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Crude exogenous organic damage of the most varying kind can produce acute psychotic clinical pictures of a basically uniform kind.

Karl Bonhoeffer, 1909

The number of medical diseases that can present with psychotic symptoms (ie, delusions, hallucinations) is legion. A thorough differential diagnosis of possible medical and toxic causes of psychosis is necessary to avoid the mistaken attribution of psychosis to a psychiatric disorder. One organizing principle separates etiology into primary psychiatric and secondary categories, the latter includes delirium (toxic psychosis), dementia, medical illnesses, and substances (Figure). This terminology avoids the term “organic,” which implies a mind-body dichotomy that is no longer tenable. Psychosis can be attributable to a combination of factors, and all possible causes must be systematically examined, hence the lack of a hierarchical organization in this nosology.

In this article, I focus on secondary psychosis due to a medical illness or substances and not on the cognitive disorders of delirium and dementia. It is important, however, to be aware that both are commonly associated with psychosis. Psychosis is a frequent ancillary symptom of delirium that can overshadow its cardinal cognitive features. It is therefore critical to routinely consider the possibility of a delirium in any patient with psychosis. Dementias are also frequently accompanied by neuropsychiatric problems, including psychosis. Psychosis is present in about 40% of patients with Alzheimer disease, the most common form of dementia. Most patients with Lewy body dementia experience psychosis as well. Hallucinations, usually visual, are the most frequent psychotic symptom; they occur in 78% of patients, followed by misidentifications in 56% and delusions in 25%.

Approach to diagnosis
Karl Bonhoeffer, one of the fathers of “organic psychiatry,” recognized 100 years ago that the psychiatric clinical picture produced by a medical condition was rather uniform and unspecfic, regardless of etiology. Unfortunately, there is also no easy way to differentiate primary from secondary psychoses on the basis of psychopathology alone. While certain symptoms suggest a medical-toxic etiology (eg, visual hallucinations, lack of Schneider first rank symptoms), there are no pathognomonic signs or symptoms that unequivocally point clinicians either way. To complicate matters, some acute, primary psychiatric presentations can include confusion and perplexity, seemingly implicating a toxic psychosis. Instead, clinicians have to rely on typicality (with regard to age at onset, symptoms, treatment response, and course) as well as temporality and biological plausibility to judge whether a medical condition is causally related to psychosis. A primary psychotic disorder, such as schizophrenia, is a diagnosis of exclusion, and all patients with new-onset psychosis need a medical workup that excludes medical-toxic causes of psychosis. The overall clinical and epidemiological situation is of utmost importance in narrowing the initially rather broad differential diagnosis of psychosis to keep the workup manageable and to determine the degree of urgency. For example, any new-onset psychosis in a hospitalized, elderly patient following hip surgery is most likely a toxic psychosis (delirium); an antisocial patient with polysubstance dependence who presents at the emergency department is likely suffering from a drug-induced psychosis.

Some medical diagnoses are difficult to make. Clinicians may be unfamiliar with a disease that is rare per se (many genetic disorders fall into this category) or rare in the clinician’s practice (eg, cerebral malaria in the United States). Clinicians might also not recognize a common disease if it presents in an atypical manner (eg, HIV infection presenting with psychosis). Table 1 provides
A thorough history and physical examination with emphasis on the neurological and cognitive parts are the cornerstones for the initial approach to psychosis. To detect fluctuations in mental status typical for a toxic psychosis, repeated visits with bedside testing of cognition may be necessary. The extent of the laboratory workup to complement the history and physical examination is a matter of debate, and there is no agreed-on workup. For test selection, test characteristics (sensitivity and specificity) as well as the prevalence of the disease are key considerations. If a disease is unlikely (low prior probability), a positive test result is probably a false positive, which argues against indiscriminate screening.

Among the tests selected for screening, the most sensitive test needs to be ordered because a negative test result removes the disease from the clinician’s differential diagnosis list. For example, the rapid plasma reagin (RPR) is not the most sensitive test for neurosyphilis, and a negative result could be a false negative; if one were to truly want to rule out neurosyphilis, a treponemal-specific test would be needed. Further complicating test selection is the unavailability of sensitive and specific tests for many diseases.

If there is a strong clinical suspicion for a disease, its diagnosis must be actively pursued with repeated tests (eg, serial electroencephalograms [EEGs] for epilepsy). Finally, a positive finding on an examination or a positive laboratory test result alone (eg, a urine drug test positive for cannabis) does not establish causality. This point is perhaps most relevant with regard to incidental findings on a sensitive neuroimaging modality, such as a brain MRI.

One possible medical workup is outlined in Table 2. The suggested laboratory battery is a compromise between broad-based screening (eg, erythrocyte sedimentation rate for inflammatory conditions) and exclusion of some specific conditions that are treatable if diagnosed (eg, HIV infection, syphilis, thyroid disease, vitamin B12 deficiency). If there is clinical concern for a delirium, EEGs, arterial blood gases, or lumbar punctures become more important.

Of note, there is no consensus regarding the need for routine brain imaging in first-episode psychosis.

CT or MRI may be reserved for patients with an atypical clinical presentation, neurological findings, or an unusual/treatment-refractory course. A normal baseline CT or MRI scan, however, is reassuring and can help patients and families accept that medical and neurological causes of illness have been excluded.

The appropriate role of routine genetic screening in patients with psychosis is an area in flux. Currently, only the Clinical Practice Guidelines for the Treatment of Schizophrenia by the Canadian Psychiatric Association recommends testing for a genetic syndrome, the velocardiofacial syndrome, but only if it is clinically suspected.

### SECONDARY PSYCHOSIS—SPECIFIC CONDITIONS

#### Psychosis from a general medical condition

**Endocrine diseases.** Endocrine diseases are the prototype for systemic illnesses that affect the brain and lead to a wide variety of neuropsychiatric symptoms. Thyroid disease in the form of hyperthyroidism or hypothyroidism (myxedema madness) can be associated with psychosis. Steroid-producing tumors, located in either the adrenal gland (Cushing disease) or other tissues (eg, ectopic Cushing syndrome from small-cell lung cancer) need to be considered, particularly in cases of refractory psychosis. Insulinomas can present with an array of psychiatric symptoms, including confusion and bizarre behavior that can be falsely attributed to psychiatric illness.

A pheochromocytoma is yet another rare hormone-producing tumor that characteristically produces episodic anxiety states but can present with psychosis.

**Metabolic diseases.** Among the metabolic disorders, only acute intermittent porphyria (AIP) is sufficiently common to be routinely considered in patients with psychosis, particularly if abdominal complaints (colicky pain, severe constipation) and peripheral motor neuropathy are present. AIP is an autosomal dominant disease of heme synthesis that results from defects in the enzyme porphobilinogen deaminase (PBGD). These defects could result in an accumulation of the porphyrin precursors, porphobilinogen (PBG) and aminolevulinic acid (ALA). A diagnosis of AIP is therefore suggested by an excess of ALA and PBG in urine and a concomitant decrease in PBGD enzyme activity in erythrocytes. The course of AIP is episodic, and patients are well between episodes.

Fasting, alcohol, and a host of porphyrogenic medications can trigger episodes.

Tay-Sachs disease (GM2 gangliosidosis type 1) and Niemann-Pick disease type C are rare storage disorders that have adult-onset variants. Psychosis is one of the possible symptoms.

**Autoimmune.** Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease for which 2
CNS symptoms, psychosis and seizures, have long been recognized as diagnostic criteria by the American College of Rheumatology. Psychosis has been well documented to occur in a significant minority of patients as a result of the immune disease itself, unrelated to medical treatment. For example, in a cohort study of 520 consecutive SLE patients, Appenzeller and colleagues found that 11% of patients with SLE had psychosis secondary to brain involvement. Moreover, psychosis correlated with markers of SLE disease activity. By contrast, psychosis as a result of corticosteroid treatment was diagnosed in only 5% of patients, and psychosis was thought to be from a primary psychiatric disorder in fewer than 1% of cases.

Other autoimmune disorders to be considered include Hashimoto encephalopathy and paraneoplastic syndromes. Hashimoto encephalopathy is associated with autoimmune thyroiditis and recurrent episodes of psychosis. It is exquisitely corticosteroid-responsive, and prompt treatment leads to rapid recovery. Paraneoplastic limbic encephalitis (PLE) can cause neuropsychiatric symptoms that are the result of autoantibodies directed toward neuronal intracellular or cell membrane antigens.

Although PLE is most commonly associated with small-cell lung cancer, many other tumors have been implicated. A young woman who presents with psychosis that progresses to seizures, autonomic instability, and unresponsiveness should have a workup for ovarian tumors because she might have encephalitis associated with N-methyl d-aspartate (NMDA) receptor antibodies. Considering PLE in progressive or poorly responsive neuropsychiatric syndromes is critical so that a tumor search is initiated.

Infections. Immigrant populations or travelers can present with diseases associated with psychosis that would be considered uncommon in the United States (eg, cerebral malaria, toxoplasmosis, neurocysticercosis, sleeping sickness). In addition to the patient’s geographic locale and travel history, immune status can help identify likely infectious agents. HIV infection and neurosyphilis are treatable diseases that affect the brain. They can present with psychosis and should specifically be considered in all patients with psychosis. In contrast to neurosyphilis, the link between chronic psychosis and another spirochetal disease, neuroborreliosis, is controversial, although it has been linked to acute psychosis in a case report. Be mindful that patients with encephalitis can inadvertently present to a psychiatric service if psychiatric symptoms dominate the clinical picture. Among the viral infections, herpes simplex encephalitis is the most urgent to consider because any delay in administering acyclovir worsens prognosis.

Narcolepsy. Narcolepsy is characterized by the tetrad of excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations (ie, vivid auditory or visual illusions that occur when falling asleep). However, the full tetrad is present in only 10% of patients. In some patients, prominent psychosis-like experiences occur throughout the day and overshadow other symptoms of narcolepsy that can lead to a mistaken diagnosis of schizophrenia. In one small series of 69 patients in a state hospital, 7% of patients with a diagnosis of schizophrenia were found to have narcolepsy. The treatment of narcolepsy with stimulants can further complicate the picture because psychosis can result from the medical treatment. The diagnosis of narcolepsy requires a nocturnal sleep study followed by a multiple sleep latency test (MSLT) to identify reduced daytime sleep latency and sleep onset rapid eye movement (SOREM) periods. Human leukocyte antigen tumor search is initiated.

Seizures. The link between seizures, particularly temporal lobe epilepsy, and psychosis is well established. Epidemiological studies have shown a higher rate of schizophrenia in patients with epilepsy and vice versa. Psychosis in the setting of seizures can occur during the ictal, postictal, and interictal phases. Ictal psychosis can occur in complex partial or absence status epilepticus. Postictal psychosis emerges close to the seizure and can last several days or weeks, rarely morphing into a chronic psychosis. Interictal psychosis typically emerges after a decade of poorly treated or poorly responsive epilepsy and is characterized by intense dysorphic affect in addition to psychosis. Earlier development of interictal psychosis suggests individual vulnerability as opposed to epilepsy-related damage.

Confusion, episodic violence, and catatonia are clinical symptoms that should raise suspicion for seizures. If a seizure or epilepsy is suspected, the diagnosis needs to be pursued appropriately. A normal, routine interictal EEG is insufficient to exclude epilepsy. Serial EEGs and optimal lead placement improve the chances of making a diagnosis of epilepsy. Frontal lobe seizures, in particular, can be very difficult to diagnose. A high index of suspicion based on history (abrupt onset and cessation of bizarre motor automatisms and vocalizations but little if any postictal confusion)
Hallucinations, particularly visual hallucinations, are a common problem associated with Parkinson finding of unclear significance. Symptoms, including psychosis. Fahr disease is characterized by bilateral basal ganglia calcifications and neuropsychiatric clinically, a definite diagnosis can be made earlier with genetic testing. While Huntington disease, an autosomal dominant disorder, is usually not difficult because always present in neuropsychiatric Wilson disease. Kayser-Fleischer rings of the cornea as detected by slitlamp examination are not irreversible end-organ damage, screening with 24-hour urinary copper and serum ceruloplasmin levels should be considered in psychotic patients, particularly if patients show evidence of liver abnormalities. Space-occupying lesions. Primary or secondary brain tumors can cause psychosis as their first manifestation and should be considered in elderly patients, particularly if there is a persistent headache or other neurological signs, including seizures. However, in the case of “silent” indolent-growing tumors, such as frontal meningiomas, neurological examination findings are often normal. Tumor histology is not as important as rapidity of growth and location for the clinical presentation. Temporal lobe location is thought to increase the likelihood of psychosis, although it must be stressed that no lesion location in the brain reliably produces psychosis. Causal attribution of psychosis to incidental neuroimaging findings (eg, cysts or vascular malformations in the temporal lobes) is therefore often unclear. Conditions that increase intracranial pressure, such as normal pressure hydrocephalus, have been associated with psychosis as well. Strokes. Rarely, psychosis can be the presenting symptom of a stroke. In some cases, stroke-related seizure activity is responsible for the psychosis. The sudden onset of complex visual hallucinations should lead to consideration of 2 lesion-related conditions: peduncular hallucinosis caused by focal midbrain (peduncular) lesions and the Charles Bonnet syndrome following occipital infarction. However, in both conditions, causes other than a stroke are possible. Head injury. A history of head injury is a risk factor for the development of a chronic psychotic syndrome that can be clinically indistinguishable from schizophrenia. Head injury-related psychosis is typically a mostly paranoid-hallucinatory syndrome that develops insidiously several years after injury. Patients experiencing psychosis can appear blunted and withdrawn, and it is critical not to ascribe apparent negative symptoms to brain damage but to consider active psychosis. The severity of head injury (as judged by the duration of loss of consciousness) and a family history of psychosis are 2 variables associated with the emergence of psychosis following head injury. Demyelinating diseases. Diseases that disrupt the integrity of white matter tracts in the brain can lead to psychosis, likely to be caused by the functional disconnectivity of critical brain regions. Demyelinating diseases would be expected to be associated with psychosis if (1) the disease affects the brain as opposed to the brain stem and spinal cord, and (2) the “right” brain regions are disconnected. Multiple sclerosis, the most common demyelinating disease, is associated with psychosis more often than can be expected by chance, although the rate of psychosis is low. Inherited leukodystrophies, such as metachromatic leukodystrophy (MLD) and adrenoleukodystrophy (ALD), on the other hand, are associated with a high prevalence of neuropsychiatric symptoms, including psychosis. MLD in particular is associated with a very high rate of psychosis, perhaps as high as 50%. MLD is an autosomal recessive disorder caused by a deficiency in the lysosomal enzyme, arylsulfatase A. ALD is an X-linked disorder in which very-long-chain fatty acids accumulate because of defective peroxisomal oxidation. While inherited leukodystrophies are typically diagnosed in childhood because of their aggressive clinical course with systemic and neurological symptoms, adult-onset cases can present with a predominantly psychiatric picture. The diagnosis of a demyelinating disorder is suggested by abnormal findings on MRI scans. Clinical red flags for inherited leukodystrophies include progressive cognitive decline, other neurological findings (eg, seizures or a neuropathy), or other systemic findings (eg, adrenal insufficiency in patients with ALD). Basal ganglia disorders. Rare, inherited basal ganglia disorders associated with psychosis include Wilson disease, Huntington disease, and Fahr disease. Wilson disease is a disorder of copper metabolism that leads to copper deposits in the liver and the lenticular nucleus of the brain (hence the term “hepatolenticular” degeneration). Since early diagnosis and treatment can prevent irreversible end-organ damage, screening with 24-hour urinary copper and serum ceruloplasmin levels should be considered in psychotic patients, particularly if patients show evidence of liver abnormalities. Kayser-Fleischer rings of the cornea as detected by slitlamp examination are not always present in neuropsychiatric Wilson disease. The diagnosis of Huntington disease, an autosomal dominant disorder, is usually not difficult because most patients will have a family history. Psychosis can precede the motor symptoms of Huntington disease and delay its recognition. While Huntington disease will eventually declare itself clinically, a definite diagnosis can be made earlier with genetic testing. Fahr disease is characterized by bilateral basal ganglia calcifications and neuropsychiatric symptoms, including psychosis. However, basal ganglia calcification can also be an incidental CT finding of unclear significance. Hallucinations, particularly visual hallucinations, are a common problem associated with Parkinson...
Nutritional deficiencies. Vitamin B12 deficiency is easily correctable and should be specifically excluded in all patients. Psychosis from vitamin B12 deficiency can predate anemia and the typical spinal symptoms. Their etiology is likely to be multifactorial and includes disease severity and dementia as well as treatment with levodopa. Thiamin deficiency is easily correctable as well; therefore, thiamin must be given in the appropriate setting (ie, alcoholism). Niacin deficiency (pellagra) is rare in the United States; symptoms include psychosis in addition to diarrhea, dermatitis, and stomatitis/glossitis.

**Psychosis due to substances**

Many toxins, drugs, and medications can cause psychosis without a delirium, although the line between secondary psychosis caused by a substance and toxic psychosis can be difficult to draw. In addition, establishing a causal link between substances and psychosis is not always possible, and in many circumstances of illicit drug use in particular, the exact relationship between psychotic symptoms and the ingested drug requires long-term follow-up. In cases of cannabis use and a psychotic illness, an interaction between drug use and genetic predisposition to schizophrenia is likely.

Inquiring about all drugs and medications taken (eg, over-the-counter, bought over the Internet, prescribed, nonprescribed, illicit) and an exposure history (occupation and hobbies such as gardening) can provide clues that guide further investigation. Many patients will not volunteer their use of “natural” herbal remedies because they do not appreciate the possibility of adverse reactions. An herbal preparation associated with psychosis is the now-banned ephedra that patients might take for weight loss. Patients who subscribe to weight lifting and body building might be taking anabolic steroids. While uncommon and most importantly idiosyncratic (as opposed to dose-related), psychosis is a possible complication of recreational anabolic steroid use. The detection of environmental toxin poisoning requires a high index of suspicion. Toxins to consider include carbon monoxide; organophosphates; and heavy metals, particularly arsenic, manganese, mercury, and thallium. In many clinical settings, alcohol, sedative-hypnotics, and illicit drugs will be common causes of psychosis. Alcohol and sedative-hypnotics can lead to psychosis during intoxication (rare), during withdrawal, or during a delirium tremens. In persons with long-term alcohol abuse, persistent psychosis in the form of alcoholic hallucinosis or pathological jealousy (Othello syndrome) can develop. Stimulant drugs (eg, cocaine, methamphetamine) and psychotomimetics (eg, lysergic acid diethylamide [LSD], hallucinogenic mushrooms, phencyclidine [PCP]) as well as cannabis are important drugs that can cause psychosis.

**Table 3** lists some medications that have been associated with psychosis.

For a diagnosis of drug-induced psychosis, it is helpful to consider which drugs are prevalent in particular geographic areas and clinical subpopulations. For example, men who have sex with men from urban centers are at risk for using methamphetamine. College students might experiment with psychotomimetic party drugs or misuse stimulants obtained (legally and illegally) for the purpose of “cramming” before exams. Clinicians need to be cognizant of the drugs included in the urine drug screen because only drugs included in it can potentially be detected.

**Summary**

Ruling out secondary causes of psychosis is important because the causation of psychosis by a medical disorder or substance can dramatically change management and prognosis. Table 4 summarizes key clinical points to consider when evaluating a patient with new-onset psychosis of unknown etiology. Readers with further interest in secondary psychosis can consult 2 excellent books—*The Schizophrenias. A Biological Approach to the Schizophrenia Spectrum Disorders* and *Secondary Schizophrenia*—that cover this topic in more detail.
Table 1. Primary or secondary psychosis? Diagnostic mistakes

Table 2. Suggested medical workup for secondary psychosis

Table 3. Medications associated with psychosis

Table 4. Key clinical points in evaluating new-onset psychosis

References:


Differential Diagnosis of Psychotic Symptoms: Medical “Mimics”
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