

Medical Illness in Patients With Schizophrenia

Larry S. Goldman, M.D.

Research into the relationship between physical illness and schizophrenia has revealed that patients with schizophrenia may be at decreased risk for certain disorders, such as rheumatoid arthritis and allergies, but at increased risk for others, including substance abuse and polydipsia. Although such knowledge may ultimately help determine the underlying causes of schizophrenia, the principal concern of practicing clinicians should be to diagnose and treat medical comorbidity in individual patients. Nearly 50% of patients with schizophrenia have a comorbid medical condition, but many of these illnesses are misdiagnosed or undiagnosed. A fragmented health care system, lack of access to care, patient inability to clearly appreciate or describe a medical problem, and patient reluctance to discuss such problems all contribute to the lack of attention to medical problems in patients with schizophrenia. Psychiatrists and primary care practitioners who treat patients with schizophrenia should make an effort to uncover medical illnesses by using a structured interview or routine physical examination whenever a patient is seen for care. (*J Clin Psychiatry* 1999;60[suppl 21]:10-15)

There is no question that managing the patient with schizophrenia can be a difficult undertaking. Some patients respond well to antipsychotic agents and others do not. Patients may discontinue taking their medication for various reasons but often do so because of intolerable adverse effects, and the potential for relapse is an ongoing concern. Although treating schizophrenia alone is challenge enough, for patients with schizophrenia and concomitant medical disorders, the picture becomes complicated indeed.

Medical illness is more common among patients with a psychiatric disorder than it is in the general population.¹ In one review of more than 4000 psychiatric patients,² nearly 50% had a significant medical illness. This percentage holds true whether patients are or are not hospitalized. Bunce et al.³ reported that 50% of 2395 psychiatric outpatients and 52% of 1448 psychiatric inpatients had a major medical disorder. Even though the percentage of mentally ill patients with concomitant medical illness is high, many patients go undiagnosed, for reasons I will discuss later. In one early study of 100 psychiatric outpatients,⁴ physical illness in 67% of patients was underdiagnosed and in 50% was not diagnosed at all. In some cases, the medical illness was the only cause of the patient's psychotic symptoms.

As patients with schizophrenia age, the likelihood of suffering one or more medical illnesses increases, as it does for all elderly persons (80% of older people have at least one chronic medical problem).⁵

Although the relationship between physical illness and schizophrenia has been commented on for some time (more than 2000 years ago, Hippocrates noted that fever sometimes alleviated psychotic symptoms⁶), few prospective, well-controlled studies have been conducted, primarily because of several methodological problems. For example, patients with concurrent mental and medical illness can be difficult to identify and study. Patients with schizophrenia may not volunteer medical complaints or may have difficulty communicating their problem to the physician.⁷ The medical history they provide may be inaccurate (even family members may not be a reliable source of medical data on the patient). Institutionalization for extended periods of time might affect data related to physical illness, as can the effects of psychotropic drugs.⁸ Substance abuse is a considerable problem among patients with schizophrenia, and one that also complicates the study of medical illness in these patients. The exclusion of patients with comorbid conditions from clinical trials of psychotropic drugs facilitates data analysis⁸ but leaves unanswered the question of how the drug under study will affect patients with schizophrenia who also have a medical illness.

Determining how to overcome these methodologic hurdles is crucial. As Tsuang et al.⁹ note, evidence that two diseases occur together more frequently than would be expected by chance might lead to improvements in identifying patients at risk for either disease and to advances in early detection and treatment. Such research might also help pinpoint the underlying causes of these disorders.⁹

From the Department of Psychiatry, University of Chicago, Ill.

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Reprint requests to: Larry S. Goldman, M.D., University of Chicago, MC 3077, 5841 South Maryland Ave., Chicago, IL 60637-1470 (e-mail: larry@yoda.bsd.uchicago.edu).

EPIDEMIOLOGIC FINDINGS

Excess Mortality

Determining the rate and causes of death among patients with schizophrenia is somewhat more straightforward than examining the relationship between psychoses and medical disease. The most common means of measuring mortality in mentally ill persons is through record linkage studies, which use identifying characteristics (such as name and date of birth) to link psychiatric records with death certificates.¹⁰ Computerized databases have simplified this task and increased the validity of the results.¹⁰ Many of the best data cited here come from the Oxford Record Linkage Study, which links the maternity and hospital records and records of births and deaths of more than 2 million persons living in 4 different counties in England.⁹ The database, which was first compiled in 1963, is constantly updated.

Patients diagnosed with schizophrenia are 2 to 4 times more likely to die prematurely than persons in the general population^{8,11}; patients with schizophrenia die on average at least 10 years earlier than their age-matched counterparts.⁸ The risk of death is greatest early in the course of the illness and decreases over time to approach that of the general population late in the course of the disease.¹¹ Female patients with schizophrenia appear to be at greater risk for death than male patients.¹¹

Unnatural causes of death, including suicide and unintentional injuries, are the principal cause of excess mortality among patients with schizophrenia. A recent meta-analysis found that unnatural causes accounted for 40% of the total excess mortality in patients with schizophrenia, with suicide accounting for 28% and accidents for 12% of the excess mortality.¹⁰ Overall, nearly 10% of patients with schizophrenia die by their own hand,¹² making suicide the single largest cause of preventable death in schizophrenia.¹⁰ Excess mortality among patients with schizophrenia also results from an increased incidence of respiratory tract diseases, gastrointestinal diseases, genitourinary diseases, and infectious diseases. In addition, the rate of death from undetermined causes is nearly 14 times greater among patients with schizophrenia than it is in the general population.¹³

Medical Conditions With Decreased Prevalence

The possibility that schizophrenia protects against the development of certain diseases is intriguing but requires further research. The strongest data thus far indicate that rheumatoid arthritis occurs much less frequently in patients with schizophrenia than it does in the general population. The idea that rheumatoid arthritis and schizophrenia are mutually exclusive was first proposed in 1936 by Nissen and Spencer,¹⁴ who noted that not one of 2200 psychiatric inpatients, most of whom had schizophrenia, had rheumatoid arthritis. Since then, several researchers have

remarked on the rarity of rheumatoid arthritis in schizophrenia.⁶ In their review of 14 epidemiologic studies conducted between 1934 and 1985, Eaton et al.¹⁵ found ample evidence of a negative association between the 2 disorders. The median prevalence of rheumatoid arthritis among patients with schizophrenia in these studies was 0.47%, while that in the general population is between 1% and 3%.¹⁶ However, a more recent investigation set the age-adjusted prevalence of rheumatoid arthritis in schizophrenia at 0.96%, which is not substantially different from that in the general population.¹⁶ The authors speculate that prolonged institutionalization might have affected the rates of rheumatoid arthritis in schizophrenia reported in earlier studies (patients hospitalized for lengthy periods may have benefited from better nutrition and reduced exposure to physical trauma and certain pathogens).¹⁶

Research on the relationship between schizophrenia and various types of cancer has been inconsistent. Early studies suggested that patients with schizophrenia were less likely to die of cancer, leading researchers to conclude that this mental illness might protect against malignancy.⁹ However, since patients with schizophrenia are at increased risk of dying from other causes, including unnatural causes such as suicide and trauma, a lower mortality rate from cancer does not necessarily mean that the prevalence of cancer is lower as well¹⁷; it might just mean that patients did not live long enough to develop and die of cancer.

Later studies with more rigorous methods indicate that the overall cancer rate in patients with schizophrenia is similar to that seen in the general population,^{8,9} with some exceptions. Gastrointestinal cancer, pancreatic cancer, and breast cancer are more common among patients with schizophrenia,⁸ for reasons not yet explained. The incidence of lung cancer, however, is less than expected in patients with schizophrenia,^{8,9} a surprising finding given the prevalence of smoking in this population and, again, one for which no satisfactory explanation exists.

Cerebrovascular disease, allergies, osteoarthritis, gallbladder disease, appendicitis, menstrual disorders, and varicose veins have all been reported to occur less often in patients with schizophrenia compared with the general population. Whether these findings will hold up in future studies and how they might apply to clinical practice remains to be determined.

Medical Conditions With Increased Prevalence

Schizophrenia has been linked to an increased prevalence of a range of medical problems (Table 1), some of which are complications of the psychotic disorder itself (e.g., polydipsia and catatonia), some that may result from patients' attempts at self-medication (e.g., substance abuse), and some that are related to patients' socioeconomic status (e.g., poor nutrition and homelessness).

Table 1. Conditions With Increased Prevalence in Schizophrenia

Catatonia
Homelessness
Irritable bowel syndrome
Osteoporosis
Polydipsia and hyponatremia
Poor nutrition
Poor pregnancy outcome
Poverty
Substance use disorders
Alcoholism
Intravenous drug use
Tobacco and marijuana smoking
Sudden death with unclear cause
Type II diabetes mellitus

Substance abuse, including use of tobacco, marijuana, intravenous drugs, and alcohol, is a common problem; between 20% and 70% of patients with schizophrenia are diagnosed as substance abusers at some time during their lives.¹¹ Cigarette smoking is especially common in patients with schizophrenia. Between 50% and 90% of these patients are nicotine dependent,¹⁸ a percentage far greater than that in the general population (in 1995, approximately 30% to 35% of adults in the United States smoked cigarettes¹¹). There is no single reason why cigarette smoking is so popular among patients with schizophrenia. Nicotine, of course, is an addictive substance whether or not a person has schizophrenia. However, patients with schizophrenia may find smoking particularly gratifying because of the effects of nicotine on dopamine activity.¹⁸ Cigarette smoking might also make patients feel better, by improving concentration and reducing boredom, anxiety, negative symptoms, and extrapyramidal symptoms.^{18,19} Smoking is also a more acceptable and common activity among members of lower socioeconomic classes, a category in which many patients with schizophrenia fall.¹⁸

Although less common than cigarette smoking, alcohol and drug abuse are still considerable problems in patients with schizophrenia. Close to 35% of these patients abuse alcohol at some point (the lifetime prevalence of alcoholism in the general population is 14%),¹¹ even though alcohol use can worsen psychotic and extrapyramidal symptoms.⁸ Between 15% and 60% of patients with schizophrenia abuse psychoactive drugs,²⁰ with use of marijuana, caffeine, hallucinogens, and possibly cocaine and stimulants all higher among patients with schizophrenia compared with the general population.

Of course, any type of substance abuse can complicate treatment. Cigarette smoking, for example, increases the metabolism of antipsychotic drugs, which might temporarily relieve adverse effects but also necessitates higher drug doses to achieve the desired clinical effect.¹¹ Patients who abuse drugs may be hospitalized more often, be less compliant with treatment regimens, and are at greater risk for suicide than non-drug-abusing schizophrenic pa-

tients.²⁰ Violent behavior is also more common among substance-abusing patients with schizophrenia.⁸

While substance abuse begins by patient choice, other comorbid conditions, such as polydipsia and catatonia, are complications of schizophrenia itself. Polydipsia (which could be considered a type of addiction) is most common among young male inpatients and can lead to hyponatremia, seizures, and possibly death.⁸ Although the incidence of catatonia has decreased in recent years, the seriousness of the condition has not. Acute renal failure with rhabdomyolysis and pulmonary embolism may develop in patients with a lethal form of catatonia.

Female patients with schizophrenia who become pregnant tend to have poorer pregnancy outcomes and more difficulty with labor and delivery than pregnant patients in the general population. Although antipsychotic medications have not been shown to possess teratogenic or mutagenic effects, drug treatment can complicate the pregnancy and be a contraindication to breastfeeding.¹¹

Patients with schizophrenia are also more likely to have abnormal variations in cardiac rate, a possible explanation for the excess number of sudden deaths from indeterminate causes in this population.²¹

Patients with schizophrenia are predisposed to developing type II diabetes mellitus, osteoporosis, and irritable bowel syndrome. Many studies have reported that diabetes, impaired glucose tolerance, and insulin resistance are more common among patients with schizophrenia and other mental illnesses than among the general population.^{8,22} However, the possibility remains that diabetes in schizophrenia may result from the use of neuroleptics, which can produce glucose intolerance, rather than from the psychotic disorder itself.⁸ Osteoporosis can be a problem in both female and male patients with schizophrenia. Possible risk factors include smoking, polydipsia, and long-term use of neuroleptics.²³ An increased prevalence of irritable bowel syndrome among patients with schizophrenia is a fairly recent observation. In one study,²⁴ the prevalence of irritable bowel syndrome was 19.5% in patients with schizophrenia compared with 2.5% in an age-matched control group. The authors noted that the patients with schizophrenia rarely reported gastrointestinal symptoms, suggesting that this condition may go undiagnosed without persistent questioning and follow-up on the part of the clinician.

Medical Problems Associated With Obesity

Patients with schizophrenia, of course, are also at risk for medical problems associated with obesity. Like any person who is overweight or obese, patients with schizophrenia who gain a considerable amount of weight are at increased risk for hypertension, type II diabetes mellitus, cardiovascular disease, stroke, gallbladder disease, hyperlipidemia, sleep apnea, osteoarthritis, some types of cancer, and psychological distress.²⁵ Many antipsychotics are

of course associated with weight gain that may at times be substantial.

Medical Curiosities

Examining the epidemiologic literature related to physical illness and schizophrenia reveals some medically interesting features of this psychotic disorder. These include relative protection from inflammatory disorders; high pain threshold; remissions during acute medical illness, especially fevers; and an association with perinatal viral infections.

The low prevalence of rheumatoid arthritis and allergies, both of which have inflammatory components, supports the idea that patients with schizophrenia may have some inherent protection against inflammatory disorders. A high pain threshold among patients with schizophrenia has been well documented^{3,26} and is one reason why certain medical conditions may be overlooked in these patients. As one example, 79% of inpatients with schizophrenia with an acute perforated ulcer and 63% of those with acute appendicitis reported pain as a presenting symptom, whereas nearly 95% of patients without schizophrenia report pain with these conditions.²⁵ Lack of pain with myocardial infarction is also common among patients with schizophrenia; only 18% of patients report pain during a heart attack compared with almost 90% of those in the general population.²⁶ Patients with schizophrenia also appear less sensitive to pain from fractures, serious burns, cancer, arthritis, and other painful medical conditions.²⁶ Although remission of psychotic symptoms during medical illness has long been observed,^{6,27} there is no satisfactory explanation for this phenomenon.

Horrobin et al.²⁸ have proposed that these medical curiosities in schizophrenia may be related to abnormalities in lipid metabolism, which can affect neurotransmitter activity. They note that several well-documented facts about schizophrenia—protection against inflammatory disorders, high pain tolerance, symptom remission during fevers, association with perinatal infection, greater prevalence in men than women, worldwide differences in severity of schizophrenia but not its incidence, and stress as a precipitating factor—are not well explained by neurotransmitter hypotheses, but can be explained by a model emphasizing lipid abnormalities.

Human Immunodeficiency Virus and Schizophrenia

Transmission of human immunodeficiency virus (HIV) provides a clear example of how behavior associated with schizophrenia places patients at greater risk for certain medical illnesses. Despite their illness, patients with schizophrenia are not necessarily sexually inactive. However, because of schizophrenia-induced thought disorder, they may be less aware of behaviors that increase their risk of acquiring HIV.²⁹ For example, patients with schizophrenia are more likely to have multiple sex partners, live in

Table 2. Barriers to Health Care for Patients With Schizophrenia

System-Related Barriers
Lack of insurance coverage
Lack of access to health care
Stigmatization by health care providers
Lack of integration of medical and mental health systems
Complexity of management
Patient-Related Barriers
Patient denial
Patient psychosis
Poor communication skills
Increased pain tolerance
Poverty
Nonadherence

situations (such as group homes or on the street) where sexual exploitation is common, engage in unprotected sex, and have male-to-male sexual encounters, even though the patients may not consider themselves homosexual.³⁰ Intravenous drug abuse also places patients at greater risk for HIV, as does their relative naivete and lack of social skills.

The coexistence of HIV infection in a patient with schizophrenia complicates diagnosis and treatment. New-onset psychotic symptoms challenge the clinician to determine whether the symptoms result from the psychotic disorder or from neuropsychiatric problems, opportunistic infections, or tumors related to the HIV infection. Drugs used to treat HIV, including acyclovir, zidovudine, and ganciclovir, can also produce psychotic symptoms.³¹ The complex “drug cocktails” currently used to treat HIV infection further complicate treatment of the patient with schizophrenia, who must remember to take not only the antipsychotic medication but several antiretroviral drugs as well. Nonadherence is a significant problem in these cases and one with life or death consequences.

TREATMENT ISSUES

Patients with schizophrenia are less likely than those in the general population to receive adequate health care for reasons that can be attributed to both the health care system and to the patients themselves (Table 2). In the current fragmented health care system in the United States, patients with comorbid mental and medical illnesses can easily fall through the cracks. There is also the question of who is best qualified to diagnose and treat the patient—the psychiatrist who is familiar with the patient’s mental illness or the primary care practitioner who treats medical problems daily. Brown¹⁰ argues that until this is decided, all physicians who care for patients with schizophrenia have an obligation to be alert for signs and symptoms of physical disease. To do so, primary care providers must overcome their reluctance to treat patients with severe mental illness, a stigma that has persisted for many years, and psychiatrists must draw on the skills learned in medical school for diagnosing physical illness. However, even

Table 3. Selected Substrates, Inhibitors, and Inducers of Three Cytochrome P450 Isoenzymes

P450 Isoenzyme	Substrate	Inhibitor	Inducer	
2D6	Clozapine (slight)	Cimetidine Mibefradil ^a	None	
	Risperidone	Nelfinavir (slight) Quinidine Ritonavir (slight)		
1A2	Clozapine	Fluoroquinolones	Caffeine	
	Olanzapine	Mibefradil ^a Nelfinavir Ritonavir Tacrine	Cigarette smoke Omeprazole Rifampin	
	3A4	Clozapine	Azole antifungals	Carbamazepine
		Quetiapine	Cimetidine	Dexamethasone
		Cisapride	Nevirapine	
		Cyclosporine	Nonnucleoside reverse transcriptase inhibitors	
		Diltiazem	Phenobarbital	
	Macrolide antibiotics	Phenytoin		
	Mibefradil ^a	Primidone		
	Nifedipine	Rifabutin		
	Protease inhibitors	Rifampin Troglitazone		

^aWithdrawn from market.

if physicians watch for medical problems, many patients with schizophrenia may not even have an opportunity to be evaluated by a health care provider, because they either lack health insurance coverage or do not have access to health care.

Patients also contribute to the lack of care they receive. An inability to communicate clearly about a medical problem (or, in the case of certain painful conditions, unawareness of the problem) makes the physician's job harder. Bunce et al.³ reported that only 23% of 102 consecutive patients admitted to the acute medical care unit of a psychiatric hospital could adequately describe the nature or location of their pain or illness. Even when patients can communicate, they may not accurately describe the problem. Bunce et al.³ also found that just 22% of 83 diagnoses made were related to the patients' description of the symptoms. Further complicating the situation, especially when continuity of care may be lacking, is that patients with schizophrenia who have been diagnosed with a medical condition may not be able to describe it (or even remember it) at a later date. Pary and Barton⁷ noted that only 4 of 28 patients could name at least one of their physical problems 2 years after diagnosis. Patients with schizophrenia, who often deny they have a mental illness, may deny a medical illness as well.

Given the problems inherent in diagnosing a patient who may be delusional, uncooperative, or in denial, what is the best approach? Jeste et al.⁸ found that a structured interview, a tool used successfully to uncover psychiatric symptoms, is also valuable for diagnosing medical problems in patients with schizophrenia. They reported that the number of expected medical diagnoses in older patients

with schizophrenia approached that of a nonschizophrenic elderly population when a structured interview was used. Clinicians should not wait for patients to volunteer complaints, since many are reluctant to do so; they must initiate and be persistent when they question patients about possible medical problems. Once physical symptoms are revealed, further efforts are required to make the differential diagnosis. Clinicians must determine whether the symptoms are real or delusional, are organic or psychogenic, result from schizophrenia itself or are a complication of schizophrenia, are caused by psychotropic drugs, or are related to a comorbid condition.

When a medical diagnosis is made in a patient with schizophrenia, obtaining informed consent is a further complication. Patients must be able to understand the treatment and its alternatives, the risks and benefits, and how to use such information rationally.¹¹ Clinicians may need to invest considerable time with patients to ensure they truly understand the treatment. In addition, patients should be given time to review the information and consult with family or friends.¹¹ Practitioners who avoid this process may find that patients are less likely to comply with treatment.

DRUG INTERACTIONS

The possibility of a drug interaction must be considered whenever a medical drug is added to an antipsychotic regimen. One means of determining potential interactions is by identifying the substrates and inhibitors of the cytochrome P450 isoenzymes, a group of more than 30 enzymes involved in the metabolism of several different types of drugs.³² Use of a substrate (a drug metabolized by the P450 system) and an inhibitor (a drug that inhibits P450 isoenzyme activity) in combination can increase plasma levels of the substrate drug, often in as little as a few days.³³ Inducers (drugs that increase P450 isoenzyme activity by increasing enzymatic binding sites, a process that can take several weeks) can also increase plasma levels of the substrate drug.³³ Once the inducer is withdrawn, plasma levels of the substrate may increase, sometimes with toxic effects, because the isoenzyme now has an increased number of sites with which to bind.

The newer antipsychotic quetiapine, for example, is a substrate for the cytochrome P450 3A4 isoenzyme, whose action is inhibited by drugs such as cimetidine and cisapride (Table 3). Clozapine and olanzapine are substrates for the cytochrome P450 1A2 isoenzyme, which is inhibited by the fluoroquinolones, ritonavir, and tacrine, among other drugs. Inducers of the P450 1A2 isoenzyme include caffeine, cigarette smoke, and certain drugs. In addition, clozapine is a substrate for the cytochrome P450 3A4 isoenzyme, which metabolizes a broad range of compounds,³² increasing the possibility of drug interactions between clozapine and several medical drugs.

CONCLUSION

As researchers continue to explore the relationship between schizophrenia and physical illness, clinicians face the daily challenge of diagnosing and treating patients with schizophrenia and comorbid medical disorders. As evidenced by the high percentage of patients with medical illness that is misdiagnosed or undiagnosed, the problem of medical comorbidity in schizophrenia deserves greater attention by both psychiatrists and other physicians. Clinicians should be more aggressive in uncovering medical illnesses in psychiatric patients, who are often reluctant or unable to discuss physical problems. A brief physical assessment whenever a patient is seen for psychiatric care can increase the likelihood of identifying a coexisting medical condition.

Drug names: acyclovir (Zovirax and others), carbamazepine (Tegretol and others), cimetidine (Tagamet and others), cisapride (Propulsid), clozapine (Clozaril and others), cyclosporine (Sandimmune and others), dexamethasone (Decadron and others), diltiazem (Cardizem and others), ganciclovir (Cytovene), nelfinavir (Viracept), nevirapine (Viramune), nifedipine (Adalat and others), olanzapine (Zyprexa), omeprazole (Prilosec), phenobarbital (Donnatal and others), phenytoin (Dilantin and others), primidone (Mysoline and others), quetiapine (Seroquel), quinidine (Quinidex and others), rifampin (Rifadin and others), rifabutin (Mycobutin), risperidone (Risperdal), ritonavir (Norvir), tacrine (Cognex), troglitazone (Rezulin), zidovudine (Retrovir and others).

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