertise, intervention fidelity, dose, outcome, setting, and exclusions with the decision at hand, and keep contradictory case-specific evidence visible in the formulation.

The literature search ended on 30 May 2025. Later evidence, revised diagnostic systems, updated safety warnings, superseded recommendations, and retractions should be checked before this review is used clinically.

XIII. CLINICAL SAFETY, URGENCY, AND SCOPE

New psychosis may constitute both a psychiatric and a medical emergency. Immediate priorities include safety, vital signs, recognition of delirium and catatonia, intoxication or withdrawal, neurological red flags, suicide or violence risk, vulnerability, safeguarding, and the ability to meet basic needs. The least restrictive safe setting should be determined individually in accordance with local law and clinical circumstances.

Risk assessment should be direct but not diagnosis-driven. Commands, intent, plans, access to means, past compliance, self-neglect, exploitation, and protective factors should be explored when clinically indicated. A known psychiatric history should never preclude urgent reassessment when new neurological or systemic features emerge.

Urgent and safeguarding considerations

- Arrange urgent medical evaluation for fluctuating consciousness, fever, seizure, a new focal neurological sign, severe headache, autonomic instability, catatonia, abnormal movements, or rapid cognitive or behavioral deterioration.
- Ask directly about suicidal thoughts, self-harm, violence, command experiences, plans, access to means, past compliance, severe self-neglect, exploitation, and the ability to remain safe.
- Assess withdrawal and medical risk before abrupt changes to substances or prescribed medication, and coordinate the relevant care.
- Escalate when severe intoxication or withdrawal, inability to meet basic needs, safeguarding concerns, or a rapidly worsening mental state is present.
- This narrative review cannot determine an individual's diagnosis, fitness for work, medication plan, or level of care. Those decisions require an appropriately qualified clinician with direct access to the person and relevant records.

Escalation should be documented operationally: which finding prompted concern, who was contacted, what level of observation or care is required, and what reassessment is planned. When capacity or memory is impaired, collateral information may be essential, but its source, consent or legal basis, and limitations should remain explicit.

XIV. LIMITATIONS AND RESEARCH NEEDS

Some high-consequence secondary causes may be uncommon, while indiscriminate testing can cause harm through false-positive or incidental findings; investigation should therefore be guided by the history, examination, course, and applicable specialist guidance. Consensus criteria for autoimmune psychosis continue to evolve. Studies of diagnostic stability differ in follow-up, treatment, and classification system, and evidence on racial disparity is strongest in particular national contexts. This review cannot define a universal investigation panel or the legal threshold for involuntary care.

Psychosis has multiple possible causes, yet diagnostic research often excludes medically complex, substance-related, developmental, and culturally diverse presentations in which error may be most consequential. Research on the therapeutic alliance in schizophrenia and related psychoses suggests associations with symptom and service outcomes but remains

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methodologically limited (Shattock et al., 2018). Future studies should test whether transparent uncertainty, high-quality communication, and planned longitudinal reassessment reduce missed medical causes, premature chronic diagnoses, and unnecessary treatment. Relevant outcomes should include time to diagnostic correction, continuity of care, treatment burden, patient trust, and functional recovery.

XV. CONCLUSION

Psychosis should be approached first as a syndrome requiring explanation, not as a diagnosis that supplies its own cause. The evidence reviewed supports a four-part diagnostic-safety process: precise description of phenomena; proportionate investigation of high-consequence alternatives; treatment of immediate risk without overstating etiological certainty; and scheduled revision against the observed course. Mood, trauma, substances, culture, development, medical illness, and structural bias belong within the formulation rather than at its margins. A provisional diagnosis is clinically useful only when it names the supporting evidence, active alternatives, planned investigations, treatment required despite uncertainty, and triggers for review. In this sense, diagnostic uncertainty is not a failure of assessment but a condition to be managed transparently. Urgency and provisionality can coexist: clinicians can act decisively on risk while keeping the diagnosis open to correction.

XVI. CONFLICTS OF INTEREST AND DISCLOSURES

Conflicts of interest—The author developed and writes about Communication-Focused Therapy (CFT). CFT is discussed as a formulation perspective, not as a substitute for established diagnostic assessment, evidence-based treatment, or independent replication. No other conflicts of interest were reported.

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Patient material—No identifiable patient material is presented. Any brief examples are generic composites created to illustrate clinical reasoning and are not case reports.

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