Secondary psychoses: an update

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Psychotic disorders due to a known medical illness or substance use are collectively termed secondary psychoses. In this paper, we first review the historic evolution of the concept of secondary versus primary psychosis and how this distinction supplanted the earlier misleading classification of psychoses into organic and functional. We then outline the clinical features and approach to the diagnosis of secondary psychotic disorders. Features such as atypical presentation, temporal relation to detectable medical cause, evidence of direct physiological causal relationship to the etiological agent, and the absence of evidence of a primary psychotic illness that may better explain the presentation suggest consideration of a secondary psychosis. Finally, we discuss how careful studies of secondary psychotic disorders can help elucidate the pathophysiology of primary, or idiopathic, psychotic disorders such as schizophrenia. We illustrate this issue through a discussion of three secondary psychotic disorders – psychoses associated with temporal lobe epilepsy, velocardiofacial syndrome, and N-methyl D-aspartate (NMDA) receptor encephalitis – that can, respectively, provide neuroanatomical, genetic, and neurochemical models of schizophrenia pathogenesis.

Key words: Secondary psychoses, temporal lobe epilepsy, velocardiofacial syndrome, NMDA receptor encephalitis, schizophrenia

(World Psychiatry 2013;12:4–15)

Classification of psychotic disorders has continued to generate debate. The idea that psychoses may be categorized into those with detectable anatomic pathology (organic) and those without such pathology (functional) has been prevalent for more than a century (1). Unfortunately, this distinction sometimes misled the field, particularly during the early decades of the 20th century, when functional was equated with psychogenic, and the etiology of schizophrenia was ascribed to psychologic factors such as parental upbringing.

Recent decades have seen a growing realization that it is more useful to categorize psychiatric disorders as secondary, when the symptoms are due to a known medical illness or substance use, and as primary (or idiopathic), if the symptoms cannot be explained by another cause. In this context, the DSM-IV dropped the terms organic and functional used in the earlier editions (2). The emphasis was shifted from the presence or absence of discernible brain pathology (which is often difficult to identify, even in many neurological disorders) to etiology (known, presumed, or unknown). The DSM-IV also made the distinction between psychotic disorders secondary to medical illness versus those secondary to substance use.

In this paper, the primary versus secondary approach has been taken to understand psychotic disorders, since the term primary has the advantage of not ruling out a neurobiological basis. While a variety of secondary psychotic disorders are described throughout this text, it is important to have an appreciation of how such understanding can elucidate the neurobiological substrates that might underlie primary (or idiopathic) psychotic illness. We seek to briefly provide an overview of what is known in this regard and offer an approach to the differential diagnosis between primary and secondary psychotic disorders.

DISORDERS PRESENTING WITH SECONDARY PSYCHOTIC SYMPTOMS

Virtually any substance, prescribed drug, or medical condition affecting nervous system function can present with psychiatric symptoms, including psychosis (Table 1). The mnemonic TACTICS MDS USE may offer the clinician an easy way to remember the main groups of disorders to consider in the differential diagnosis.

Traumatic brain injury

Traumatic brain injury (TBI) has been proposed as a risk factor for schizophrenia-like psychosis, though there have been few systematic studies of the relationship between these two conditions.

Fujii and Ahmed (3) conducted a review of case reports in which they retroactively applied DSM-IV criteria to a total of 69 cases and concluded that TBI can be either a primary cause of psychosis or contribute to the development of psychosis through inducing seizures, though this study was limited by the heterogeneity of the case reports. A cohort study of 3552 Finnish World War II veterans (4) reported a rate of psychosis of 8.9% following TBI, but the proportion of open injuries, potential comorbidities, and lack of standard diagnostic tools call into question the generalizability of these findings.

Evidence from additional studies, including epidemiologic and case control studies, indicates that TBI may marginally increase the risk of psychosis, though the increased risk may be significantly higher for individuals with a genetic predisposition to psychosis (5-7). The risk of psychosis appears to be elevated when TBI is severe, diffuse, involves the frontal and temporal lobes, and is associated with abnormal findings on electroencephalography and

Table 1 Possible causes of secondary psychoses

	Examples	Investigations
Trauma	Traumatic head injury	CT, MRI
Autoimmune disorders	Systemic lupus erythematosus, NMDA receptor encephalitis	Autoantibody titers
Cytogenetic/congenital disorders	Velocardiofacial syndrome, agenesis of corpus callosum	Karyotyping, MRI
Toxic/substance-induced disorders	PCP, MDMA, LSD, cannabis, alcohol Lead, mercury or arsenic poisoning	Careful medication history; urine screen for drugs, heavy metal screen; trial off the offending agent
Iatrogenic disorders	Antimalarials, steroids, isoniazid	Careful medication history; trial off the offending agent
Cerebrovascular disorders	Stroke, subdural hematomas	CT, MRI
Space-occupying disorders	Cerebral tumors	CT, MRI
Metabolic disorders	Phaeochromocytoma, metachromatic leukodystrophy, Wilson's disease	Urinary catecholamines; arylsulphatase-A levels, copper and ceruloplasmin levels
Dietary disorders	Pellagra, B12 deficiency; vitamin D deficiency	B12, Folate, D3 levels
Sepsis/infectious disorders	Neurosyphilis, toxoplasmosis, HIV disease	RPR to rule out syphilis; HIV antibody titers; glucose, protein in CSF
Unknown cause/degenerative/ demyelinating disorders	Lewy body dementia, Parkinson's disease, Huntington's disease, multiple sclerosis, Fredreich's ataxia	MRI, CT, EEG, evoked potentials
Seizure disorders	Partial complex seizures, temporal lobe epilepsy	EEG, including sleep deprivation; telemetric EEG as indicated
Endocrine disorders	Hyperthyroidism, hypothyroidism, hyperparathyroidism	Serum calcium, thyroid/parathyroid hormone levels

CT – computed tomography; MRI – magnetic resonance imaging; NMDA – *N*-methyl D-aspartate; PCP – phencyclidine; MDMA – 3,4-methylenedioxy-*N*-methylamphetamine; LSD – lysergic acid diethylamide; RPR – rapid plasma reagin; HIV – human immunodeficiency virus; CSF – cerebrospinal fluid; EEG – electroencephalography

neuroimaging investigations (8-10). When psychosis does occur in the setting of TBI, it is characterized by prominence of persecutory delusions and auditory hallucinations, with a relative paucity of negative symptoms (3,8). Given this evidence, further research examining the interaction between TBI and genetic risk factors for schizophrenia is warranted.

Autoimmune disorders

Psychotic symptoms are a rare, but known, manifestation of systemic lupus erythematosus (SLE), with a reported prevalence ranging from 1 to 11% (11-13). Retrospective analyses reveal that, when psychosis does occur in SLE, it tends to appear early in the disease course. Approximately 30–60% of the patients found to have psychosis were psychotic when diagnosed with SLE and up to 80% developed these symptoms within 1 year of SLE diagnosis (13-15). While psychosis can be the presenting symptom in SLE, it occurs more frequently in the context of other lupus symptoms, most commonly cutaneous involvement and arthritis (13).

Symptomatically, lupus psychosis is frequently characterized by paranoia, auditory and visual hallucinations, and delusions of grandeur (14). Immunosuppressive treatment, including steroids and antimalarials, typically results in resolution of the psychotic symptoms, although these medications themselves can induce psychotic symptoms and contribute to diagnostic difficulty (14).

Autoimmune disease as a cause of psychotic symptoms is not limited to SLE. Psychosis may be the presenting symptom in multiple sclerosis (16,17) and has been documented to occur in Hashimoto's disease (18,19).

Congenital/cytogenetic disorders

Velocardiofacial syndrome (VCFS), discussed in further detail below, is caused by a heterozygous chromosome 22q11.2 deletion and is associated with the strongest link yet identified between a genetic condition and psychosis, with 25–30% of VCFS patients developing symptoms analogous to schizophrenia (20-23).

VCFS is of particular interest because the neurocognitive findings, brain structural abnormalities, psychotic symptoms, and patterns of treatment response seen in this disorder are all highly similar to those seen in schizophrenia (24).

Other genetic disorders in which psychosis can occur include Prader-Willi syndrome (in which the rate of schizophrenia-like psychosis is approximately 16%) (25,26), Huntington's disease (rate of 5–16%) (27,28), and Fahr's disease/syndrome (29,30).

Toxic/drug-induced disorders

Individuals using psychoactive substances can experience psychotic symptoms in various contexts, including acute intoxication, withdrawal, delirium induced by either intoxication or withdrawal, substance-induced mood disorder with psychotic features, and substance-induced psychosis (SIP). SIPs are best conceptualized as those conditions where the psychosis begins in the context of substance use but persists for days to weeks in the absence of continued substance use.

The substances with the clearest psychotogenic properties include stimulants (amphetamine, cocaine) (31-33), cannabis (34,35), and the psychotomimetics (phencyclidine, ketamine) (36,37). Opiates and nicotine have not been clearly shown to produce psychosis, while alcohol and benzodiazepines may induce psychosis just in acute withdrawal states (33,38,39). Lysergic acid diethylamide and 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) can produce hallucinations in acute intoxication, but there is no clear evidence that they induce an ongoing psychotic disorder (40,41).

The interaction between susceptibility to psychotic disorders and to substance abuse disorders is complex, with evidence suggesting both that genetic vulnerability to psychosis in combination with drug abuse can bring about psychosis and that individuals with such vulnerability may be more likely to abuse substances.

Toxic psychosis can also occur in the context of exposure to heavy metals, including lead (42), mercury, and arsenic (43).

Iatrogenic psychoses

Toxic psychosis can be caused by numerous centrally active medications and is often characterized by acutely impaired cognitive function in addition to psychotic symptoms.

The reported rates of psychotic symptoms in patients receiving glucocorticoids have varied widely, although there is evidence that mood disorders secondary to glucocorticoids are associated with psychotic symptoms more frequently than are primary mood disorders. While onset of psychotic symptoms usually occurs within several days of initiating glucocorticoid treatment, the symptoms can occur anytime from hours to weeks after the first dose is administered (44).

Elderly patients are at particular risk for developing toxic psychosis in reaction to medications with anticholinergic properties (45,46) and to benzodiazepines (47,48). The development of psychotic symptoms following initiation of isoniazid treatment has been documented in a growing number of case reports (49), and ascribed to alteration in catecholamine and serotonin levels via monoamine oxidase inhibition. Antimalarial drugs including chloroquine and mefloquine have been linked to psychotic symptoms, with evidence that the risk is higher in patients with a history of psychiatric illness (50,51). Additional classes of medications that have been linked to toxic psychosis include antidepressants (52), anticonvulsants (53), antiemetics (54), antiparkinsonian agents (55), antipsychotics (47), opioids (47), histamine antagonists (56), and antibiotics (57), particularly when toxic blood levels occur.

Cerebrovascular disorders

Post-stroke psychosis prevalence rates are estimated at 3–4% (58,59). While psychotic symptoms have occurred in association with strokes in numerous brain regions, they are most common in temporo-parietal-occipital lesions (59). The nature of the psychotic symptoms differs from schizophrenia, with post-stroke psychosis more likely to include visual, tactile, and olfactory hallucinations (60-62). Hallucinatory behavior in post-stroke patients has been further classified into frank hallucinations and hallucinosis, the latter distinguished by ego-dystonia and retained insight into the fact that the perceptions are not real (63).

There has been little systematic study of the link between vascular dementia and the development of psychotic symptoms, though the fact that psychosis occurs at similar rates in both vascular and Alzheimer's dementia argues against a psychotogenic mechanism specific to the cerebrovascular disturbance (64).

Studies that have searched for evidence of cerebrovascular injury in patients who develop late-onset psychotic symptoms have produced conflicting results (65). Based on the limited data currently available, it is difficult to conclude to what extent cerebrovascular disease predisposes a patient to the development of psychotic symptoms, and further research is needed to confirm or disprove this link.

Space-occupying intracranial disorders

Brain tumors are an uncommon, but important, cause of secondary psychosis, and there is evidence that the prevalence of intracranial tumors is increased in patients with psychiatric illness (66-68). Symptomatically, psychosis secondary to intracranial tumors can be indistinguishable from schizophrenia, although it is more commonly associated with visual hallucinations, simple unelaborated delusions, and absence of formal thought disorder (69-72).

Tumors located in the temporal lobes or limbic structures are the most likely to produce psychosis, with one study demonstrating that 20% of tumors in the temporal lobe resulted in psychotic symptoms (69,73). There has been no demonstrated link between the histological type of tumor and the frequency of psychosis, though low-grade, slow-growing tumors seem most likely to produce psychotic symptoms in the absence of neurological signs (74).

Neuroimaging with either computed tomography (CT) or magnetic resonance imaging (MRI) is recommended in older patients presenting with new-onset psychosis

and in patients who present with focal neurological findings on exam (75).

Metabolic disorders

Disordered neural connectivity, the putative mechanism for the symptoms of schizophrenia, can also occur in metabolic disorders that result in disrupted neuronal function or neuronal death. For example, although lysosomal storage disorders typically produce early severe neurological deficits and often death, there are adolescent or adult forms of these disorders that are associated with secondary psychosis. These disorders, such as Niemann-Pick disease type C (NPC), Tay Sachs disease, and alpha mannosidosis, likely produce psychotic symptoms through the interaction of the neuropathological processes with neurodevelopmental changes including synaptic pruning, myelination, and changes in connectivity (76-78). A similarly disordered interplay of functional connectivity and neurodevelopment is seen in the leukodystrophies, with the late-onset form of metachromatic leukodystrophy (MLD) as the prototypical example of the link between this group of disorders and secondary psychosis (76,79).

Psychotic symptoms have been reported to occur in up to 50% of patients with late-onset NPC and MLD (76). In addition, there have been case reports of patients with mitochondrial disorders presenting with psychotic symptoms, and it is thought that the leukodystrophy that can occur in mitochondrial disorders is implicated in the psychosis (80-82).

Wilson's disease, involving abnormal deposition of copper in the liver and brain, has reported prevalence rates of psychosis ranging from 2 to 11% (83,84). The psychosis in Wilson's disease is characterized not only by typical symptoms of hallucinations, delusions, and thought disorders, but also by a myriad of additional symptoms, including euphoria, sexual preoccupation, hebephrenia, and catatonia (85).

Dietary disorders

The link between nutritional deficiencies and psychiatric symptoms has been investigated and debated for decades. There is evidence that psychiatric symptoms of cobalamin deficiency may occur without evidence of hematological or neurological abnormalities (86,87). Case reports of psychosis secondary to cobalamin deficiency describe symptoms of persecutory delusions, auditory and visual hallucinations, disorganized thought processes, and psychomotor agitation that were unresponsive to treatment with antipsychotic medications but resolved completely after parenteral cobalamin therapy (88-90). Additional evidence in support of this connection includes a study in which depressed patients with psychotic depression had significantly lower cobalamin levels than those with nonpsychotic depression (91).

Although the link between folate deficiency and psychosis is tenuous, there is some evidence that folate supplementation in patients with schizophrenia enhances recovery (92). Psychotic symptoms including auditory hallucinations, persecutory delusions, and delusional parasitosis can very rarely develop in the setting of pellagra (niacin deficiency), though this occurs almost exclusively in chronic alcohol abuse (93,94).

Sepsis/infectious diseases

Historically, neurosyphilis has been closely tied to psychiatric hospitalization. In 1900, approximately 5% of institutionalized mental patients were diagnosed with general paresis of the insane (95). Syphilis infection rates have increased since the appearance of human immunodeficiency virus (HIV), and patients presenting with exclusively psychiatric symptoms in the setting of neurosyphilis have been noted (96). Such patients can present with both affective and psychotic symptoms that are indistinguishable from primary psychiatric disorders (97). Treatment of neurosyphilis with antibiotics, and adjunctive antipsychotic medications as necessary, typically halts, but does not reverse, mental status deterioration due to neuronal loss (98), although there are case reports of significant clinical improvement (99,100).

Estimates of new-onset psychosis associated with HIV infection have ranged between 0.23% and 15%, with symptoms generally presenting either in late-stage HIV or when patients have transitioned to acquired immunodeficiency syndrome (AIDS) (101,102). Symptomatically, HIV-related psychosis is characterized by persecutory, grandiose, and somatic delusions, with hallucinations as a second prominent symptom cluster (103). The effect of treatment with highly active antiretroviral therapy on psychotic symptoms remains unclear, and is further complicated by the fact that side effects of antiretrovirals include hallucinations (102). Although antipsychotics are generally effective in HIV psychosis, patients with HIV are at increased risk of developing extrapyramidal symptoms and tardive dyskinesia, particularly with the use of typical antipsychotics (101,104).

Additional infectious causes of secondary psychosis have been postulated, including infection with *Toxoplasma gondii*. This link is based on the fact that studies have demonstrated an increased prevalence of antibodies to *Toxoplasma gondii* in patients with schizophrenia (105,106). Moreover, toxoplasmosis has been linked to psychotic symptoms including delusions and auditory hallucinations, even in the absence of concurrent AIDS (107,108).

Finally, there is increasing evidence to support prenatal infections as potential risk factors for schizophrenia. Although still inconclusive, prenatal infections with influenza, toxoplasmosis, rubella, herpes simplex virus, and

syphilis have been associated with the development of secondary psychosis (109-113).

Unknown cause/degenerative/demyelinating disorders

Although the data on psychosis in multiple sclerosis (MS) have been inconsistent, recent evidence suggest that MS does increase the likelihood of developing psychotic symptoms (17). A large, population-based study from Canada reported that 2–4% of patients with MS became psychotic (114). Delusions are the primary psychotic symptom observed in MS, while hallucinations and negative symptoms are rarely seen (115). Reports of a temporal correlation between MS symptoms and psychosis, however, have been conflicting (74,115). Psychotic symptoms may be related to increased lesion burden in the periventricular white matter and temporal horns, though a precise mechanism remains to be elucidated (116). Chronic psychosis due to MS seems to be rare.

Estimates of the prevalence and incidence of psychotic symptoms in Alzheimer's disease (AD) have varied, with one review of 55 studies reporting an overall prevalence of 41%, consisting of 36% of patients with delusions and 18% with hallucinations (117). The first three years of AD are characterized by an increasing incidence of psychotic symptoms, after which there seems to be a plateau (117,118). Psychotic symptomatology in AD most often consists of delusions, typically of theft or suspicion, visual hallucinations more frequently than auditory hallucinations, and misidentifications (119). These symptoms are typically coincident with other psychiatric symptoms including aggression, agitation, apathy, and depression (120).

While psychotic symptoms appear to be less common in the fronto-temporal dementias, they have been noted in approximately 20% of patients, with higher rates in particular subtypes (121,122).

Seizure disorders

Schizophrenia-like psychosis has been associated with epilepsy for more than a century, and there is strong evidence that chronic psychosis occurs more frequently in patients with epilepsy than in the general population. Psychotic syndromes in epilepsy have traditionally been categorized based on their temporal association with clinical seizures. Ictal psychoses represent psychotic symptoms occurring in the context of an active nonconvulsive seizure, tend to last for minutes to hours, and consist of prominent hallucinations and paranoid delusions (65). Post-ictal psychoses are brief psychotic episodes that typically occur hours to days following a seizure cluster, consist of delusions, hallucinations, and affective symptoms, and generally resolve within several days (123,124). The development of a chronic psychosis associated with epilepsy is also well documented, with a recent study reporting a relative risk of 2.48 (125,126).

Phenomenologically, psychosis associated with epilepsy is difficult to distinguish from schizophrenia, as suggestions that it is characterized by a more benign course and relative lack of negative symptoms have not been verified in the literature (65,125). Risk factors for developing secondary psychosis include a more severe form of epilepsy with multiple seizure types (127), history of status epilepticus (125), and resistance to medication treatment (65). The preferential, though not exclusive, association of temporal lobe epilepsy and the development of psychotic symptoms is discussed in further detail below.

Endocrine disorders

While psychotic symptoms secondary to abnormal thyroid functioning are rare, there are case reports of psychosis developing secondary to hyperthyroidism, hypothyroidism, and even rapid alteration of thyroid state. Psychosis has been described as the presenting symptom of thyrotoxicosis in Graves disease (128), thyroid storm (129), toxic nodular goiter (130), subacute thyroiditis (131), and painless thyroiditis (132). Similarly, hypothyroidism has been associated with psychosis, with one study reporting that as many as 5–15% of myxedematous patients have some form of psychotic symptoms (133-135).

Thyroid-associated psychosis does not contain a characteristic psychotic symptom cluster, as patients have presented with auditory and visual hallucinations, delusions, and paranoia. The majority of patients present with affective disturbance (130,136). Treatment of the underlying thyroid abnormality tends to result in resolution of the psychosis, such that antipsychotic medications are necessary only in the acute setting (128,132,136). Interestingly, however, rapid correction of abnormal serum thyroid hormone levels can both induce and exacerbate thyroid-associated psychosis (137,138).

The association of hyperparathyroidism and hypercalcemia with significant psychiatric symptoms is well known, although the specific prevalence of psychosis in patients with hyperparathyroidism remains unclear. Case reports describe patients presenting with auditory and visual hallucinations, persecutory delusions, and disorganized thought processes in the setting of hyperparathyroidism-induced hypercalcemia (139,140). The available evidence indicates that correction of the hypercalcemia, generally via parathyroidectomy, results in resolution of the psychotic symptoms with no subsequent recurrence (139-141).

Although less common and investigated, hypoparathyroidism can also present with psychosis. A review of 268 cases of hypoparathyroidism published in 1962 reported

that 11% of the patients had psychotic symptoms, often in the setting of surgically induced hypoparathyroidism (142). Subsequent case reports have supported the occurrence of psychotic symptoms in hypoparathyroidism and emphasized the fact that symptomatic improvement requires normalization of magnesium and calcium levels, in addition to treatment with antipsychotics (141,143).

INVESTIGATING SECONDARY PSYCHOSIS VERSUS SCHIZOPHRENIA

Establishing a cause-effect relationship between substance use/medical illness and psychosis is not easy. Suspecting an underlying medical illness is a logical initial step when encountering psychosis in general medical settings. Comorbid medical illnesses are also quite common in patients presenting with psychotic symptoms, especially among the elderly. Suspecting and identifying an underlying medical illness in younger patients with psychosis in mental health settings is more challenging.

In making the distinction between primary and secondary psychosis, it is important to first establish the presence of the general medical condition. The next step – establishing the cause-effect relationship between the medical condition and psychosis – is often difficult, but can be helped by considering the following three key principles: atypicality, temporality, and explicability.

Is the presentation of the psychosis atypical?

An underlying medical cause for psychosis should be especially suspected if the presentation is atypical. An example is later age of onset: new onset of psychosis in a 70-year-old man should raise suspicion of an underlying medical illness. It is to be kept in mind that no single clinical feature or combination of symptoms reliably distinguishes between primary and secondary psychotic disorders. If, however, a particular feature predominates, that should raise a red flag. Thus, a strong component of severe disorientation and/or confusion must raise suspicion. Catatonic symptoms, altered states of consciousness (i.e., confusional or "dream like" states), and visual hallucinations are more frequent in secondary psychoses. Certain delusions, such as those involving beliefs of mistaken identity of others (i.e., Capgras delusions), are thought to be more common in secondary psychoses than in schizophrenia. The presence of multimodality hallucinations (e.g., visual and tactile) also increases the likelihood of a secondary psychotic disorder.

Accompanying symptoms that are disproportionate to what may be expected from a psychotic disorder should also make one consider a potential underlying medical disease. For example, a large weight loss that may not be easily explained by the mild depression in a psychotic patient may trigger suspicion of a medical illness.

Specific types of psychotic symptoms may also often point to regional alterations in brain function and raise suspicion of neurological disease. Thus, denial of blindness that may appear delusional should trigger suspicion of Anton's syndrome (cortical blindness, due to visual cortex lesions) and denial of paralysis should lead to a consideration of anosognosia (due to lesions in the nondominant parietal cortex). Likewise, both an isolated delusion of misidentification (Capgras syndrome) and olfactory hallucinations are suggestive of temporal lobe disease.

Is the medical condition or substance use temporally related to the psychosis?

Secondary psychosis is likely when the psychosis begins following the onset of the medical condition, varies in severity with the severity of the medical condition, and resolves when the medical condition improves. An example is the appearance of delusions when a patient with hypothyroidism stops taking thyroid treatment and the resolution of the symptoms after resuming medication. This rule, however, has many exceptions; for example, psychosis in temporal lobe epilepsy appears several years after the onset of the seizures. Conversely, a medical illness may simply worsen or trigger a relapse of schizophrenia without being the direct cause of the illness.

Is the psychosis not better explained by a primary psychotic disorder or another mental disorder?

Comorbid medical illness is very common in patients with chronic psychotic disorders such as schizophrenia. In some cases, even if a concomitant medical illness may raise suspicion of a secondary psychosis, the presence of a strong family history of schizophrenia and a premorbid schizoid personality point to a diagnosis of schizophrenia. Similarly, in patients with a known history of an affective illness, the appearance of psychotic symptoms is likely related to the affective illness rather than a medical condition.

Is psychosis a direct physiological consequence of a medical illness or substance use?

The answer to this question depends first on establishing the presence of an underlying medical condition or substance use that might be the etiological agent. This will require a careful history, physical, and neurological examination, along with appropriate laboratory investigations. Second, even if such a causal agent exists, it is often difficult to ascertain whether the symptoms of psychotic illness are a direct physiological consequence of that factor. Sometimes such a direct link may be obvious. For example, the presence of autonomic hyperactivity (e.g., dilated pupils, tachycardia) along with paranoid anxiety might suggest a sympathomimetic agent such as amphetamine, phencyclidine, or an adrenal tumor.

In every patient with a first episode of psychosis, it is critical to obtain a detailed history and complete

physical, including neurological examination and laboratory evaluation to rule out common medical disorders (Table 2). Additional investigations such as brain imaging, cerebrospinal fluid and electrophysiologic studies may be needed, especially for those with atypical presentations and those in whom there is reason to rule in a primary disorder.

The question of whether to conduct a brain scan in a patient with suspected schizophrenia on a routine basis is debatable. When brain scans, commonly structural (such as MRI or CT), have been used clinically as part of the work-up of a psychotic patient, the purpose has been to rule out a space occupying lesion or developmental malformation as potentially causative of the psychosis. Although incidental findings have been reported in MRI studies of patients who present with psychosis (144), and indeed occur even in healthy individuals (145), such findings are rare. Thus, in the absence of quantitative analysis, routine brain imaging cannot aid in the differential diagnosis of psychosis without considering the clinical presentation (146).

Table 2 Approach to investigating patients to rule out secondary psychoses

First line assessments (to be routinely considered in all first psychotic episode patients)
Detailed medical and neurological/psychiatric history
Physical/neurological examination
Neuropsychological tests
Laboratory tests: complete and differential blood count, erythrocyte sedimentation rate, glucose, electrolytes, thyroid function tests, liver function tests, urinary drug screen
Second line assessments (to be considered when above assessments raise specific diagnostic possibilities)
Laboratory tests: rapid plasma reagin to rule out syphilis; HIV testing; serum heavy metals; copper and ceruloplasmin levels; serum calcium levels; autoantibody titres (e.g., antinuclear antibodies for lupus); B12, folate levels; arylsulfatase-A levels; urine: culture and toxicology, drug screen
Neuroimaging: computed tomography, magnetic resonance imaging, positron emission tomography, single proton emission tomography
Electroencephalography, polysomnography, evoked potentials
Cerebrospinal fluid investigations: glucose, protein, cultures, cryptococcal antigen
Karyotyping

CAN SECONDARY PSYCHOSES ILLUMINATE PATHOPHYSIOLOGY OF SCHIZOPHRENIA?

Schizophrenia, a common and highly disabling disease with unclear causation, is a broad heterogeneous entity that may comprise several idiopathic psychotic disorders (147). To unravel its complexity, it is important to identify homogeneous subgroups within this illness to better characterize its pathophysiology. One approach to address this is to examine syndromes of known etiology that present with clinical manifestations similar to schizophrenia, that is, phenocopies of this illness.

To identify suitable phenocopies of schizophrenia to study, one needs to first define what we know about the pathophysiology of schizophrenia. At an anatomical level, schizophrenia is characterized by brain structural abnormalities in frontal, temporal, parietal, basal ganglia, thalamic, and limbic regions (148). Functional imaging studies suggest impaired function of prefrontal regions (hypofrontality) and impaired interhemispheric and intrahemispheric connectivity. At a neurochemical level, increasing evidence points to dopaminergic, glutamatergic, and GABAergic dysfunction in the pathophysiology of psychosis, with the *N*-methyl D-aspartate (NMDA) hypofunction hypothesis as a leading theory to describe the pathogenesis of schizophrenia. Several lines of evidence also point to alterations in immune and oxidative stress mechanisms in schizophrenia (149). From an etiological point of view, schizophrenia is thought to be highly heritable (heritability $> 70\%$), but several environmental factors including viruses, drugs of abuse, head trauma, and obstetric complications have been implicated (150). It is thus likely that the symptoms of the illness arise through the combination of genetic vulnerability and environmental stressors.

Given the substantive heterogeneity of schizophrenia, it would be difficult to envision any individual secondary psychosis being an adequate model to explain all aspects of that disorder. Not surprisingly, several psychotic disorders stemming from the etiological factors listed in Table 2 demonstrate only partial similarity to what we clinically identify as schizophrenia. Some disorders, however, are more likely to show clinical, pathophysiological, or etiological parallels to schizophrenia; we discuss them briefly as they may provide clues to better understand that disease.

Temporal lobe epilepsy: an anatomical model of schizophrenia

Psychosis appears to occur in 7–11% of patients with epilepsy, a rate much higher than in the general population (151). Psychosis, when it occurs in temporal lobe epilepsy, has been thought to closely resemble schizophrenia, as described by Slater in a classic early paper (125). The emergence of psychoses in temporal lobe epilepsy has been associated with onset of epilepsy under the age of 20 years, a history of epilepsy lasting for more than 10 years, a history of complex partial seizures, and lesions on the left side (152).

The occurrence of psychoses in temporal lobe epilepsy is consistent with the medial temporal structural alterations reported in schizophrenia (148). In particular, positive symptoms such as auditory hallucinations and formal thought disorder have been linked to structural alterations in the auditory association areas in the superior temporal gyri (148). The striking prominence of positive symptoms

in temporal lobe epilepsy has led to the question whether there might be a resemblance between temporal lobe epilepsy and the neurochemical models of schizophrenia. Ando et al (153) examined alterations of central dopaminergic systems in the kainate model of temporal lobe epilepsy using methamphetamine-induced locomotor activity as an index of dopaminergic sensitivity in adult rats. They found evidence of dopaminergic hypersensitivity, which can clearly explain the mechanisms underlying epileptic psychosis and can also indicate similar alterations in idiopathic psychoses.

Velocardiofacial syndrome (VCFS): a genetic model of schizophrenia

While the etiology of schizophrenia remains unclear, it is widely agreed that genetic factors have a substantial contribution, with heritability estimates of greater than 70%. Currently, schizophrenia is thought to be polygenic and multifactorial, with a small proportion of cases due to copy number variations, such as microdeletions or microduplications of chromosomal regions. A large portion of the genetic etiology of schizophrenia remains uncharted, necessitating the study of discrete genetic syndromes that present with schizophrenia-like features.

VCFS is characterized by a large deletion on one copy of chromosome 22 (comprising up to 30 genes), which can be detected with genetic testing. It is the most common chromosomal microdeletion in humans, and is characterized by congenital abnormalities of the heart, facial dysmorphism, and cognitive deficits in childhood. A substantial proportion of affected individuals develop major psychiatric illnesses in adolescence or early adulthood, with schizophrenia spectrum disorders occurring in 25–30% of affected individuals (20-23).

VCFS may offer a model of the relationship between genetic liability and risk of symptomatic manifestations of schizophrenia. The cognitive deficits in schizophrenia have been linked to a polymorphism of the gene coding for catechol *O*-methyltransferase (COMT), an enzyme involved in the degradation of dopamine. Individuals who have the Val/Val polymorphism have reduced prefrontal dopamine because of increased activity of COMT, and as a result, may have impaired cognitive function (154). VCFS is associated with similar cognitive impairments to those seen in schizophrenia, including deficits in executive control, memory, and attention. Individuals with VCFS who have the hemizygous COMT Val(158)Met genotype have been shown to have improved cognition associated with decreased enzymatic degradation of dopamine (154). Brain morphologic brain abnormalities, including prefrontal and cingulate gray matter loss, similar to those seen in schizophrenia, are also observed in VCFS, and such abnormalities appear to be correlated with cognitive impairments (155). Longitudinal studies suggest that brain structural alterations in VCFS appear to predict the emergence of psychotic symptoms (156), though further research is needed to identify the neurobiological and genotypic signatures of VCFS patients that go on to develop secondary psychoses. Studies, such as these, of the neurobiological basis of psychosis in VCFS will likely elucidate the pathophysiology of at least a subgroup of patients with schizophrenia.

NMDA encephalitis: a pathophysiological model of schizophrenia

While there has been considerable progress in our understanding of the pathophysiological substrate of schizophrenia, the core dysfunctions remain a matter of debate. A leading theory is that glutamatergic and GABAergic dysfunction may underlie the developmental pathophysiology of psychosis, perhaps through glutamatergic NMDA receptor hypofunction (157,158). This model is supported by clinical observations of a psychosis closely resembling schizophrenia that is caused by the NMDA receptor antagonist phencyclidine as well as by neuropathological observations of altered NMDA receptor binding and expression in postmortem brains of patients with schizophrenia (159). The NMDA receptor, therefore, provides a natural biological model for further study and may provide insight into the complex pathophysiological heterogeneity of schizophrenia.

Glutamatergic dysfunction may result from a failure of GABA-mediated regulation of predominantly glutamatergic pyramidal neurons. This theory is supported by observations of reduced GABA synthesis, as reflected by decreased neuronal activity of the 67-kDa isoform of glutamic acid decarboxylase (GAD67), in patients with schizophrenia (160). Several lines of evidence also point to alterations in immune mechanisms in schizophrenia (161). There is a need to draw connections between the NMDA/GABA alteration model and theories of immune system modulation in schizophrenia; studies of the appropriate forms of secondary psychoses might be one way to further elucidate this model.

An intriguing form of secondary psychosis that leads to a hypofunctioning NMDA receptor state may provide insight into the pathophysiology of schizophrenia. Since 2007, many case reports described a form of encephalitis in which patients presenting with neurological and psychiatric symptoms were found to have positive autoantibodies to the NR1/NR2 heteromers of the NMDA receptor. Dalmau and colleagues (162,163) examined 100 patients presenting with NMDA receptor encephalitis and showed that 77% presented with a variety of psychiatric symptoms that included anxiety, insomnia, fear, grandiosity, delusions, hyper-religiosity, mania, and paranoia.

A model that integrates NMDA receptor encephalitis with GABA/glutamate dysfunction includes the idea that an antibody-mediated decrease in NMDA receptors may inactivate GABAergic neurons, which normally serve to inhibit extracellular glutamate. Without the regulating presence of GABA,

the resultant excessive glutamate may induce and exacerbate psychosis. A similar mechanism may be present in schizophrenia, though definitive evidence of alterations of brain glutamatergic neurotransmission in this disease has yet to be produced. The NMDA receptor provides a biological mechanism for the development of psychosis that warrants further study, with the further possibility that variations in the nature of NMDA receptor dysfunction could inform the complex pathophysiological heterogeneity of schizophrenia.

CONCLUSIONS

The historical distinction between organic (or structural) and functional (purely psychological) disease has not served the field and stunted systematic investigation in the disorders that were earlier deemed purely psychological. Classification of psychiatric disorders into those with or without identifiable etiology has been more clinically meaningful.

Identification of an underlying medical, toxic, or iatrogenic cause in a patient presenting with psychosis can be diagnostically challenging. Careful history taking, physical examination, and judicious use of modern medical testing, combined with an informed mind, can help the clinician to arrive at a timely diagnosis and optimum intervention, which can be quite gratifying.

In appreciating the causes of secondary psychoses, the clinician-scientist also gains potential insight into the puzzling pathophysiology and etiology of primary psychotic disorders such as schizophrenia.

References

1. Mendel LB. The American Physiological Society. Science 1907; 26:765.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed., text revision. Washington: American Psychiatric Association, 2000.
3. Fujii D, Ahmed I. Characteristics of psychotic disorder due to traumatic brain injury: an analysis of case studies in the literature. J Neuropsychiatry Clin Neurosci 2002;14:130-40.
4. Achté KA, Hillbom E, Aalberg V. Psychoses following war brain injuries. Acta Psychiatr Scand 1969;45:1-18.
5. Silver JM, Kramer R, Greenwald S et al. The association between head injuries and psychiatric disorders: findings from the New Haven NIMH Epidemiologic Catchment Area Study. Brain Inj 2001;15:935-45.
6. Harrison G, Whitley E, Rasmussen F et al. Risk of schizophrenia and other non-affective psychosis among individuals exposed to head injury: case control study. Schizophr Res 2006;88:119-26.
7. David AS, Prince M. Psychosis following head injury: a critical review. J Neurol Neurosurg Psychiatry 2005;76 (Suppl. 1):i53-60.
8. Sachdev P, Smith JS, Cathcart S. Schizophrenia-like psychosis following traumatic brain injury: a chart-based descriptive and case-control study. Psychol Med 2001;31:231-9.
9. Cutting J. The phenomenology of acute organic psychosis. Comparison with acute schizophrenia. Br J Psychiatry 1987;151:324-32.
10. Miller BL, Benson DF, Cummings JL et al. Late-life paraphrenia: an organic delusional syndrome. J Clin Psychiatry 1986;47:204-7.
11. Sibley JT, Olszynski WP, Decoteau WE et al. The incidence and prognosis of central nervous system disease in systemic lupus erythematosus. J Rheumatol 1992;19:47-52.
12. Stojanovich L, Zandman-Goddard G, Pavlovich S et al. Psychiatric manifestations in systemic lupus erythematosus. Autoimmun Rev 2007;6:421-6.
13. Pego-Reigosa JM, Isenberg DA. Psychosis due to systemic lupus erythematosus: characteristics and long-term outcome of this rare manifestation of the disease. Rheumatology 2008;47:1498-502.
14. Appenzeller S, Cendes F, Costallat LTL. Acute psychosis in systemic lupus erythematosus. Rheumatol Int 2008;28:237-43.
15. Ward MM, Studenski S. The time course of acute psychiatric episodes in systemic lupus erythematosus. J Rheumatol 1991;18:535-9.
16. Carrieri PB, Montella S, Petracca M. Psychiatric onset of multiple sclerosis: description of two cases. J Neuropsychiatry Clin Neurosci 2011;23:E6.
17. Kosmidis MH, Giannakou M, Messinis L et al. Psychotic features associated with multiple sclerosis. Int Rev Psychiatry 2010;22: 55-66.
18. Lee M-J, Lee H-S, Hwang J-S et al. A case of Hashimoto's encephalopathy presenting with seizures and psychosis. Korean J Pediatr 2012;55:111-3.
19. de Holanda N, de Lima D. Hashimoto's encephalopathy: systematic review of the literature and an additional case. J Neuropsychiatry Clin Neurosci 2011;23:384-90.
20. Shprintzen RJ, Goldberg R, Golding-Kushner KJ et al. Late-onset psychosis in the velo-cardio-facial syndrome. Am J Med Genet 1992;42:141-2.
21. Pulver AE, Nestadt G, Goldberg R et al. Psychotic illness in patients diagnosed with velo-cardio-facial syndrome and their relatives. J Nerv Ment Dis 1994;182:476-8.
22. Papolos DF, Faedda GL, Veit S et al. Bipolar spectrum disorders in patients diagnosed with velo-cardio-facial syndrome: does a hemizygous deletion of chromosome 22q11 result in bipolar affective disorder? Am J Psychiatry 1996;153:1541-7.
23. Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. Arch Gen Psychiatry 1999;56:940-5.
24. Chow EWC, Watson M, Young DA et al. Neurocognitive profile in 22q11 deletion syndrome and schizophrenia. Schizophr Res 2006;87:270-8.
25. Vogels A, Matthijs G, Legius E et al. Chromosome 15 maternal uniparental disomy and psychosis in Prader-Willi syndrome. J Med Genet 2003;40:72-3.
26. Vogels A, De Hert M, Descheemaeker MJ et al. Psychotic disorders in Prader-Willi syndrome. Am J Med Genet A 2004;15; 127A:238-43.
27. Folstein SE, Chase GA, Wahl WE et al. Huntington disease in Maryland: clinical aspects of racial variation. Am J Hum Genet 1987;41:168-79.
28. Shiwach R. Psychopathology in Huntington's disease patients. Acta Psychiatr Scand 1994;90:241-6.
29. Bourgeois JA. Fahr's disease – a model of neuropsychiatric illness with cognitive and psychotic symptoms. Acta Psychiatr Scand 2010;121:78.
30. Shakibai SV, Johnson JP, Bourgeois JA. Paranoid delusions and cognitive impairment suggesting Fahr's disease. Psychosomatics 2005;46:569-72.
31. Curran C, Byrappa N, McBride A. Stimulant psychosis: systematic review. Br J Psychiatry 2004;185:196-204.
32. Post RM. Cocaine psychoses: a continuum model. Am J Psychiatry 1975;132:225-31.
33. Thirthalli J, Benegal V. Psychosis among substance users. Curr Opin Psychiatry 2006;19:239-45.
34. Fergusson DM, Horwood LJ, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. Psychol Med 2003;33:15-21.

35. Fergusson DM, Horwood LJ, Ridder EM. Tests of causal linkages between cannabis use and psychotic symptoms. Addiction 2005; 100:354-66.
36. Erard R, Luisada PV, Peele R. The PCP psychosis: prolonged intoxication or drug-precipitated functional illness? J Psychedelic Drugs 1980;12:235-51.
37. Jansen KL. A review of the nonmedical use of ketamine: use, users and consequences. J Psychoactive Drugs 2000;32:419-33.
38. Hambrecht M, Häfner H. Do alcohol or drug abuse induce schizophrenia? Nervenarzt 1996;67:36-45.
39. Dalmau A, Bergman B, Brismar B. Psychotic disorders among inpatients with abuse of cannabis, amphetamine and opiates. Do dopaminergic stimulants facilitate psychiatric illness? Eur Psychiatry 1999;14:366-71.
40. Cami J, Farré M, Mas M et al. Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. J Clin Psychopharmacol 2000;20:455-66.
41. Cole JC, Sumnall HR. Altered states: the clinical effects of Ecstasy. Pharmacol Ther 2003;98:35-58.
42. Kahan VL. Paranoid states occurring in leaded-petrol handlers. J Ment Sci 1950;96:1043-7.
43. Schenk VW, Stolk PJ. Psychosis following arsenic (possibly thallium) poisoning. A clinical-neuropathological report. Psychiatr Neurol Neurochir 1967;70:31-7.
44. Dubovsky AN, Arvikar S, Stern TA et al. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. Psychosomatics 2012;53:103-15.
45. Feinberg M. The problems of anticholinergic adverse effects in older patients. Drugs Aging 1993;3:335-48.
46. Peters NL. Snipping the thread of life. Antimuscarinic side effects of medications in the elderly. Arch Intern Med 1989;149:2414-20.
47. Schor JD, Levkoff SE, Lipsitz LA et al. Risk factors for delirium in hospitalized elderly. JAMA 1992;267:827-31.
48. Marcantonio ER, Juarez G, Goldman L et al. The relationship of postoperative delirium with psychoactive medications. JAMA 1994;272:1518-22.
49. Schrestha S, Alao A. Isoniazid-induced psychosis. Psychosomatics 2009;50:640-1.
50. Tran TM, Browning J, Dell ML. Psychosis with paranoid delusions after a therapeutic dose of mefloquine: a case report. Malar J 2006;5:74.
51. Alisky JM, Chertkova EL, Iczkowski KA. Drug interactions and pharmacogenetic reactions are the basis for chloroquine and mefloquine-induced psychosis. Med Hypotheses 2006;67:1090-4.
52. Gustafson Y, Berggren D, Brännström B et al. Acute confusional states in elderly patients treated for femoral neck fracture. J Am Geriatr Soc 1988;36:525-30.
53. Meador KJ. Cognitive side effects of antiepileptic drugs. Can J Neurol Sci 1994;21:S12-6.
54. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA 1996;275:852-7.
55. Bowen JD, Larson EB. Drug-induced cognitive impairment. Defining the problem and finding solutions. Drugs Aging 1993; 3:349-57.
56. Martin NJ, Stones MJ, Young JE et al. Development of delirium: a prospective cohort study in a community hospital. Int Psychogeriatr 2000;12:117-27.
57. Snavely S. The neurotoxicity of antibacterial agents. Ann Intern Med 1984;101:92-104.
58. Almeida OP, Xiao J. Mortality associated with incident mental health disorders after stroke. Aust N Z J Psychiatry 2007;41:274-81.
59. Kumral E, Oztürk O. Delusional state following acute stroke. Neurology 2004;62:110-3.
60. Nagaratnam N, O'Neile L. Delusional parasitosis following occipito-temporal cerebral infarction. Gen Hosp Psychiatry 2000; 22:129-32.
61. Beniczky S, Kéri S, Vörös E et al. Complex hallucinations following occipital lobe damage. Eur J Neurol 2002;9:175-6.
62. Nye E, Arendts G. Intracerebral haemorrhage presenting as olfactory hallucinations. Emerg Med 2002;14:447-9.
63. Starkstein S, Robinson R. Post-stroke hallucinatory delusional syndromes. Neuropsychiatry Neuropsychol Behav Neurol 1992; 5:114-8.
64. Lyketsos CG, Steinberg M, Tschanz JT et al. Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. Am J Psychiatry 2000;157:708-14.
65. Sachdev PS, Keshavan MS. Secondary schizophrenia. Cambridge: Cambridge University Press, 2010.
66. Waggoner RW, Bagchi BK. Initial masking of organic brain changes by psychic symptoms: clinical and electroencephalographic studies. Am J Psychiatry 1954;110:904-10.
67. Klotz M. Incidence of brain tumors in patients hospitalized for chronic mental disorders. Psychiatr Q 1957;31:669-80.
68. Larson C. Intracranial tumors in mental hospital patients a statistical study. Am J Psychiatry 1940;97:49-58.
69. Mulder DW, Daly D. Psychiatric symptoms associated with lesions of temporal lobe. JAMA 1952;150:173-6.
70. Selecki BR. Intracranial space-occupying lesions among patients admitted to mental hospitals. Med J Aust 1965;1:383-90.
71. Malamud N. Psychiatric disorder with intracranial tumors of limbic system. Arch Neurol 1967;17:113-23.
72. Galasko D, Kwo-On-Yuen PF, Thal L. Intracranial mass lesions associated with late-onset psychosis and depression. Psychiatr Clin North Am 1988;11:151-66.
73. Edwards-Lee T. Focal lesions and psychosis. In: Bogousslavsky J, Cummings JL (eds). Behavior and mood disorders. Cambridge: Cambridge University Press, 2000:419-36.
74. Davison K, Bagley CR. Schizophrenia-like psychoses associated with organic disorder of the central nervous system: a review of the literature. In: Herrington RN (ed). Current problems in neuropsychiatry. Ashford: Headley Brothers, 1969:1-45.
75. Hollister LE, Boutros N. Clinical use of CT and MR scans in psychiatric patients. J Psychiatry Neurosci 1991;16:194-8.
76. Benes F. Why does psychosis develop during adolescence and early adulthood? Curr Opin Psychiatry 2003;16:317-9.
77. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? J Psychiatr Res 1982; 17:319-34.
78. Benes FM. Myelination of cortical-hippocampal relays during late adolescence. Schizophr Bull 1989;15:585-93.
79. Weinberger DR, Lipska BK. Cortical maldevelopment, anti-psychotic drugs, and schizophrenia: a search for common ground. Schizophr Res 1995;16:87-110.
80. Mizukami K, Sasaki M, Suzuki T et al. Central nervous system changes in mitochondrial encephalomyopathy: light and electron microscopic study. Acta Neuropathol 1992;83:449-52.
81. Suzuki T, Koizumi J, Shiraishi H et al. Psychiatric disturbance in mitochondrial encephalomyopathy. J Neurol Neurosurg Psychiatry 1989;52:920-2.
82. Amemiya S, Hamamoto M, Goto Y et al. Psychosis and progressing dementia: presenting features of a mitochondriopathy. Neurology 2000;55:600-1.
83. Huang CC, Chu NS. Wilson's disease: clinical analysis of 71 cases and comparison with previous Chinese series. J Formos Med Assoc 1992;91:502-7.
84. Rathbun J. Neuropsychological aspects of Wilson's disease. Int J Neurosci 1996;85:221-9.
85. Wilson S. Progressive lenticular degeneration. BMJ 1912; 2:1645.4.
86. Lindenbaum J, Healton EB, Savage DG et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med 1988;318:1720-8.

87. Hutto BR. Folate and cobalamin in psychiatric illness. Compr Psychiatry 1997;38:305-14.
88. Evans DL, Edelsohn GA, Golden RN. Organic psychosis without anemia or spinal cord symptoms in patients with vitamin B12 deficiency. Am J Psychiatry 1983;140:218-21.
89. Masalha R, Chudakov B, Muhamad M et al. Cobalamin-responsive psychosis as the sole manifestation of vitamin B12 deficiency. Isr Med Assoc J 2001;3:701-3.
90. Payinda G, Hansen T. Vitamin B(12) deficiency manifested as psychosis without anemia. Am J Psychiatry 2000;157:660-1.
91. Levitt AJ, Joffe RT. Vitamin B12 in psychotic depression. Br J Psychiatry 1988;153:266-7.
92. Godfrey PS, Toone BK, Carney MW et al. Enhancement of recovery from psychiatric illness by methylfolate. Lancet 1990; 336:392-5.
93. Prakash R, Gandotra S, Singh LK et al. Rapid resolution of delusional parasitosis in pellagra with niacin augmentation therapy. Gen Hosp Psychiatry 2008;30:581-4.
94. Rudin DO. The major psychoses and neuroses as omega-3 essential fatty acid deficiency syndrome: substrate pellagra. Biol Psychiatry 1981;16:837-50.
95. Hare EH. The origin and spread of dementia paralytica. J Ment Sci 1959;105:594-626.
96. Sobhan T, Rowe HM, Ryan WG et al. Unusual case report: three cases of psychiatric manifestations of neurosyphilis. Psychiatr Serv 2004;55:830-2.
97. Klaus MV, Amarante L, Beam TR. Routine screening for syphilis is justified in patients admitted to psychiatric, alcohol, and drug rehabilitation wards of the Veterans Administration Medical Center. Arch Dermatol 1989;125:1644-6.
98. Hutto B. Syphilis in clinical psychiatry: a review. Psychosomatics 2001;42:453-60.
99. Taycan O, Ugur M, Ozmen M. Quetiapine vs. risperidone in treating psychosis in neurosyphilis: a case report. Gen Hosp Psychiatry 2006;28:359-61.
100. Güler E, Leyhe T. A late form of neurosyphilis manifesting with psychotic symptoms in old age and good response to ceftriaxone therapy. Int Psychogeriatr 2011;23:666-9.
101. Sewell DD. Schizophrenia and HIV. Schizophr Bull 1996; 22:465-73.
102. Dolder CR, Patterson TL, Jeste DV. HIV, psychosis and aging: past, present and future. AIDS 2004;18 (Suppl. 1):S35-42.
103. Harris MJ, Jeste DV, Gleghorn A et al. New-onset psychosis in HIV-infected patients. J Clin Psychiatry 1991;52:369-76.
104. Shedlack KJ, Soldato-Couture C, Swanson CL. Rapidly progressive tardive dyskinesia in AIDS. Biol Psychiatry 1994;35:147-8.
105. Yolken RH, Dickerson FB, Fuller Torrey E. Toxoplasma and schizophrenia. Parasite Immunol 2009;31:706-15.
106. Torrey EF, Yolken RH. Schizophrenia and toxoplasmosis. Schizophr Bull 2007;33:727-8.
107. Kramer W. Frontiers of neurological diagnosis in acquired toxoplasmosis. Psychiatr Neurol Neurochir 1966;69:43-64.
108. Freytag HW, Haas H. Psychiatric aspects of acquired toxoplasmosis. A case report. Nervenarzt 1979;50:128-31.
109. Brown AS. Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. Dev Neurobiol (in press).
110. Brown AS, Begg MD, Gravenstein S et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry 2004;61:774-80.
111. Mortensen PB, Nørgaard-Pedersen B, Waltoft BL et al. Toxoplasma gondii as a risk factor for early-onset schizophrenia: analysis of filter paper blood samples obtained at birth. Biol Psychiatry 2007;61:688-93.
112. Babulas V, Factor-Litvak P, Goetz R et al. Prenatal exposure to maternal genital and reproductive infections and adult schizophrenia. Am J Psychiatry 2006;163:927-9.
113. Brown AS, Cohen P, Harkavy-Friedman J et al. Prenatal rubella, premorbid abnormalities, and adult schizophrenia. Biol Psychiatry 2001;49:473-86.
114. Patten SB, Svenson LW, Metz LM. Psychotic disorders in MS: population-based evidence of an association. Neurology 2005; 65:1123-5.
115. Feinstein A. The neuropsychiatry of multiple sclerosis. Can J Psychiatry 2004;49:157-63.
116. Feinstein A, Boulay du G, Ron MA. Psychotic illness in multiple sclerosis. A clinical and magnetic resonance imaging study. Br J Psychiatry 1992;161:680-5.
117. Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. Am J Psychiatry 2005;162:2022-30.
118. Paulsen JS, Ready RE, Stout JC et al. Neurobehaviors and psychotic symptoms in Alzheimer's disease. J Int Neuropsychol Soc 2000;6:815-20.
119. Jeste DV, Finkel SI. Psychosis of Alzheimer's disease and related dementias. Diagnostic criteria for a distinct syndrome. Am J Geriatr Psychiatry 2000;8:29-34.
120. Rapoport MJ, van Reekum R, Freedman M et al. Relationship of psychosis to aggression, apathy and function in dementia. Int J Geriatr Psychiatry 2001;16:123-30.
121. Gustafson L, Brun A, Passant U. Frontal lobe degeneration of non-Alzheimer type. Baillieres Clin Neurol 1992;1:559-82.
122. Edwards-Lee T, Miller BL, Benson DF et al. The temporal variant of frontotemporal dementia. Brain 1997;120 (Pt 6):1027-40.
123. Logsdail SJ, Toone BK. Post-ictal psychoses. A clinical and phenomenological description. Br J Psychiatry 1988;152:246-52.
124. Kanner AM, Stagno S, Kotagal P et al. Postictal psychiatric events during prolonged video-electroencephalographic monitoring studies. Arch Neurol 1996;53:258-63.
125. Slater E, Beard AW, Glithero E. The schizophrenia-like psychoses of epilepsy. Br J Psychiatry 1963;109:95-150.
126. Qin P, Xu H, Laursen TM et al. Risk for schizophrenia and schizophrenia-like psychosis among patients with epilepsy: population based cohort study. BMJ 2005;331:23.
127. Standage KF, Fenton GW. Psychiatric symptom profiles of patients with epilepsy: a controlled investigation. Psychol Med 1975;5:152-60.
128. Katsigiannopoulos K, Georgiadou E, Pazarlis P et al. Psychotic disorder as a manifestation of Graves' disease. Psychosomatics 2010;51:449-50.
129. Chen T-S, Wen M-J, Hung Y-J et al. A rare storm in a psychiatric ward: thyroid storm. Gen Hosp Psychiatry 2012;34:210.e1–4.
130. Brownlie BE, Rae AM, Walshe JW et al. Psychoses associated with thyrotoxicosis – "thyrotoxic psychosis". A report of 18 cases, with statistical analysis of incidence. Eur J Endocrinol 2000;142:438-44.
131. Rizvi AA. "Thyrotoxic psychosis" associated with subacute thyroiditis. South Med J 2007;100:837-40.
132. Kobayashi N, Tajiri J, Takano M. Transient psychosis due to painless thyroiditis in a patient with anxiety disorder: a case report. J Med Case Reports 2011;5:534.
133. Sathya A, Radhika R, Mahadevan S et al. Mania as a presentation of primary hypothyroidism. Singapore Med J 2009;50:e65-7.
134. Tor PC, Lee HY, Fones CSL. Late-onset mania with psychosis associated with hypothyroidism in an elderly Chinese lady. Singapore Med J 2007;48:354-7.
135. Hall R. Psychiatric effects of thyroid hormone disturbance. Psychosomatics 1983;24:7-11.
136. Heinrich TW, Grahm G. Hypothyroidism presenting as psychosis: myxedema madness revisited. Prim Care Companion J Clin Psychiatry 2003;5:260-6.
137. Irwin R, Ellis PM, Delahunt J. Psychosis following acute alteration of thyroid status. Aust N Z J Psychiatry 1997;31:762-4.

138. Schofield A, Bracken P. Thyroid-induced psychosis in myxoedema. Ir Med J 1983;76:495-6.
139. Papa A, Bononi F, Sciubba S et al. Primary hyperparathyroidism: acute paranoid psychosis. Am J Emerg Med 2003;21:250-1.
140. Watson LC, Marx CE. New onset of neuropsychiatric symptoms in the elderly: possible primary hyperparathyroidism. Psychosomatics 2002;43:413-7.
141. Velasco PJ, Manshadi M, Breen K et al. Psychiatric aspects of parathyroid disease. Psychosomatics 1999;40:486-90.
142. Denko JD, Kaelbling R. The psychiatric aspects of hypoparathyroidism. Acta Psychiatr Scand 1962;38 (Suppl. 164):1-70.
143. Ang AW, Ko SM, Tan CH. Calcium, magnesium, and psychotic symptoms in a girl with idiopathic hypoparathyroidism. Psychosom Med 1995;57:299-302.
144. Lisanby S, Kohler C, Swanson C. Psychosis secondary to brain tumor. Semin Clin Neuropsychiatry 1998;3:12-22.
145. Illes J, Kirschen M, Edwards E et al. Incidental findings in brain imaging research: what should happen when a researcher sees a potential health problem in a brain scan from a research subject? Science 2006;311:783-84.
146. Lawrie SM, Abukmeil SS, Chiswick A et al. Qualitative cerebral morphology in schizophrenia: a magnetic resonance imaging study and systematic literature review. Schizophr Res 1997; 24;25:155-66.
147. Keshavan MS, DeLisi LE, Seidman LJ. Early and broadly defined psychosis risk mental states. Schizophr Res 2011;126:1-10.
148. Shenton ME, Whitford TJ, Kubicki M. Structural neuroimaging in schizophrenia: from methods to insights to treatments. Dialogues Clin Neurosci 2010;12:317-32.
149. Keshavan MS, Tandon R, Boutros NN et al. Schizophrenia, "just the facts": what we know in 2008. Part 3: Neurobiology. Schizophr Res 2008;106:89-107.
150. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, "just the facts": what we know in 2008. 2. Epidemiology and etiology. Schizophr Res 2008;102:1-18.
151. Trimble M. The psychoses of epilepsy. New York: Raven, 1991.
152. Torta R, Keller R. Behavioral, psychotic, and anxiety disorders in epilepsy: etiology, clinical features, and therapeutic implications. Epilepsia 1999;40 (Suppl. 10):S2-20.
153. Ando N, Morimoto K, Watanabe T et al. Enhancement of central dopaminergic activity in the kainate model of temporal lobe epilepsy: implication for the mechanism of epileptic psychosis. Neuropsychopharmacology 2004;29:1251-8.
154. Shashi V, Keshavan MS, Howard TD et al. Cognitive correlates of a functional COMT polymorphism in children with 22q11.2 deletion syndrome. Clin Genet 2006;69:234-8.
155. Shashi V, Kwapil TR, Kaczorowski J et al. Evidence of gray matter reduction and dysfunction in chromosome 22q11.2 deletion syndrome. Psychiatry Res 2010;181:1-8.
156. Kates WR, Antshel KM, Faraone SV et al. Neuroanatomic predictors to prodromal psychosis in velocardiofacial syndrome (22q11.2 deletion syndrome): a longitudinal study. Biol Psychiatry 2011;69:945-52.
157. Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 1995;52:998-1007.
158. Moghaddam B. Bringing order to the glutamate chaos in schizophrenia. Neuron 2003;40:881-4.
159. Harrison PJ, Law AJ, Eastwood SL. Glutamate receptors and transporters in the hippocampus in schizophrenia. Ann N Y Acad Sci 2003;1003:94-101.
160. González-Burgos G, Hashimoto T, Lewis DA. Alterations of cortical GABA neurons and network oscillations in schizophrenia. Curr Psychiatry Rep 2010;12:335-44.
161. Potvin S, Stip E, Sepehry AA et al. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry 2008;63:801-8.
162. Dalmau J, Tüzün E, Wu H-Y et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25-36.
163. Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. Lancet Neurol 2008;7:327-40.

DOI 10.1002/wps.20001