Psychotic Symptoms in Patients with Medical Disorders

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Psychotic symptoms frequently occur in patients with comorbid medical disorders and present a diagnostic and treatment challenge. They may be a part of an independent psychiatric illness associated with the underlying medical condition or induced by substance use or medications. The presence of psychotic symptoms can contribute to misdiagnosis or complicate the management of the comorbid medical illness. Psychiatrists must be familiar with the assessment and management of psychotic disorders in patients with comorbid medical disorders. Medications that may be used to treat psychosis include antipsychotic agents, benzodiazepines, or possibly certain anticonvulsants. Selecting the appropriate medication requires knowledge of the pharmacokinetics of different agents and their side effect profile. Understanding the neuropsychiatric effects of medications and drug-drug interactions may help in preventing psychotic symptoms.

Introduction

Psychotic symptoms can be a manifestation of a variety of disorders, including primary psychotic disorders, such as schizophrenia, schizoaffective disorder, and bipolar disorder, as well as secondary psychotic disorders, because of a general medical condition or induced by psychoactive substances or medications. Medical conditions may directly contribute to psychotic symptoms or complicate the management of primary psychotic disorders. Medications used to treat psychotic disorders can affect the underlying medical condition and its management. Although atypical antipsychotic medications are increasingly used as first-line agents in the treatment of primary psychotic disorders, there is relatively little information regarding their use in secondary psychotic disorders. When patients with a medical illnesses manifest psychotic symptoms, they often present a diagnostic and treatment challenge.

Primary Psychotic Disorders with Comorbid Medical Illness

In a patient with psychotic symptoms and a comorbid medical illness, the possibility of a primary psychotic disorder coexisting with a medical disorder, or of psychosis contributed by the medical illness or psychoactive substance use, has to be considered. Patients with primary psychotic disorders, in particular schizophrenia, have an increased risk for medical comorbidities [1,2]. Nearly 50% of patients with schizophrenia have at least one comorbid medical condition [3]. Patients with a primary psychotic disorder often do not volunteer information about their medical conditions, leading to a missed diagnosis of the comorbid medical disorder. When primary psychotic disorders occur along with general medical illnesses, the treatment of the psychosis has to take the medical illness into account.

Secondary Psychotic Disorders

In the assessment of a patient with psychotic symptoms, a wide range of differential diagnoses should be entertained. This is especially true if a general medical illness, psychoactive substance, or medication known to cause psychosis is present. Thus, the possibilities of a cognitive disorder (delirium or dementia), a psychotic disorder caused by general medical condition, and a substance-induced psychotic disorder should be considered in addition to a primary psychotic disorder. Observe that the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV-TR) "diagnosis of psychotic disorder due to general medical condition" excludes psychotic symptoms attributed to delirium, dementia, or substance use disorders [4]. Substance-induced psychotic disorder includes psychosis caused by use of or withdrawal from psychoactive substances or medications [4].

The terms *primary* and *secondary psychosis* are no longer used by the DSM-IV-TR [4]. However, most clinicians have no difficulty understanding this distinction. We find that these terms are meaningful to distinguish conditions in which the only pathology is the psychotic disorder itself, that is, "primary" psychosis, from conditions in which the psychotic symptoms are a manifestation of another medical or substance-related disorder, that is, "secondary" psychosis.

Table 1. Causes of secondary psychotic symptoms

Cerebral disorders	Systemic disorders
CNS infections (eg, herpes encephalitis, HIV encephalopathy)	Adrenal disease
Alzheimer's disease	Cushing's syndrome
Cerebrovascular disease	Hypo- or hyperthyroidism
Tumors	Vitamin deficiency (eg, B1, B12)
Trauma	Hyponatremia
Epilepsy	Hepatic encephalopathy
CNS vasculitis (eg, systemic lupus erythematosus)	Uremia
Multiple sclerosis	Acute intermittent porphyria
Normal pressure hydrocephalus	
Basal ganglia disorders (Huntington's disease, Wilson's disease)	

CNS—central nervous system.

Etiology of Secondary Psychotic Symptoms

Comprehensive lists of the potential causes of psychosis in the medically ill are found in several textbooks; however, their usefulness is often limited by their over-inclusiveness. Although it is true that, until proven otherwise, almost any disease or medication can cause psychotic symptoms, it is clinically unrealistic to consider every possible cause. Rather it is more useful to follow the advice, "When you hear hoofs in the street, think of horses, not zebras!" Table 1 summarizes common medical conditions associated with psychotic symptoms. Similarly, psychoactive substances and commonly prescribed medications that may produce psychotic symptoms are listed in Table 2.

In patients with comorbid medical illness, the most common causes of psychotic symptoms are delirium and dementia. Delusions occur in approximately 20% of patients with delirium and 47% of those with dementia [5].

When psychotic symptoms are caused by parenchymal brain disease, the lesion is most frequently located subcortically or in the temporal lobes. A review of the literature [6] found that "organic" delusions occur most commonly in toxic-metabolic processes and in disorders affecting the limbic system and basal ganglia. Delusions (7%) and hallucinations (10%) also occur in multiple sclerosis and are present between exacerbations, but there is no consistent correlation with magnetic resonance imaging findings [7]. Psychotic symptoms often occur in dementia of the Alzheimer's type that affects neocortical association areas and the hippocampus, and vascular dementia that results from multifocal lesions. Left-sided temporal lobe lesions have been known to be more likely associated with chronic psychotic symptoms [8]. However, right parietotemporal lesions are associated with more transient psychosis [9].

Hallucinations were reported in 37% patients with Parkinson's disease; 29% had only visual hallucinations, 8% had visual and auditory hallucinations, and no patient reported auditory hallucinations alone [10]. In this study, hallucinations were not correlated with age, duration of illness, or treatment with dopamine agonists, but cognitive impairment was much more common in patients with hallucinations. Patients with more severe neuropsychologic impairment (*eg,* dementia of the Alzheimer's type, vascular dementia) demonstrate simple, loosely held, persecutory beliefs that are often transient [6]. Patients with more complex delusions tend to have less cognitive impairment, but the delusions are more frequently chronic and relatively resistant to treatment [6]. The latter occur in patients with extrapyramidal disorders or with traumatic, neoplastic, or cerebrovascular lesions involving the subcortical nuclei or the limbic system.

The prevalence of any psychotic disorder in patients with epilepsy was 4% in an outpatient seizure clinic [11]. Psychosis related to seizure disorders is more common during the interictal phase, after a long history of seizures, and in patients who have evidence of temporal lobe lesions or left-sided foci [6]. Psychotic symptoms related to epilepsy can occur in the ictal, postictal, or interictal phases. A brief ictal psychosis can occur in a nonconvulsive status epilepticus, most commonly with partial complex status [12]. In such cases, automatisms (*eg,* lip smacking or picking at clothes), mutism, altered consciousness, or amnesia may be present. Classically, with postictal psychoses, there is a flurry of seizures, then a few relatively uneventful days, and finally onset of the psychosis [11]. Postictal psychosis is usually limited to a few days or a couple of weeks and mood symptoms are often present. Lastly, interictal psychosis often appears in patients with longstanding and frequent seizures, but also has been reported in patients with relatively infrequent seizures, usually lasting for only a week or two, but can be much more prolonged. Compared with postictal psychosis, interictal psychosis tends to resolve when one or more seizures occur [12]. The clinical presentation of chronic interictal psychosis, although generally similar to that of schizophrenia, has better preservation of affect, as well as greater mood swings, mystical experiences, and visual hallucinations [13].

The most common causes of substance-induced psychotic disorder are intoxication with amphetamines, cocaine, and phencyclidine. The psychosis may persist even after the causative drug has been eliminated from the body [14,15]. Cannabis rarely induces a full-blown psychosis, though transient paranoia is more frequently seen. Psychotic symptoms

Table 2. Psychoactive substances or medications causing secondary psychosis

Psychoactive substances	Alcohol withdrawal and hallucinosis
	Amphetamine intoxication
	Cocaine intoxication
	Hallucinogen intoxication
	Phencyclidine intoxication
	Sedative hypnotic withdrawal
Cardiology	Digitalis
	Beta blockers
	Anti-arrhythmics (procainamide, tocainide, mexiletime, quinidine, and lidocaine)
Oncology	Asparaginase
	Cytarabine
	Fluorouracil
	Ifosfamide
	Methotrexate
	Vincristine
Infectious diseases	Ciprofloxacin
	Antitubercular (isoniazid, cycloserine)
	Antimalarials
	Antivirals (acyclovir, vidarabine, interferon, and zidovudine)
Neurology	Dopamine agonists (amantadine, bromocriptine, and levodopa)
Psychiatry	Antidepressants (bupropion, tricyclic antidepressants)
	Anticholinergics (benztropine, diphenhydramine)
Gastroenterology	Cimetidine
	Ranitidine
Analgesia	Pentazocine
	Meperidine
	Indomethacin
General	Corticosteroids
	Metrizamide
	Methysergide
	Baclofen
	Ephedrine

also can be present during withdrawal from substances such as alcohol and sedative hypnotics.

Differential Diagnosis of Primary Versus Secondary Psychosis

This distinction often is difficult because the clinical presentation tends to be similar, and even when a potential cause for the psychosis is present, there is difficulty determining if a cause-and-effect relationship exists. Secondary psychosis should be suspected whenever, on history, examination, or laboratory tests, evidence of a disease or psychoactive substance is known to cause psychotic symptoms. Secondary psychosis is more likely if there are atypical clinical features, a family history of a primary psychotic disorder is lacking, or the psychosis starts at a later age. A "secondary" psychosis also is more likely if autonomic disturbance is present and if the psychosis is resistant to treatment.

In secondary psychosis, consciousness may be impaired, and if the level of consciousness is fluctuating, this is of even greater diagnostic value. Other aspects of cognitive function, such as orientation, short-term memory, and language, may be impaired as well. Focal neurologic signs and symptoms or incontinence of bladder or bowel may be present. However, significant thought disorder is not frequently found, and the delusions are more often simple and fragmented. Presence of visual, tactile, olfactory, or gustatory hallucinations should suggest the possibility of a secondary psychosis. Although affect tends to be better preserved in secondary psychoses than in schizophrenia, frontal lobe epilepsy patients with interictal psychosis show marked emotional withdrawal and blunted affect [16].

Significant effort is needed to elicit the temporal relationship between the alleged causative factor and the onset of the psychosis, but if this is obtained, it provides a key to the diagnosis. In particular, if the onset and the resolution of the psychosis coincide with the putative causative factor, the causal inference is greatly strengthened.

Laboratory Tests

When secondary psychotic symptoms are suspected, a complete blood count, metabolic panel, serum calcium, liver function tests, thyroid stimulating hormone levels, urinalysis, and a urine toxicology screen should be done. In addition, a chest radiograph, serum drug levels (*eg*, theophylline), arterial blood gases, vitamin B_{12} and folate levels, and testing for HIV may be needed. A computed tomography or magnetic

resonance imaging scan, or a lumbar puncture, also may be indicated if intracranial pathology is suspected.

Complications

A nearly twofold increase in mortality has been shown for schizophrenia patients compared with the general population [17], and this is, at least in part, because of comorbid medical conditions [18]. Schizophrenia patients often have poor health habits (*eg,* diet and exercise) and increased rates of smoking and substance abuse [19,20]. They are more likely to be obese and are at a greater risk for non–insulin-dependent diabetes mellitus [21]. Comorbid medical illnesses in patients with schizophrenia are often undiagnosed or diagnosed late [22••]. For example, a population-based study showed that patients with psychosis are less likely to receive medical treatment for arthritis [23]. Patients with schizophrenia have limited access to health care because of noncompliance, delusions regarding the illness or its treatment, and social withdrawal in general. Not surprisingly, homeless individuals with schizophrenia have been shown to have fewer medical visits than those with depression. They also were found to be less likely to have had careful physical examinations or medical screenings [24]. In a follow-up study, compliance with antipsychotic medications averaged 58% compared with 65% for antidepressants and 76% for medications for medical disorders [25]. Psychosis also impairs the patient's ability to communicate medical information to health care providers. Furthermore, impaired processing of perceptual information may lead to physical symptoms being misperceived by patients and clinicians. A series of cases were recently reported in which somatic symptoms occurred in psychotic patients and worsened their psychosis, but only later were recognized as physical problems [26]. Physicians often regard psychotic individuals as unpredictable and limit their clinical contact. Studies have found that a prior diagnosis of schizophrenia may lead medical professionals to discount the patient's somatic complaints [27,28]. Schizophrenia patients tend to have an increased pain tolerance [29], which may lead to reduced reporting of physical problems and increased morbidity [30]. Finally, system-related barriers, such as poor integration between mental health care and general health care, disrupts continuity of care for these patients.

Treatment

In primary and secondary psychosis, the psychosis and the comorbid medical illness need to treated simultaneously. If the patient is very agitated, physical or chemical restraints or one-on-one observation may be needed for the safety of the patient and staff. In the medical setting, the competency of a patient with psychosis to provide informed consent for treatment is often questioned. In many instances, such patients are capable of understanding procedures and treatment if explained in a simple and straightforward manner.

Primary psychosis in patients with comorbid medical illness

Schizophrenia patients are as frightened of their illness as other patients [31•]. Although they may seem distant, they also may be quite dependent, and appreciate any concern or kindness shown to them by the staff.

Psychotic patients who are unstable should not undergo repeated interviews by groups of medical students, interns, residents, or other personnel. These patients appreciate straightforward information rather than elaborate descriptions of medical interventions. Efforts should be made to psychiatrically stabilize any unstable patients before medical or surgical procedures. It is imperative that a high level of communication and cooperation be established between the medical and psychiatric teams. Issues such as the unit of the hospital (*ie,* medical or psychiatric) in which the interventions will occur, criteria for transfer between the medical and psychiatric wards, and plans for follow-up after discharge should be clearly understood by all parties.

Secondary psychosis

All nonessential medications should be discontinued or reduced in dosage if they are suspected to be contributing to the psychosis. Treatment to address any medical conditions implicated in the psychosis should be promptly initiated.

Antipsychotic medications are often necessary for symptom control. Although haloperidol has long been used in the treatment of delirium, atypical antipsychotics are being increasingly used for this indication [31•,32]. In dementia with psychotic symptoms, low-potency typical antipsychotics (*eg,* thioridazine) or adjunctive anticholinergics should be avoided. A low dose of an atypical antipsychotic should be used. Withdrawal from alcohol or sedative hypnotics is the main indication for the use of benzodiazepines. For psychosis associated with epilepsy, although anticonvulsants alone may be sufficient, addition of an antipsychotic is often indicated. If there is a rapid and complete resolution of symptoms, the possibility that there is an "organic" cause that has been reversed should be considered. In such cases, an attempt should be made to taper off the antipsychotic.

Antipsychotics in delirium

Antipsychotics are the medications of choice in the treatment of delirium [33]. A randomized, double-blind, controlled trial demonstrated the clinical superiority of antipsychotics over benzodiazepines in treatment of delirium [34]. Supported by evidence from clinical trials, haloperidol has been the gold standard in the treatment of delirium [35,36]. Droperidol, a butryphenone with a rapid onset of action and short half-life that is more sedating than haloperidol, also has been effective in the treatment of agitated patients [37]. Concerns regarding the use of droperidol, center on its association with lengthening of QTc interval and risk of *Torsades de Pointes* and postural hypotension.

A series of uncontrolled trials and case reports have shown that atypical antipsychotics are effective in the treat-

Table 3. Choice of antipsychotic agents by comorbid medical illness

	Choice of medication			
Illness	**Preferred**	**Caution**	**Avoid**	**Rationale**
Cardiac disease	Aripiprazole	Olanzapine, clozapine		Weight gain, increased lipids; hypotension
	Risperidone	Low-potency typicals†		Tachycardia; hypotension
	Quetiapine	Ziprasidone		QT prolongation
	High-potency typicals*			
Obesity, diabetes mellitus, and hyperlipidemia	Aripiprazole	Quetiapine		Weight gain
	Ziprasidone		Clozapine	Greater weight gain, diabetes, and hyperlipidemia
	Risperidone		Olanzapine	
	Haloperidol		Phenothiazines	
Glaucoma and prostate enlargement	Aripiprazole		Low-potency typicals†	Greater anticholinergic effects
	Risperidone		Clozapine	
	Quetiapine		Olanzapine	
	High-potency typicals*			
Parkinson's disease	Clozapine			Specifically effective without worsening motor function
	Quetiapine		High-potency typicals*	Worsens motor function
			Olanzapine	
Epilepsy	Atypicals (first choice)‡		Clozapine	
	High-potency typicals*		Low-potency typicals†	Greater lowering of seizure threshold

*For example, haloperidol at 1 to 10 mg per day.
†For example, chlorpromazine or thioridazine at 100 to 600 mg per day.
‡Aripiprazole (15 to 30 mg per day), olanzapine (5 to 20 mg per day), quetiapine (50 to 800 mg per day), risperidone (1 to 6 mg per day), or clozapine (200 to 800 mg per day).

ment of delirium. Open-label studies have found olanzapine to be effective for treatment of delirium [34,38], with studies suggesting that it may be comparable wtih haloperidol in its efficacy, with fewer extrapyramidal side effects [39]. Open-label studies also have demonstrated that risperidone (mean dose of 1.7 mg per day) and quetiapine (mean dose 44.9 mg per day) are effective and well tolerated in the treatment of delirium [40,41]. A case report has found that ziprasidone successfully controlled symptoms of delirium [42].

Atypical antipsychotics for psychosis in dementia

Conventional antipsychotics, such as haloperidol, have been long used to treat psychosis, agitation, and aggressive behavior in patients with dementia; however, the atypical antipsychotics are increasingly used for this indication, and some have been effective in clinical trials. A large, double-blind, randomized, placebo-controlled trial in 625 patients with dementia found that risperidone was effective for reducing psychosis and aggression, and that risk-benefit ratio suggested that 1 mg per day was the optimum dose of risperidone in this population [43]. Another randomized, placebo-controlled study found that 5 to 10 mg per day of olanzapine was effective for psychosis and behavioral symptoms in Alzheimer's disease, without increasing extrapyramidal adverse effects [44]. In various case series, quetiapine has been effective for the treatment of visual hallucinations in patients with dementia with Lewy bodies [45–47].

Use of antipsychotics in patients with comorbid medical illness

The elderly and patients with comorbid medical illness are particularly sensitive to the adverse effects of antipsychotics [48,49], but the patients also tend to respond to lower doses. Thus, it is important to "start low and go slow." However, this principle does not preclude increasing gradually to full doses if clinically indicated and tolerated.

Antipsychotic medications are generally selected based on potential side effects, some of which may be desired (Table 3). Although there are few data from controlled studies, clinical experience suggests that atypical antipsychotics may be safe and effective in patients with comorbid medical illness and have the advantages of less extrapyramidal side effects compared with older agents [50–54]. Haloperidol, however, has the advantage of causing minimal sedation, having little anticholinergic properties. For agitated patients,

atypical agents with sedative properties, such as quetiapine, may be appropriate. However, when sedation is not necessary, agents such as risperidone, aripiprazole, or ziprasidone should be considered.

If the patient has difficulty swallowing pills or there is a suspicion of "cheeking" the pills, the antipsychotic can be given as a liquid (*eg,* haloperidol, risperidone, or ziprasidone) or as an orally disintegrating tablet [55]. If the patient is unable to take oral medication, or a rapid response is needed, intramuscular haloperidol or ziprasidone should be considered. If multiple parenteral doses are needed, intravenous haloperidol should be used. Because dehydration increases the risk of neuroleptic malignant syndrome, fluid intake should be carefully monitored when patients with comorbid medical illness are given antipsychotic agents.

Elderly

In elderly patients, low-potency typical antipsychotics are more likely to cause orthostatic hypotension and lead to falls. The greater anticholinergic properties of low-potency typical antipsychotics may cause cognitive impairment or even delirium. Thus, atypical antipsychotics should be used in older patients. In patients with Parkinson's disease, high-potency typical antipsychotics, and even olanzapine, can worsen motor symptoms. Low-dose clozapine has been effective in double-blind, placebo-controlled studies for psychosis in Parkinson's disease [56]. Quetiapine also has been effective for this condition in retrospective chart reviews [57] and case series [58].

Cardiac diseases

Cardiac disease, including an acute myocardial infarction, is not an absolute contraindication to using antipsychotic agents. However, low-potency typical antipsychotics should be avoided because they may cause orthostatic hypotension or prolongation of the QT interval on the electrocardiogram. In general, haloperidol has been used safely, though intravenous use in patients with cardiomyopathy has been reported to cause *Torsades de Pointes* [59]. There are no published reports of arrhythmias resulting from the use of atypical antipsychotics, except with clozapine [60]. Atrial fibrillation, cardiomyopathy, and myocarditis also have been reported with clozapine [59]. Thioridazine is associated with the greatest increase in QTc interval. Among the newer atypical antipsychotics, ziprasidone is associated with a numerically greater QTc prolongation, but the actual clinical significance of this is not clear, and there have been no published reports of *Torsades de Pointes*. Hypokalemia and hypomagnesiumia are risk factors for the development of arrhythmias in patients with prolonged QT intervals. Caution is needed if the patient is on any other medication that could prolong the QT interval (*eg,* quinidine, droperidol). An electrocardiogram is needed before using clozapine in any patient, or ziprasidone in the elderly, critically ill, or if there is preexisting cardiac disease.

Obesity and diabetes

Atypical antipsychotics can be associated with considerable weight gain [61–63], and this has to be taken into consideration especially for patients with diabetes, obesity, or coronary artery disease. The weight gain is most pronounced with clozapine, olanzapine, quetiapine, and low-potency antipsychotics. Aripiprazole and ziprasidone are least likely to cause weight gain. The incidence of weight gain of 7% or more of the initial body weight during short-term treatment has been reported at 29% for olanzapine, 23% for quetiapine, 18% for risperidone, and 10% for ziprasidone [64••]. The weight gain is probably mediated by histamine-1 receptor antagonism, is not clearly related to the dose of antipsychotic, and tends to plateau in a few months, but this may take nearly a year or more for olanzapine and clozapine [64••].

Schizophrenia also has been associated with insulin resistance and impaired glucose tolerance, even without the use of an antipsychotic medication [65]. However, numerous reports have shown that atypical antipsychotics can be associated with impaired glucose tolerance, worsening of diabetes, new-onset diabetes, or even diabetic ketoacidosis. Clozapine and olanzapine have the highest propensity to cause this, and ziprasidone and aripiprazole have the least propensity. The cumulative incidence of diabetes in patients on clozapine may be up to 35% [66]. Hypertriglyceridemia may be observed with atypical antipsychotic use, and this is not clearly related to weight gain alone. Once again, clozapine and olanzapine are most likely to be involved. Hyperlipidemia has not been reported with aripiprazole, and ziprasidone has been reported to decrease cholesterol and triglycerides, independent of changes in weight [67].

Liver diseases

Chlorpromazine in particular has been associated with cholestatic jaundice, but hepatic toxicity has been reported rarely with many other antipsychotics, including haloperidol, clozapine, and risperidone [59]. In addition, asymptomatic elevation of hepatic enzymes of little clinical significance has been often associated with clozapine and less often with olanzapine. The risk of hepatotoxicity of antipsychotics is probably not increased in the presence of liver disease. Because all antipsychotics are metabolized in the liver to a large extent, they should be used more cautiously in patients with hepatic failure. Reduction in quetiapine dose has been recommended for the elderly and for patients with hepatic impairment [68]. Mild-to-moderate hepatic impairment does not significantly alter the pharmacokinetics of ziprasidone [69]. Similarly, the pharmacokinetics of risperidone were not significantly altered in cirrhosis patients [70]. Unfortunately, there is no liver function test, or combination of tests, that can quantify impairment of liver function in a manner analogous to serum creatinine or creatinine clearance for renal impairment [71]. Because antipsychotics are considerably protein bound, the reduced protein production in chronic liver disease results in an increased free fraction of the medication. Among the typi-

Table 4. Selected clinically important pharmacokinetic drug interactions with atypical antipsychotic agents

Drug	Increased levels	Decreased levels
Aripiprazole	Ketoconazole, quinidine, and paroxetine	Carbamazepine
Clozapine	Erythromycin, fluoroquinolones, paroxetine, fluvoxamine, ketoconazole, quinidine, risperidone, and ritonavir	Carbamazepine and phenytoin; smoking
Olanzapine	Fluvoxamine	Carbamazepine and phenytoin; smoking
Quetiapine	None	Carbamazepine, rifampin, and phenytoin
Risperidone	Fluoxetine and paroxetine	None
Ziprasidone	None	None

cal antipsychotics, haloperidol is usually the best choice in liver disease, because it has only one important metabolite. Serum haloperidol levels also can be observed; a range of 5 to 30 ng/mL is usually effective [72]. Ziprasidone is metabolized by two different competing pathways—the aldehyde oxidase and the P450 3A4—with the latter mediating only a third of its metabolism [73]. There are no genetic polymorphisms of aldehyde oxidase and no clinical reports of interactions between ziprasidone and inhibitors and inducers of aldehyde oxidase. These characteristics make pharmacokinetic interactions with ziprasidone unlikely, and this may be an advantage in patients with significant liver disease (Table 4).

Renal diseases

In patients with renal failure, because the clearance of risperidone is decreased, it should be started at lower doses than usual, and the dose increases should be gradual [70]. For the other atypical antipsychotics, dose adjustments in renal failure have not specifically been recommended. For example, the pharmacokinetics of ziprasidone are not significantly affected by mild-moderate renal impairment or by hemodialysis [71].

Neurologic diseases

After head trauma, antipsychotic medications can cause respiratory depression or seizures. Because low-potency typical antipsychotics tend to lower seizure threshold to a greater extent, they should be avoided in patients with head injury [74]. Antipsychotics, particularly those of low potency, are associated with a lowering of the seizure threshold. Clozapine has been associated with the greatest risk of seizures (4.4% in those receiving greater than 600 mg per day [75]), and should not be the first-line agent in patients with seizure disorders.

Other medical conditions

The greater anticholinergic activity of low-potency antipsychotics also makes them unsuitable for use in patients with prostate enlargement or narrow-angle glaucoma. Antipsychotics rarely have been associated with agranulocytosis, and this risk is elevated in treatment with clozapine. Thus, if neutropenia appears in a patient on antipsychotics, consideration should be given to this etiologic relationship, unless an obvious alternative cause is present.

Other medications

Benzodiazepines are used to control agitation, especially in delirious patients. They are first-line agents in the treatment of psychosis that is a part of alcohol or sedative-hypnotic withdrawal. They also are used in combination with antipsychotics. Although the data are not uniformly consistent, some studies have shown that benzodiazepines can be used as an adjunct to antipsychotics in the treatment of schizophrenia [76]. However, whether benzodiazepines have a specific antipsychotic effect is not clear. Lorazepam and oxazepam are preferred because of their lack of active metabolites and short half-lives. Benzodiazepines should be avoided in brain-injured patients or patients with compromised respiratory status because of their tendency to produce sedation, respiratory depression, and disinhibition. If a benzodiazepine is used for control of severe agitation, lorazepam intramuscularly (1 mg, repeated after one hour if needed) is preferred because of its reliable absorption. Lorazepam also can be given intravenously (0.5 to 1 mg administered over 2 minutes). Great caution is needed in using a benzodiazepine with clozapine because of the possibility of respiratory collapse [77].

Anticonvulsants have a role in the treatment of psychotic symptoms attributed to seizure disorders or bipolar disorder. They also have been used to augment response to antipsychotics in the treatment of psychosis [75]. The likelihood of drug interactions and toxicity with anticonvulsants is higher in patients with medical illnesses. Therefore, serum monitoring of drug levels to guide dosing is particularly important in such patients.

Conclusions

Psychosis in a medically ill patient poses a diagnostic and therapeutic challenge. A high index of suspicion and a careful assessment usually lead to an accurate diagnosis. Certain clinical precautions can minimize psychosis that is a part of medical illness, including being aware of drug-drug interactions, using low doses of medications that have neuropsychiatric effects, and avoiding multiple medications, especially psychotropic medications. If an antipsychotic agent is indicated, the selection should be guided by the adverse effect profile of the agent, as well as the underlying medical condition. Atypical antipsychotics are gaining popularity as first-line agents

because of their favorable side effect profile; however, haloperidol is an effective alternative and has the most data supporting its use in this population. Benzodiazepines and anticonvulsants have a role in specific conditions. Early recognition and treatment of psychotic symptoms can significantly reduce morbidity in medically ill patients.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Jeste DV, Gladsjo JA, Lindamer LA, Lacro JP: **Medical comorbidity in schizophrenia.** *Schizophr Bull* 1996, **22:**413–430.
2. Gupta S, Masand PS, Kaplan D, Bhandary A: **The relationship between schizophrenia and IBS.** *Schizophr Res* 1997, **23:**265–268.
3. Goldman LS: **Medical illness in patients with schizophrenia.** *J Clin Psychiatry* 1999, **60:**10–15.
4. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* edn 4 (Text Revision). Washington, DC: American Psychiatric Association; 2000.
5. Rabins PV, Mase NL, Lucas MJ: **The impact of dementia on the family.** *JAMA* 1982, **248:**333–335.
6. Cummings JL: **Organic delusions: phenomenology, anatomical correlations, and review.** *Br J Psychiatry* 1985, **146:**184–197.
7. Diaz-Olavarrieta C, Cummings JL, Velazquez J, Garcia de la Cadena C: **Neuropsychiatric manifestations of multiple sclerosis.** *J Neuropsychiatry Clin Neurosci* 1999, **11:**51–57.
8. Hillbom E: **After-effects of brain injuries.** *Acta Psychiat Neurol Scand* 1960, **142(suppl):**1–135.
9. Levine DN, Finklestein S: **Delayed psychosis after right temporoparietal stroke or trauma: relation to epilepsy.** *Neurology* 1982, **32:**267–273.
10. Inzelberg R, Kipervasser S, Korczyn AD: **Auditory hallucinations in Parkinson's disease.** *J Neurol Neurosurg Psychiatry* 1998, **64:**533–535.
11. Blumer D, Wakhlu S, Montouris G, Wyler AR: **Treatment of the interictal psychoses.** *J Clin Psychiatry* 2000, **61:**110–122.
12. Sachdev P: **Schizophrenia-like psychosis and epilepsy: the status of the association.** *Am J Psychiatry* 1998, **155:**325–336.
13. Slater E, Beard AW, Glithero E: **The schizophrenia-like psychoses of epilepsy.** *Br J Psychiatry* 1963, **109:**95–150.
14. Hill KP, Patkar AA, Weinstein SP: **Folie a famille associated with amphetamine use.** *Jefferson J Psychiatry* 2001, **16:**26–31.
15. Serper MR, Alert M, Richardson N, *et al.*: **Clinical effects of recent cocaine use on patients with acute schizophrenia.** *Am J Psychiatry* 1995, **152:**1464–1469.
16. Adachi N, Onuma T, Nishiwaki S, *et al.*: **Inter-ictal and post-ictal psychoses in frontal lobe epilepsy: a retrospective comparison with psychoses in temporal lobe epilepsy.** *Seizure* 2000, **9:**328–335.
17. Allebeck P, Wistedt B: **Mortality in schizophrenia: a ten-year follow-up based on the Stockholm County inpatient register.** *Arch Gen Psychiatry* 1986, **43:**650–653.
18. Brown S: **Excess mortality in schizophrenia: a meta analysis.** *Br J Psychiatry* 1997, **171:**502–508.
19. Dixon L: **Health, medical comorbidities and diabetes in schizophrenia.** *Drug Benefit Trends* 2003, **4(suppl):**6–11.
20. Patkar AA, Gopalakrishnan R, Lundy A, *et al.*: **Relationship between tobacco smoking and positive and negative symptoms in schizophrenia.** *J Nerv Ment Dis* 2002, **190:**604–610.
21. Dixon L, Weiden P, Delahanty J, *et al.*: **Prevalence and correlates of diabetes in national schizophrenia samples.** *Schizophr Bull* 2000, **26:**903–912.
22. •• Green AI, Canuso CM, Brenner MJ, Wojcik JD: **Detection and management of comorbidity in patients with schizophrenia.** *Psychiatr Clin North Am* 2003, **26:**115–139.

This is a broad-based review to assess and treat medical illnesses in patients with schizophrenia.

23. Redelmeier DA, Tan SH, Booth GL: **The treatment of unrelated disorders in patients with chronic medical diseases.** *N Engl J Med* 1998, **338:**1516–1520.
24. Folsom DP, McCahill M, Bartels SJ, *et al.*: **Medical comorbidity and receipt of medical care by older homeless people with schizophrenia or depression.** *Psychiatr Serv* 2002, **53:**1456–1460.
25. Cramer JA, Rosenheck R: **Compliance with medication regimens for mental and physical disorders.** *Psychiatr Serv* 1998, **49:**196–201.
26. Reeves RR, Torres RA: **Exacerbation of psychosis by misinterpretation of physical symptoms.** *South Med J* 2003, **96:**702–704.
27. Alexander RC, Patkar AA, McCarthy HH, Horner R: **Schizencephaly and psychosis.** *J Neurol Neurosurg Psychiatry* 1997, **24:**345–347.
28. Duwe BV, Turetsky BI: **Misdiagnosis of schizophrenia in a patient with psychotic symptoms.** *Neuropsychiatry Neuropsychol Behav Neurol* 2002, **15:**252–260.
29. Dworken RH: **Pain insensitivity in schizophrenia: a neglected phenomenon and some implications.** *Schizophr Bull* 1994, **20:**235–248.
30. Adler LE, Griffith JM: **Concurrent medical illness in the schizophrenic patient: epidemiology, diagnosis, and management.** *Schizophr Res* 1991, **4:**91–107.
31. • Schwartz TL, Masand PS: **The role of atypical antipsychotics in the treatment of delirium.** *Psychosomatics* 2002, **43:**171–174.

This paper discusses data supporting the use of atypical antipsychotics in the management of patients with delerium.

32. Sipahimalani A, Sime R, Masand PS: **Treatment of delirium with risperidone.** *Int J Geri Psychopharmacol* 1997, **1:**24–26.
33. American Psychiatric Association: **Practice guidelines for the treatment of patients with delirium.** *Am J Psychiatry* 1999, **156(suppl):**1–20.
34. Breitbart W, Tremblay A, Gibson C: **An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients.** *Psychosomatics* 2002, **43:**175–182.
35. Rosen H: **Double-blind comparison of haloperidol and thioridazine in geriatric patients.** *J Clin Psychiatry* 1979, **40:**17–20.
36. Smith G, Taylor C, Linkous P: **Haloperidol versus thioridazine for the treatment of psychogeriatric patients: a double-blind clinical trial.** *Psychosomatics* 1974, **15:**134–138.
37. Thomas H, Schwartz E, Petrilli R: **Droperidol versus haloperidol for chemical restraint of agitated and combative patients.** *Ann Emerg Med* 1992, **21:**407–413.
38. Sipahimalani A, Masand PS: **Olanzapine in the treatment of delirium.** *Psychosomatics* 1998, **39:**422–430.
39. Skrobik YK, Bergeron N, Dumont M, Gottfried SB: **Olanzapine vs haloperidol: treating delirium in a critical care setting.** http://www.springerlink.com. Accessed January 26, 2004.
40. Horikawa N, Yamazaki T, Miyamoto K, *et al.*: **Treatment for delirium with risperidone: results of a prospective open trial with 10 patients.** *Gen Hosp Psychiatry* 2003, **25:**289–292.
41. Sasaki Y, Matsuyama T, Inoue S, *et al.*: **A prospective, open-label, flexible-dose study of quetiapine in the treatment of delirium.** *J Clin Psychiatry* 2003, **64:**1316–1321.
42. Leso L, Schwartz TL: **Ziprasidone treatment of delirium.** *Psychosomatics* 2002, **43:**61–62.
43. Katz IR, Jeste DV, Mintzer JE, *et al.*: **Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group.** *J Clin Psychiatry* 1999, **60:**107–115.

44. Street JS, Clark WS, Gannon KS, *et al.*: **Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group.** *Arch Gen Psychiatry* 2000, **57:**968–976.
45. Fernandez HH, Trieschmann ME, Burke MA, Friedman JH: **Quetiapine for psychosis in Parkinson's disease versus dementia with Lewy bodies.** *J Clin Psychiatry* 2002, **63:**513–515.
46. Terao T, Shimomura T, Izumi Y, Nakamura J: **Two cases of quetiapine augmentation for donepezil-refractory visual hallucinations in dementia with Lewy bodies.** *J Clin Psychiatry* 2003, **64:**1520–1521.
47. Takahashi H, Yoshida K, Sugita T, *et al.*: **Quetiapine treatment of psychotic symptoms and aggressive behavior in patients with dementia with Lewy bodies: a case series.** *Prog Neuropsychopharmacol Biol Psychiatry* 2003, **27:**549–553.
48. Masand PS: **Atypical antipsychotics for elderly patients with neurodegenerative disorders and medical conditions.** *Psychiatr Ann* 2000, **30:**202–208.
49. Masand PS: **Side effects of antipsychotics in the elderly.** *J Clin Psychiatry* 2000, **61:**43–49.
50. Caley CF, Cooper CK: **Ziprasidone: the fifth atypical antipsychotic.** *Ann Pharmacother* 2002, **36:**839–851.
51. Duggan L, Fenton M, Dardennes RM, *et al.*: **Olanzapine for schizophrenia.** *Cochrane Database Syst Rev* 2003, **1:**CD001359.
52. Marder SR, McQuade RD, Stock E, *et al.*: **Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials.** *Schizophr Res* 2003, **61:**123–136.
53. Nasrallah HA, Tandon R: **Efficacy, safety, and tolerability of quetiapine in patients with schizophrenia.** *J Clin Psychiatry* 2002, **63(suppl):**12–20.
54. Masand PS: **Atypical agents in nonschizophrenic disorders.** *J Clin Psychiatry* 1998, **59:**322–328.
55. Reeves RR, Torres RA: **Orally disintegrating olanzapine for the treatment of psychotic and behavioral disturbances associated with dementia.** *South Med J* 2003, **96:**699–701.
56. The Parkinson Study Group: **Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease.** *N Engl J Med* 1999, **340:**757–763.
57. Fernandez HH, Trieschmann ME, Burke MA, *et al.*: **Long-term outcome of quetiapine use for psychosis among Parkinsonian patients.** *Mov Disord* 2003, **18:**510–514.
58. Targum SD, Abbott JL: **Efficacy of quetiapine in Parkinson's patients with psychosis.** *J Clin Psychopharmacol* 2000, **20:**54–60.
59. Robinson MJ, Levenson JL: **The use of psychotropics in the medically ill.** *Curr Psychiatry Rep* 2000, **2:**247–255.
60. Varma S, Achan K: **Dysrhythmia associated with clozapine.** *Aust N Z J Psychiatry* 1999, **33:**118–119.
61. Allison DB, Mentore JL, Heo M, *et al.*: **Antipsychotic-induced weight gain: a comprehensive research synthesis.** *Am J Psychiatry* 1999, **156:**1686–1696.
62. Masand PS: **Weight gain with psychotropics: size does matter.** *J Clin Psychiatry* 1999, **60:**3–4.
63. Masand PS: **Weight gain associated with psychotropics.** *Expert Opin Pharmacother* 2000, **1:**377–389.
64.•• Wirshing DA, Pierre JM, Erhart SM, Boyd JA: **Understanding the new and evolving profile of adverse drug effects in schizophrenia.** *Psychiatr Clin North Am* 2003, **26:**165–190.

This is a recent, comprehensive, clinically based review of side effect profiles of antipsychotic agents.

65. Ryan MC, Collins P, Thakore JH: **Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia.** *Am J Psychiatry* 2003, **160:**284–289.
66. Henderson DC, Cagliero E, Gray CO, *et al.*: **Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study.** *Am J Psychiatry* 2000, **157:**975–981.
67. Kingsbury SJ, Fayek M, Trufasiu D, *et al.*: **The apparent effects of ziprasidone on plasma lipids and glucose.** *J Clin Psychiatry* 2001, **62:**347–349.
68. Nemeroff CB, Kinkead B, Goldstein J: **Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing.** *J Clin Psychiatry* 2002, **63(suppl):**5–11.
69. Everson G, Lasseter KC, Anderson KE, *et al.*: **The pharmacokinetics of ziprasidone in subjects with normal and impaired hepatic function.** *Br J Clin Pharmacol* 2000, **49(suppl):**21S–26S.
70. Snoek E, Van Peer A, Sack M: **Influence of age, renal and liver impairment on the pharmacokinetics of risperidone in man.** *Psychopharmacology (Berlin)* 1995, **122:**223–229.
71. Aweeka F, Jayeskara D, Horton M, *et al.*: **The pharmacokinetics of ziprasidone in subjects with normal and impaired renal function.** *Br J Clin Pharmacol* 2000, **49(suppl):**27S–33S.
72. Rubey RN, Lydiard RB: **Psychopharmacology in the medically ill.** *Adv Psychosom Med* 1994, **21:**1–27.
73. Beedham C, Miceli JJ, Obach RS: **Ziprasidone metabolism, aldehyde oxidase, and clinical implications.** *J Clin Psychopharmacol* 2003, **23:**229–232.
74. Stoudemire A, Moran MG, Fogel BS: **Psychotropic drug use in the medically ill: part II.** *Psychosomatics* 1991, **32:**34–46.
75. Devinsky O, Honiegfeld G, Patin J: **Clozapine-related seizures.** *Neurology* 1991, **41:**369–371.
76. Conley RR, Kelly DL: **Management of treatment resistance in schizophrenia.** *Biol Psychiatry* 2001, **50:**898–911.
77. Tupala E, Niskanen L, Tiihonen J: **Transient syncope and ECG changes associated with the concurrent administration of clozapine and diazepam.** *J Clin Psychiatry* 1999, **60:**619–620.