Medical Comorbidity in Schizophrenia

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Abstract

The extent and consequences of medical comorbidity in patients with schizophrenia are generally underrecognized. Patients with comorbid conditions are usually excluded from research studies, although they probably represent the majority of individuals with schizophrenia. Elderly patients are especially likely to have comorbid disorders. In this article, we review selected literature on medical comorbidity in schizophrenia, including physical illnesses, substance use, cognitive impairment, sensory deficits, and iatrogenic comorbidity. Data from the University of California, San Diego Clinical Research Center on late-life psychosis are also presented. Older schizophrenia patients report fewer comorbid physical illnesses than healthy comparison subjects, but their illnesses tend to be more severe. These results suggest that schizophrenia patients may receive less than adequate health care. Substance abuse is more common in patients with schizophrenia than in the general population and may exacerbate psychiatric symptoms in these patients. Although generalized cognitive impairment is associated with schizophrenia, the main contributors to dementia in older patients are more likely to be comorbid neurological and other physical disorders, substance abuse, and medication side effects. Iatrogenic comorbidity results primarily from the use of neuroleptic (e.g., tardive dyskinesia) and anticholinergic (e.g., confusion) medications. Clinical and research recommendations are made for management of comorbidity in schizophrenia.

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Mens sana in corpore sano.
(Sound mind in a sound body.)
[Juvenal, 2nd Century A.D.; cited in *New Encyclopedia Britannica*, 1993, p. 667]

The comorbidity of physical and mental illnesses has implications for the treatment, health care utilization and cost, quality of life, and understanding of the pathophysiology of those disorders. A number of studies have examined the relationship between depression and physical illnesses (see Schulberg et al. 1987). Medical comorbidity in schizophrenia, however, has been studied to a much smaller extent.

Anosognosia for Medical Comorbidity in Schizophrenia?

Anosognosia is broadly defined as ignorance, real or feigned, of the presence of disease (specifically of paralysis) (Stedman 1990). We believe that, in a larger sense, there is an insufficient awareness of (or "anosognosia" for) medical comorbidity in schizophrenia on the part of patients, caregivers, health care providers, and researchers. Medical comorbidity has often been underrecognized and underdiagnosed in psychiatric patients, especially among those with schizophrenia (Koranyi 1979; Sheline 1990). Some data suggest that schizophrenia patients may have a greater pain tolerance than healthy subjects (Dworkin 1994). This deficit in schizophrenia patients' sensitivity to physical pain, combined

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with poor insight, may result in a lower rate of schizophrenia patients reporting physical problems to their physicians. Neuroleptics—the most commonly used treatment for psychosis—may reduce pain sensitivity (Patt et al. 1994) and have indeed been used to treat pain due to cancer and other chronic conditions. Thus, many patients with chronic schizophrenia may not seek, and therefore may not receive, diagnosis and treatment of physical illness. By focusing solely on the presenting psychiatric symptoms or by viewing physical complaints as "psychosomatic" symptoms, health-care professionals also may tend to overlook coexisting medical conditions in their mentally ill patients. Koranyi (1979) studied detection of physical illnesses by physicians referring patients to a psychiatric clinic and found that nonpsychiatric physicians missed one-third and psychiatrists missed one-half of their patients' comorbid medical conditions. In a study examining the prevalence of physical disease in psychiatric patients in the California public health system, Koran et al. (1989) reported that only 47 percent of the patients' physical illnesses were recognized by the mental health staff. Among the undiagnosed medical conditions, 16 percent of the physical illnesses were considered "causative" (i.e., entirely responsible for the presenting psychiatric symptoms), whereas 45 percent were believed to have exacerbated a preexisting psychiatric disorder.

The tendency for researchers to exclude from their studies subjects with comorbid medical conditions in order to eliminate the possible confounding effects of physical illnesses is another factor that may contribute to the lack of awareness of the impact of physical illnesses on schizophrenia patients. The exception has been research that has sought to uncover associations between schizophrenia and certain medical disorders, in order to identify risk factors or possible etiological mechanisms for either disorder. Even studies examining physical comorbidity in schizophrenia often have been narrowly focused on a single medical condition, or they have been limited by methodological problems that restrict the validity and generalizability of the conclusions (Harris 1988). One major limitation has been the diagnosis of schizophrenia itself. Across studies, different diagnostic systems have been employed to diagnose schizophrenia, making it difficult to compare results. Neuroleptic medication has adverse effects, such as glucose intolerance and tardive dyskinesia (TD) (discussed later); researchers must control the effects of neuroleptic medication when they are investigating medical illnesses in individuals with schizophrenia. In addition to the methodological problems, numerous other confounds, such as the effects of aging, institutionalization, and other health-related behaviors (e.g., smoking, lack of exercise), may have an impact on comorbidity findings in schizophrenia. Despite these limitations, it is important to investigate medical comorbidity in schizophrenia.

Relatively few studies have examined concurrent medical and psychiatric disorders in elderly mentally ill patients. The likelihood of someone having a medical problem increases with age (Kovar 1977). The projection that 130 million people in the United States will be over the age of 45 by 2050 suggests that there will be a large number of middle-aged and elderly persons with coexisting psychiatric diagnoses and medical problems. Sheline (1990) examined the prevalence of physical illnesses in geriatric psychiatric inpatients and found that 92 percent of the patients had at least one comorbid physical disorder. Cardiovascular disease was most prevalent (34%), followed by neurological (22%), genitourinary (17%), respiratory (17%), and gastrointestinal (17%) disorders.

Diagnosis of comorbid conditions in schizophrenia patients has important implications for their care and quality of life. Unrecognized physical diseases may exacerbate the symptoms of psychiatric illness by affecting brain function or by affecting other organ systems.

In this article, we will review the literature on the prevalence and risk factors or associations of five main categories of comorbidity in schizophrenia: (1) physical illnesses; (2) substance abuse and dependence, including alcohol use, smoking, illicit drug use, caffeine consumption, and polydipsia; (3) cognitive impairment; (4) sensory deficits; and (5) iatrogenic disorders. In each of these categories, we will briefly summarize selected literature and will refer the reader to more comprehensive reviews of these areas. We will also present data on comorbidity from our cohort of older schizophrenia patients. Finally, we will offer clinical and research recommendations.

Physical Comorbidity

Literature Review. A number of research reports have suggested that schizophrenia patients have a lower prevalence of some physical illnesses and a higher prevalence of other physical illnesses than people in the general population and, often, patients with other psychiatric conditions.

Rheumatoid arthritis. Several studies have reported a negative association between rheumatoid

arthritis and schizophrenia. Rheumatoid arthritis—a largely genetically transmitted autoimmune disorder that causes peripheral vascular and inflammatory changes in the joints—affects approximately 1 to 3 percent of the population (Sorensen 1990). More than 15 years before the introduction of neuroleptics, Nissen and Spencer (1936) reported that they did not observe a single case of rheumatoid arthritis in 2,200 psychiatric inpatients, with the predominant psychiatric disorder being schizophrenia. Recently, Eaton et al. (1992) reviewed 14 epidemiological studies conducted between 1934 and 1985 and concluded that, despite various methodological shortcomings, there was ample evidence supporting the negative association between these two disorders. In 12 of the 14 studies, there was a reduced prevalence of rheumatoid arthritis, and this lower risk appeared to be specific to schizophrenia. In one study, frequencies of rheumatoid arthritis in patients with schizophrenia, with "affective psychosis," and with "neurosis" were compared (Allebeck et al. 1985). In this study, there were no significant differences in the prevalence of rheumatoid arthritis between patients with "neurosis" and people in the general population, but only half of the expected number of cases of rheumatoid arthritis were found among the schizophrenia patients. The rate of rheumatoid arthritis also was somewhat low in "affective psychosis"; however, this sample was not well defined and the difference from the general population was not statistically significant. Researchers have proposed various metabolic, neurochemical and neuroendocrine (especially pertaining to prostaglandins and corticosteroids), genetic, immunologic, and viral theories to explain the negative relationship between rheumatoid arthritis and schizophrenia, but the reason for the decreased prevalence of rheumatoid arthritis in schizophrenia is as yet unknown (Vinogradov et al. 1991).

Cancer. The relationship between schizophrenia and cancer has been studied extensively, but the findings have been inconsistent. In 1909, the Board of Control of State Hospitals suggested that hospitalized psychiatric patients, especially those with schizophrenia, had some immunity from cancer (cited in Baldwin 1979). Many other early studies concurred with this finding; however, more recent and more methodologically rigorous research has found no significant difference in the overall prevalence of cancers in persons with schizophrenia as compared with persons in the general population. Tsuang et al. (1983) reviewed the literature on cancer in schizophrenia and concluded that previous reports of decreased cancer incidence were flawed by an inappropriate use of proportionate mortality-rate comparisons and other methodological problems. Results of some single-site studies (e.g., Craig and Lin 1981; Mortensen 1989) suggest that the incidence of some cancers, such as pancreatic cancer and breast cancer, may be increased, while the risk for other cancers, particularly lung cancer, may be decreased. A recent study that included Denmark, Japan, and the United States (Gulbinat et al. 1992) and employed a large study sample showed that the overall risk of cancer was no different for schizophrenia patients than for normal individuals. Significant geographical and gender differences in cancer incidence were noted and were attributed to probable environmental and hereditary differences. Findings that suggest a reduced prevalence of lung cancer in schizophrenia are surprising, given the high rates of smoking among schizophrenia patients (discussed later). Some researchers have hypothesized that neuroleptic medication may have an anticancer effect (Mortensen 1992), but this theory remains speculative.

Other illnesses. Other illnesses appear to be more common in patients with schizophrenia than in other psychiatric patients or in normal comparison subjects. Several researchers (Tsuang et al. 1983; Harris 1988) have reported that compared to the general population, schizophrenia patients may have an increased risk of cardiovascular disorders, including myocardial infarction and coronary artery disease. Baldwin (1980) has reported, however, that this higher prevalence is not specific to schizophrenia; increased risk of cardiovascular disorders was found in affective disorder patients as well. A few preliminary reports (Brambilla et al. 1976; McKee et al. 1986) have suggested a positive association between non-insulin-dependent diabetes mellitus and schizophrenia. Because neuroleptics are known to produce glucose intolerance (Mukherjee et al. 1989*a*), it is unclear whether the increased risk of non-insulin-dependent diabetes mellitus is related to schizophrenia or whether it is secondary to neuroleptic use.

Several authors (Baldwin 1979; Tsuang et al. 1983; Harris 1988) have comprehensively reviewed the association of schizophrenia and various other physical disorders, including infectious disease, Parkinson's disease, ulcers, epilepsy, coeliac disease, and asthma. It appears that in schizophrenia patients, some of these diseases may be more common while others may be less common than in persons without schizophrenia. However, the exact prevalence rates

as well as possible mechanisms for the apparent differences in prevalence between individuals with versus those without schizophrenia are unknown. It is possible that confounding factors such as health habits or psychotropic medications, rather than schizophrenia per se, may account for at least some of the reported variations in physical comorbidity. For the most part, it appears that patients with schizophrenia may not differ significantly from the population at large in terms of the total number of coexisting physical illnesses.

Mortality. Reports suggest that mortality in persons with schizophrenia is 2 to 4 times higher than that in the general population (Koranyi 1979; Tsuang et al. 1983; Allebeck 1989). The average lifespan of the schizophrenia patient is approximately 10 years shorter than that of a normal person. This discrepancy between individuals with schizophrenia and normal individuals is due in part to an elevated risk for suicide in schizophrenia patients. Approximately 10 percent of schizophrenia patients commit suicide (Caldwell and Gottesman 1990). Schizophrenia patients are 8 times more likely to die from traumatic injuries and 14 times more likely to have an undetermined cause of death registered in their autopsy reports than are normal individuals (Allebeck 1989). The latter finding suggests that among patients with schizophrenia, physical diseases are likely to be missed as the cause of death. Mortensen and Juel (1990) noted that at least some proportion of mortality in schizophrenia may be directly associated with side effects of neuroleptic medication.

University of California at San Diego (UCSD) Studies. We previously reported (Lacro and Jeste 1994) on the number of physical illnesses and number of medications associated with middle-aged and elderly patients with schizophrenia (n = 78), Alzheimer's disease (AD; n = 62), and major depression (n = 41). The data were obtained by interviewing patients and available caregivers and by reviewing the medical charts. The patients with schizophrenia reported fewer physical illnesses (mean = 1.0) than did AD and depressed patients (means = 1.4 and 2.4, respectively, $p < 0.0001$). The prevalence of degenerative joint disease, hypertension, coronary artery disease, and congestive heart failure was significantly lower in schizophrenia patients than in patients with AD or major depression. There were no significant group differences in the prevalence of diabetes mellitus, chronic obstructive pulmonary disease, gastrointestinal disease, thyroid disease, or neurological illnesses. Schizophrenia patients also received significantly fewer nonpsychotropic medications than did the other two groups.

In an attempt to assess comorbidity in a more quantitative fashion, we recently examined physical comorbidity in a sample of outpatients with schizophrenia (n = 53) and healthy comparison subjects (n = 38), all over the age of 45 years, who were participating in our Clinical Research Center, using the Cumulative Illness Rating Scale for Geriatrics (CIRS–G; Miller et al. 1992; Parmelee et al. 1995). The CIRS–G yields quantitative measures of physicians' ratings of physical illness severity in 14 organ systems (e.g., upper gastrointestinal, respiratory). Each item is rated on a scale of 0 to 4 (0 is absent, 4 is most severe). The CIRS–G has five summary variables: number of categories endorsed; severity index (average severity per category); number of illnesses with level 3 severity (severe/constant significant disability/uncontrollable chronic problems); number of illnesses with level 4 severity (extremely severe/immediate treatment required/end organ failure or severe impairment in function); and total score. Because we wished to compare physical comorbidity only, we omitted the category rating presence and severity of psychiatric illness.

We first examined the mean number of illnesses reported on Axis III of the *DSM–III–R* (American Psychiatric Association 1987), based on the combined information from subject and caregiver interviews, medical records, and the physician's history and physical examination. The number of illnesses for the patients with schizophrenia (mean = 1.3) was lower than that for the normal comparison subjects (mean = 2.1, $p < 0.03$). Although the two groups were comparable in terms of mean education level (13 years) and gender distribution (> 60% male), the comparison subjects were significantly older than the schizophrenia patients (67.6 and 56.0 years, respectively; $p < 0.0001$). Despite the age discrepancy between the two groups, the mean number of CIRS–G categories endorsed was similar for the normal and schizophrenia subjects (2.2 categories). The severity index, total score, and number of illnesses with level 3 severity also did not differ between the patient and comparison groups. None of the subjects in either group had illnesses of level 4 severity. In other words, it appeared that the schizophrenia patients endorsed a greater number of illnesses when they were assessed in a structured manner using the CIRS–G than they did when assessed with unstructured, subjective reporting. The total

number of illnesses reported for the schizophrenia patients was similar to that reported for the normal subjects who were, on an average, 12 years older. It is possible that caregivers and health care professionals may be unaware of the physical illnesses of their schizophrenia patients unless the illnesses are more severe. Among the schizophrenia subjects, the CIRS–G total score did not correlate with education, duration of illness, severity of negative symptoms based on the Scale for the Assessment of Negative Symptoms (SANS; Andreasen and Olsen 1982), or degree of cognitive impairment on the Mini-Mental State Examination (MMSE; Folstein et al. 1975) and the Mattis Dementia Rating Scale (Mattis 1976). Surprisingly, in the schizophrenia subjects, age was not correlated with any measure of physical comorbidity, although in normal subjects, age correlated significantly with CIRS–G indices ($p < 0.01$). This could be related to a wider age range and to the older mean age of the normal subjects compared with those with schizophrenia. Significant positive correlations were noted for the CIRS–G total score with age at onset of schizophrenia (Spearman's $r = 0.34$, $p < 0.02$), severity of positive symptoms on the Scale for the Assessment of Positive Symptoms ($r = 0.29$, $p < 0.05$) (SAPS; Andreasen and Olsen 1982), depressive symptoms using the Hamilton Depression Rating Scale (Hamilton 1967) ($r = 0.37$, $p < 0.01$), and overall psychopathology assessed with the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962, 1988) ($r = 0.40$, $p < 0.006$).

Thus, the CIRS–G total score correlated positively with three measures of psychopathology severity in schizophrenia patients. One possible interpretation is that the more severe positive symptoms that a patient has, the more likely it is that both the patient and the health care staff may underestimate or ignore co-occurring medical illnesses. Using a triage model, treating a patient's comorbid physical conditions may be seen as relatively less important in the context of a florid psychosis. It is also possible that comorbid physical illness may exacerbate certain psychotic symptoms. The positive relationship observed between depressive symptoms and CIRS–G total score could also be bidirectional. Schizophrenia patients with more severe depressive symptoms may experience reduced motivation or feelings of hopelessness and, consequently, be less likely to seek care for their medical illnesses. Alternately, patients with a comorbid medical condition may have depressive symptoms secondary to their illness.

One limitation of the present study was the age difference between the schizophrenia subjects and the normal comparison group. The normal comparison group was, on average, 12 years older than the patient group. In general, as people age, they tend to have an increasing number of illnesses, and these illnesses tend to be more severe. The older age of the normal subjects would tend to bias the results in favor of finding more severe illnesses in the normal group. Thus, despite the age difference, schizophrenia patients endorsed a comparable number of illnesses as did the comparison subjects who were significantly older. The present study demonstrates the need for systematic assessment of physical illnesses in patients with schizophrenia. We plan to use the CIRS–G to examine comorbid physical illnesses in larger groups matched for age.

In a related study at UCSD (Jeste et al. 1995*b*), we followed a cohort of patients with late-onset schizophrenia (LOS). LOS was defined as schizophrenia manifesting after the age of 45 (American Psychiatric Association 1987). Twenty-two outpatients with LOS were followed for an average of 5 years (range of 2–9 years). The mean age at illness onset was 57 years, the mean duration of illness at study entry was 4 years, and the baseline mean MMSE score was 27/30. We initially hypothesized that some of the schizophrenia subjects would develop dementia during the course of the study at a rate greater than that in the age-comparable general population. At 5-year followup, none of the subjects had become demented or institutionalized. Five LOS subjects had died, however, with two suicides, two deaths from cancer, and one death from cardiac arrest. This mortality rate was more than twice what would be expected for the general population over this time period (U.S. Department of Health and Human Services 1994). This suggests that LOS patients have an increased mortality rate, as has been reported for schizophrenia in general.

Specific Management Considerations. Schizophrenia patients, caregivers, and clinicians frequently may be unaware of the patients' comorbid physical illnesses. It may be helpful to use a standardized instrument, such as the CIRS–G, to systematically assess physical comorbidity in schizophrenia patients, especially among the older individuals. By recognizing physical illnesses sooner, patients may benefit from early treatment, thereby preventing at least some of the later complications.

Substance Abuse and Dependence

Literature Review. Patients with schizophrenia are much more likely

to abuse a wide variety of substances than are healthy comparison subjects. There is considerable evidence that schizophrenia patients have higher than average rates of alcohol and illicit drug use, cigarette smoking, and polydipsia (excessive water drinking). Our experience suggests that schizophrenia patients may have higher than average rates of caffeine consumption as well. In the Epidemiological Catchment Area study, the lifetime prevalence of alcohol abuse or dependence in persons meeting *DSM–III–R* criteria for schizophrenia was 3.3 times higher than that in the general population, with 33 percent of the subjects with schizophrenia being affected (Regier et al. 1990). The odds of having a lifetime illicit drug-abuse disorder are 6 times higher for individuals with schizophrenia (27.5%) than for individuals without a mental disorder. Prevalence of smoking has been reported to be 50 to 90 percent (Masterson and O'Shea 1984; Hughes et al. 1986), and polydipsia may affect up to 20 percent of chronically institutionalized schizophrenia patients (de Leon et al. 1994). It is possible that some deaths of undetermined causes may be due to undiagnosed polydipsia that resulted in water intoxication (Kushnir et al. 1990).

Substance use. Estimates of the prevalence of substance-abuse disorders in schizophrenia have varied somewhat because of differences in sample demographic characteristics, study methodology, and assessment techniques. Cuffel (in press) reviewed prevalence studies of drug and alcohol abuse in schizophrenia and found that the prevalence estimates of substance abuse were correlated with the year in which the data were collected. This finding was attributed to the use of increasingly more sophisticated measures to collect data on substance use.

Comorbid substance abuse and dependence have significant effects on the course of illness, on physical health, on hospitalization, and on quality of life (Mueser et al. 1992). For example, recent research examining alcohol use in schizophrenia demonstrated that higher alcohol use was associated with more severe psychiatric symptoms, more disturbed behavior, and more severe orofacial dyskinesia (Duke et al. 1994). Use of illicit drugs such as marijuana (Negrete et al. 1986) and cocaine (Brady et al. 1990) was also associated with more severe psychiatric symptoms and worse prognoses. Several researchers (Drake et al. 1989; Mueser et al. 1992) have reported poorer medication compliance, higher rates of rehospitalization, and poorer adjustment and treatment response in schizophrenia patients with comorbid drug and alcohol abuse or dependence than in those patients without such abuse or dependence. Increased likelihood of violent behavior (Cuffel et al. 1994) and greater use of emergency services (Day and Graham 1991) are also associated with substance abuse in schizophrenia. Most available research confirms the clinical dictum that substance abuse exacerbates psychiatric symptoms.

Smoking. Studies examining rates of cigarette smoking have found higher rates in schizophrenia patients than in normal subjects (even when demographic variables and socioeconomic status were controlled for) and in patients with other psychiatric disorders as well (e.g., Hughes et al. 1986). Smoking increases neuroleptic metabolism and consequently may be associated with the use of higher neuroleptic doses (Goff et al. 1992). It has been speculated that nicotine increases the release of dopamine in some areas of the brain (Giorguieff-Chesselet et al. 1979). Animal researchers have shown that nicotine increases the release of dopamine in the nucleus accumbens (Imperato et al. 1986). Some investigators have suggested that smoking may actually be therapeutic for patients, as the increased release of dopamine may alleviate negative symptoms (Glassman 1993). Adler et al. (1993) reported that cigarette smoking could transiently normalize the impairment of auditory sensory gating in schizophrenia patients. A related study examined nonsmoking relatives of schizophrenia patients who shared the auditory gating defect reported in schizophrenia. In a double-blind, placebo-controlled procedure, use of nicotine gum transiently normalized this sensory gating deficit (Adler et al. 1992).

Some epidemiological studies have found an inverse relationship between cigarette smoking and the prevalence of idiopathic Parkinson's disease (Baron 1986). Smoking may also decrease neuroleptic-induced parkinsonism; in one study, the number of cigarettes smoked daily correlated inversely with ratings of neuroleptic-induced parkinsonism in schizophrenia patients (Goff et al. 1992). Some researchers have reported a positive association between nicotine use and increased prevalence of TD (Yassa et al. 1987), although this finding has not been replicated by others (Menza et al. 1991).

Polydipsia. This is an unusual and poorly understood condition that is seen most frequently in male Caucasian inpatients with schizophrenia (Jos et al. 1986). It is associated with an early age at onset of schizophrenia, heavy tobacco use, poor response to neuroleptic medication, and increased prevalance of TD

(Kirch et al. 1985; de Leon et al. 1994). Polydipsia may lead to water intoxication, hyponatremia, and death. There is some suggestion that patients who develop polydipsia may also exhibit other substance-use disorders.

A number of explanations have been proposed for the observed high rates of substance abuse in the schizophrenia population. Self-medication has been the most frequently offered hypothesis for increased rates of smoking as well as for alcohol and illicit drug abuse. Use of a particular substance appears to be related more to the availability of that substance than to a selective matching of substance effects with specific symptoms (Schneier and Siris 1987; Cuffel, in press). There is also evidence that individuals often tend to use multiple substances, such as alcohol, illicit drugs, and cigarettes; according to the Epidemiologic Catchment Area data, 21 percent of all individuals with alcohol abuse or dependence had another lifetime substance-use disorder (Regier et al. 1990). The effects of combined substance use may serve to further exacerbate symptoms of psychosis and cognitive impairment.

Investigations into the risk factors associated with substance abuse have revealed some surprising results. It appears that better premorbid functioning is associated with an increased risk of comorbid drug and alcohol use among schizophrenia patients (Mueser et al. 1990; Dixon et al. 1991). Mueser et al. (1990) have suggested that drug-abusing patients may have milder clinical symptoms, which are reflected in better social skills and an ability to take part in the social interactions related to acquiring and using drugs. Earlier studies in this area (Cohen and Klein 1970) also noted that more severely ill patients lacked the social skills necessary to participate in heavy drug use.

UCSD Studies. A UCSD study examining cognitive abilities in younger schizophrenia patients (Zisook et al. 1992) found that patients who abused drugs or alcohol performed better on neuropsychological testing than did nonabusers. One possible explanation consistent with the results of the above-mentioned studies is that acquiring and using drugs and/or alcohol require some amount of cognitive (and social) abilities.

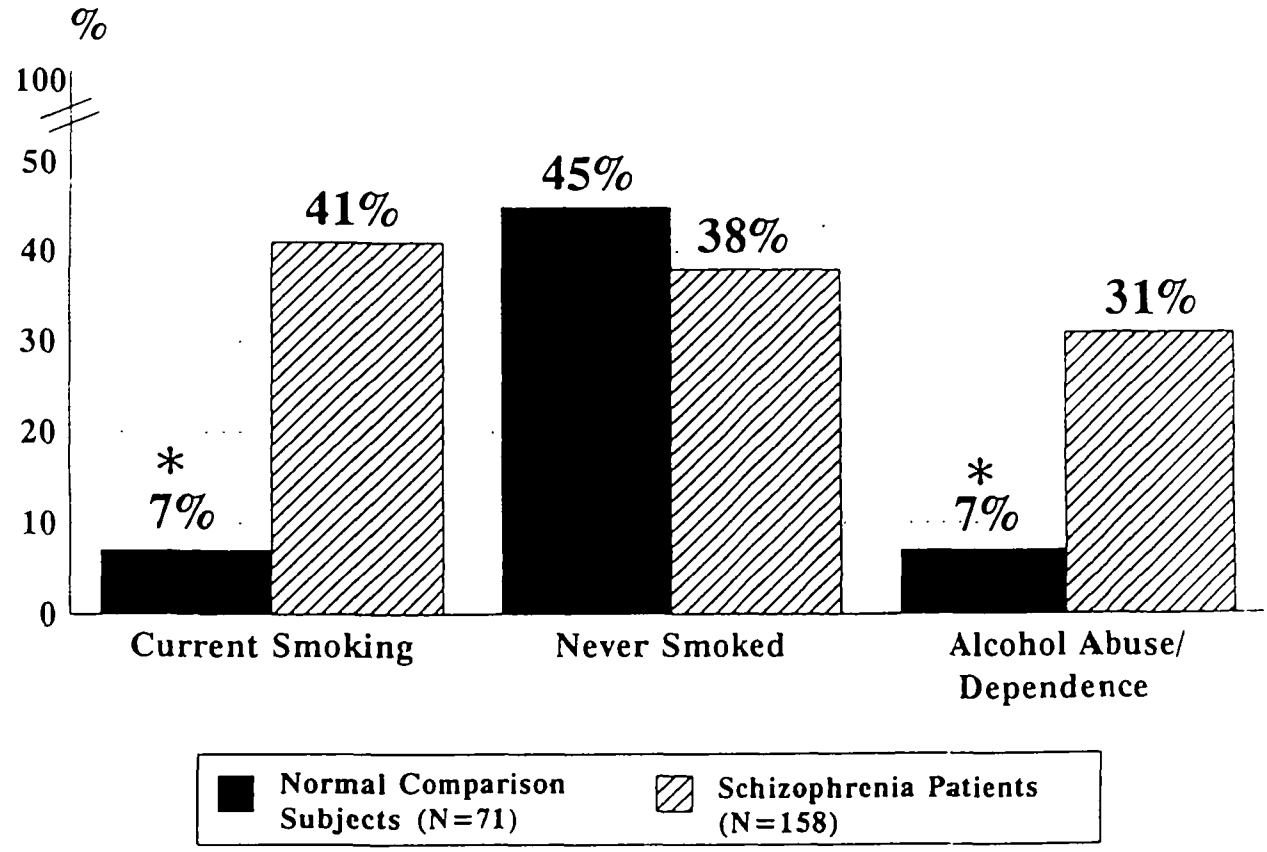
In our sample of older schizophrenia patients (mean age = 60 years), the prevalence of *DSM–III–R* lifetime alcohol abuse or dependence was 31 percent, compared with 8 percent in normal comparison subjects (χ^2 = 15.36, df = 1, $p < 0.0001$). Among the schizophrenia patients, those with a comorbid diagnosis of alcohol abuse or dependence performed significantly better on attention measures ($p < 0.01$) and overall cognitive functioning ($p < 0.05$). The groups with those without alcohol abuse or dependence did not differ in terms of age, gender, age at onset or duration of schizophrenia, education, BPRS total, SAPS or SANS total, and daily neuroleptic or anticholinergic dose. In another study, comorbid alcohol abuse or dependence was found to be associated with an increased incidence of TD (Jeste et al. 1995*b*). It has been hypothesized that the central nervous system changes associated with heavy alcohol use may result in a "premature aging" of the brain, thereby increasing the risk for TD.

The prevalence of current cigarette smoking was nearly 6 times higher among our older schizophrenia patients than among the normal comparison subjects (40% and 7%, respectively; χ^2 = 26.25, df = 2, $p < 0.0001$; figure 1). Current smoking in patients with schizophrenia was related to younger current age ($p < 0.01$), earlier onset of illness ($p < 0.01$), and higher daily neuroleptic dose ($p < 0.001$).

Specific Management Considerations. Substance abuse and dependence in schizophrenia are frequently associated with medication noncompliance, psychosocial problems, medical and iatrogenic complications, psychotic exacerbation, and worse overall prognosis. As with nonpsychiatric individuals, patients with schizophrenia may minimize or be inaccurate in reporting their substance use. It is therefore important to routinely screen for substance-use disorders when working with schizophrenia patients. Substance-use screening tests, such as the Michigan Alcohol Screening Test (Selzer 1971), CAGE (Mayfield et al. 1974), Drug Abuse Screening Test (Skinner 1982), and urine toxicology tests may be helpful in identifying individuals with comorbid substance-use disorders.

Many substance-abusing individuals use multiple substances. Relatively little research has been done to address the consequences of multiple-substance abuse in schizophrenia, but it seems likely that substance interactions may further compromise health status, cognitive functioning, and psychiatric symptoms (Koczapski et al. 1990). Substance use may also be associated with an increased risk of side effects, such as akathisia (Duke et al. 1994) and TD (Binder et al. 1987; Jeste et al. 1995*a*). It is important to consider that substance abuse is also associated with a heightened risk of suicide in the general population. Schizophrenia patients with comorbid substance abuse may be

Figure 1. Prevalence of smoking and alcohol abuse/dependence in 71 normal comparison subjects and 158 patients with schizophrenia



All subjects were over 45 years of age $p < 0.001$ (χ^2 test).

even more likely to act on suicidal ideas (Cohen et al. 1990). Hence, appropriate assessment and management of polysubstance-use disorders in schizophrenia are critical.

Cognitive Impairment

Literature Review. A large body of existing research demonstrates that schizophrenia is associated with moderate generalized cognitive impairment (reviewed by Heaton and Drexler 1987; Davidson and Haroutunian 1995; and Goldberg et al. 1995). Cognitive deficits are thought to be an integral feature reflecting brain dysfunction in schizophrenia. Against the background of generalized cognitive impairment, some researchers have noted particular deficits in abstraction and problem solving (Bornstein et al. 1990; Braff et al. 1991; Beatty et al. 1994) and selective impairment in memory and learning (Saykin et al. 1991). It is less clear what proportion of patients with schizophrenia develop dementia. When Kraepelin (1919/1971) described *dementia praecox*, it was assumed that schizophrenia was associated with a downward course and eventual dementia, although Kraepelin defined dementia as a "destruction of the psychic personality" and a loss of volition over thinking, feeling, and behavior. Kraepelin himself later questioned the use of the term "dementia," as he observed that the disorder did not always result in permanent deterioration. Past research addressing the prevalence of dementia in late-life schizophrenia has yielded conflicting re-

sults. Most cross-sectional (Heaton et al. 1994; Hyde et al. 1994) and longitudinal (Bleuler 1968; Ciompi 1980) studies investigating cognitive decline in schizophrenia suggest that schizophrenia is associated with a stable cognitive deficit rather than dementia, although some studies have found evidence indicating a progressive deterioration during the initial course of the disease (Bilder et al. 1992).

Two recent studies focusing on chronically institutionalized patients from State hospitals in New York reported somewhat different findings regarding the risk of AD in schizophrenia. Davidson and Haroutunian (1995) reported that 60 percent of schizophrenia patients who were chronically institutionalized were demented, with MMSE scores near zero. Despite the severity of their dementia, the pattern of deficits in impaired schizophrenia patients could be distinguished from that seen in AD patients. Neuropathological examinations of the subjects' brains did not reveal cellular changes characteristic of AD. In contrast, Prohovnik et al. (1993) studied a similar cohort of subjects and found that 28 percent of the chronically institutionalized patients with schizophrenia had AD-like neuropathology at autopsy.

In their review of more than 100 studies focusing on the effects of aging in schizophrenia, Heaton and Drexler (1987) concluded that the cognitive deficit associated with schizophrenia was not significantly related to aging. With the exception of a subset of patients, cognitive performance in most schizophrenia patients appears to be relatively stable and is not associated with progressive deterioration despite chronic illness or long-term treatment. It is likely that the apparent dementia observed in older schizophrenia patients may be at least partly secondary to depression, medication side effects, alcohol and drug use, comorbid medical problems, sensory deficits, or prolonged institutionalization. Untreated depression in schizophrenia patients may manifest as the so-called "pseudodementia" similar to that seen in other elderly patients (Jeste et al. 1990). Anticholinergic medications, which are given to treat the extrapyramidal side effects of neuroleptics, may have detrimental effects on the integrity of memory and cognitive functions (Spohn and Strauss 1989; Paulsen et al. 1995). Both institutionalized and independently living elderly patients often receive multiple medications, and these medications may have synergistic and sedative effects that may mimic dementia. Comorbid substance abuse in schizophrenia patients may predispose them to dementia. Neurological and other physical disorders, such as diabetes mellitus and cardiovascular and cerebrovascular disorders, may also result in brain damage and associated dementia. Sensory deficits are discussed later. Finally, prolonged institutionalization may contribute to real or apparent cognitive deterioration. Any of these factors superimposed on schizophrenia may lead one to misattribute progressive cognitive declines to chronic schizophrenia per se.

UCSD Studies. We previously reported on the influence of age and chronicity of schizophrenia on neuropsychological deficits in patients with schizophrenia (Heaton et al. 1994). We compared the performance of three groups of schizophrenia outpatients (early-onset young [EOS–Y; n = 85], early-onset old [EOS–O; n = 35], and LOS [n = 22]) with patients with AD (n = 42) and normal comparison subjects (n = 38) on a comprehensive neuropsychological test battery. There were no significant differences among the schizophrenia groups in the level or pattern of neuropsychological functioning, but the schizophrenia patients differed significantly from both the normal comparison subjects and the AD patients. The schizophrenia patients performed worse than the normal subjects and demonstrated mild to moderate impairment in all the cognitive ability areas except for memory, which was within normal limits. Consistent with previous studies (Heaton and Drexler 1987; Saykin et al. 1991; Goldberg and Weinberger 1994), our patients with schizophrenia were mildly to moderately impaired in learning, abstraction, motor skills, attention, verbal ability, psychomotor speed, and sensory abilities. Neuropsychological impairment in schizophrenia was unrelated to current age, age at onset of schizophrenia, or duration of illness. These findings provide further support for the notion that the cognitive impairment associated with schizophrenia is essentially nonprogressive. Unlike people with AD, the schizophrenia patients, including the comparably aged patients with LOS, did not have rapid forgetting of newly learned information.

In a study comparing the clinical and neuropsychological characteristics of LOS and EOS (Jeste et al. 1995*b*), we evaluated 25 patients with LOS (i.e., patients with schizophrenia onset after age 45), 39 patients with EOS, and 35 healthy comparison subjects. We found that the LOS patients were similar to the EOS patients but different from the normal subjects on most variables assessed, including the overall pattern of neuropsychological impairment, although the

degree of cognitive impairment was slightly milder in the LOS than in the EOS patients. But at the time of assessment, the LOS patients were taking lower daily doses of neuroleptic medication than were the EOS subjects. Many previous studies have reported some normalization of neuropsychological deficits with neuroleptic treatment (reviewed in Spohn and Strauss 1989). When neuroleptic dosage was controlled for, however, the results of the neuropsychological deficits still did not differ.

Another UCSD study examined the characteristics of the learning and memory impairment seen in schizophrenia (Paulsen et al. 1995). Schizophrenia patients (n = 175) performed worse than healthy comparison subjects (n = 229) on all measures of learning, free recall, and recognition memory. Greater impairment was associated with earlier age at onset of schizophrenia, more severe negative symptoms as assessed by the SANS, and higher daily anticholinergic dosages. The pattern of the schizophrenia patients' learning and memory performance was consistent with a mild encoding deficit and a prominent retrieval deficit. Use of a discriminant function analysis that differentiated subjects with cortical dementia, subcortical dementia, and normal learning and memory patterns categorized 50 percent of the schizophrenia patients as having a subcortical profile, 35 percent as having a normal profile, and 15 percent as having a cortical profile. This finding reflected the heterogeneity seen in the clinical presentation of schizophrenia. It also provided support for the notion that schizophrenia may be associated with primarily subcortical pathology.

A recently completed UCSD study (Paulsen et al., in press) sought to investigate the mechanisms of the language impairment commonly observed in schizophrenia. Using multidimensional scaling and Pathfinder analysis (Dearholt and Schvaneveldt 1990) on responses to an animal fluency task, the semantic networks of 56 schizophrenia patients and 28 normal subjects were compared. Consistent with previous findings, the schizophrenia patients showed significantly less fluency than did healthy subjects. Detailed semantic network analysis found that the performance varied with the age at onset and the subtype of schizophrenia. Patients with an earlier age at onset of illness and those with nonparanoid subtypes had more disorganized semantic networks, suggesting an association between some of the cardinal symptoms of schizophrenia (e.g., thought disorder) and impaired neuropsychological performance.

Specific Management Considerations. It is important to consider that performance on tests of cognitive functioning may appear to be spuriously lower in patients who are severely delusional or hallucinating or markedly apathetic than in patients who are not actively psychotic. If dementia is observed in an elderly psychotic patient, a comprehensive medical workup is indicated to rule out untreated depression, medication side effects, substance or alcohol abuse, neurological or other physical comorbidity, sensory impairment, or institutionalization as possible contributors to the cognitive impairment. Treatment of the appropriate conditions may result in some improvement in cognitive functioning.

Research on the cognitive impairment associated with schizophrenia has consistently demonstrated deficits in learning. This deficit is clinically relevant to working with schizophrenia patients and should have important implications for therapeutic interactions. For example, when providing a patient with instructions on taking medication, it may be important to present the information repeatedly in more than one modality (e.g., oral and written instructions), to provide cues or reminders to help the patient remember, or to associate taking medication with some other part of the patient's normal routine. Behavior perceived as noncompliance or resistance to treatment may actually reflect the patient's encoding and retrieval problems. Thus, incorporating research information into clinical interactions may improve treatment response.

Sensory Deficits

Literature Review. Houston and Royce (1954) proposed that sensory deficits, especially deafness, may predispose individuals to develop schizophrenia and other paranoid psychoses in late life. It was suggested that as a person began to have hearing impairment, he or she might have difficulty understanding speech and might tend to misinterpret what others were saying. This perceptual problem might lead to misperceptions that others were talking about the individual (ideas of reference), eventually progressing to delusions of persecution. Several other investigators (e.g., Kay and Roth 1955, 1961) have supported the association between "late-life paraphrenia" and sensory deficits.

In 1993, we reviewed 27 published studies examining the possible association between sensory (visual or hearing) impairment and late-life psychosis with paranoid features (Prager and Jeste 1993). Although the validity and generalizability of this

literature are limited by methodological flaws such as vague diagnostic criteria, inadequate assessment of hearing and vision, and lack of appropriate comparison groups, the majority of these studies seem to indicate an association between hearing deficits and late-onset psychosis. The causality, however, was not determined.

Using a crossover design, Kreeger et al. (1995), recently investigated the impact of hearing deficits on mental status ratings in geriatric psychiatric patients. The investigators found that hearing-impaired patients displayed less psychopathology and improved MMSE performance when they were assessed while wearing a functional (compared with a nonfunctional) hearing aid.

UCSD Studies. We (Prager and Jeste 1993) conducted a case-control study of 87 subjects over age 45, including 16 patients with LOS, 25 with EOS, 20 mood disorder patients, and 26 healthy comparison subjects. Using standardized audiometry and visual acuity measures, raters who were blind to psychiatric diagnosis assessed both corrected and uncorrected sensory deficits (i.e., sensory deficits of the subjects were assessed with and without corrective measures such as hearing aids or eyeglasses, if any, that the subjects were using). Subjects also completed a self-report questionnaire about hearing in which they were asked about subjective problems with social conversation and other situations. There were no significant differences among the groups in terms of uncorrected (constitutional) hearing or visual abilities, but all the psychiatric groups had significantly more problems with corrected social hearing and vision (i.e., with any hearing aids or eyeglasses that the subjects were using) than did the normal subjects. This suggested that older psychiatric patients were at a disadvantage in getting appropriate correction of their hearing and visual deficits. Our results question the notion that sensory deficits predispose older persons to developing LOS or other paranoid psychosis; instead, they suggest that suboptimal (or correctability) of sensory deficits may be related to problems associated with severe psychopathology.

It appears that older schizophrenia patients may be at a particular disadvantage in getting appropriate correction for their sensory deficits. Anecdotally, we have discussed the problem of adequate treatment of our patients with ear, nose, and throat surgeons. These physicians report difficulty with assessing sensory functioning in psychotic patients. For example, doctors may have trouble determining if a patient's complaints of hearing noises represent tinnitus or an auditory hallucination. In everyday practice, schizophrenia patients may also experience other barriers to adequate assessment and treatment, such as a lack of medical insurance and trouble communicating their needs clearly to their physicians.

Specific Management Considerations. Sensory impairments are common in the elderly. Hearing impairment is the second most common medical problem in the geriatric population, with approximately 25 percent of the individuals between the ages of 65 and 74 and 50 percent of those over age 75 being so affected (Mhoon 1990). In terms of visual impairment, 75 percent of persons over age 60 have cataracts, with about 15 percent experiencing a significant visual loss (Rich 1990). When assessing a patient's cognitive functioning and psychiatric symptomatology, it is important to first determine whether the patient has any major sensory deficits. Objective testing may compensate for the patient's reduced awareness of any such deficits. Hearing and visual deficits are generally correctable, at least in part. Uncorrected sensory deficits may result in overestimation of symptoms and deficits and may reduce the quality of life for the patients.

Iatrogenic Comorbidity

Literature Review. Medications used for the treatment of schizophrenia may result in adverse effects such as akathisia, parkinsonism, neuroleptic malignant syndrome, TD, other tardive syndromes, and even sudden death. Other iatrogenic effects may include glucose intolerance and cardiovascular disease.

TD. TD represents the most common persistent iatrogenic movement disorder in patients with schizophrenia. The reported prevalence of TD ranges widely due to methodological variations as well as differences in study populations and criteria for TD. In their review and reanalysis of data from 76 published studies, Yassa and Jeste (1992) found a reported TD prevalence of 3 to 62 percent among neuroleptic-treated patients, with a mean of 24.2 percent. Some researchers (Kane et al. 1988) have pointed out that the reported prevalence of TD may be artificially lowered due to the masking of symptoms by neuroleptics.

There has been some evidence that aging (Kane et al. 1992), female gender (Yassa and Jeste 1992), substance abuse (Dixon et al. 1992), brain damage or dysfunction (Manschreck et al. 1990), and comorbid diabetes mellitus (Ganzini et al. 1991) may increase a person's risk of developing TD. Other studies have reported data

suggesting that African-Americans (Glazer et al. 1994) and patients with mood disorders (Mukherjee et al. 1986; Casey and Keepers 1988) have an increased risk of developing TD. Kane et al. (1988) followed 850 young schizophrenia patients (mean age = 29 years) over 6 years. They found that the incidence of TD increased with the duration of neuroleptic treatment. Cumulative incidence of TD in this population was 5, 10, and 15 percent after 1, 2, and 3 years, respectively, and increased to 26 percent by the end of the 6th year.

Other side effects. *DSM–IV* (American Psychiatric Association 1994*a*) includes a section on medication-induced movement disorders. All but one of the disorders listed are secondary to neuroleptic use. These disorders may masquerade as other comorbid medical conditions. They may be upsetting to patients and may lead to noncompliance (American Psychiatric Association 1994*b*).

A number of preliminary reports have suggested an association between impaired glucose tolerance and schizophrenia (Brambilla et al. 1976; Mukherjee et al. 1989*b*), especially in patients with TD. It is still not clear whether schizophrenia and impaired glucose tolerance or familial Type II diabetes mellitus are related via some genetic association or whether impaired glucose tolerance represents a side effect of neuroleptic use (McKee et al. 1986).

Older patients appear to be at a higher risk for the development of many side effects. Older age is associated with alterations in pharmacokinetic and pharmacodynamic responses, with an increased sensitivity to medication. Concurrent medical illnesses and polypharmacy may further alter drug metabolism and, consequently, the side effect profile.

Atypical antipsychotics such as clozapine and risperidone (in lower doses) appear to have a lower risk for extrapyramidal side effects, probably a lower risk of TD (Kane et al. 1993), and possibly less cognitive impairment (Jeste et al., in press). On the other hand, clozapine is associated with other iatrogenic problems, including agranulocytosis, seizures, and anticholinergic toxicity; risperidone is associated with postural hypotension.

UCSD Studies. We (Jeste et al. 1995*a*) followed a group of patients over age 45 (n = 266, mean age = 65 years) who had a median duration of 21 days of lifetime neuroleptic exposure at baseline. Twenty-five percent of the subjects were neuroleptic-naive at baseline, while 45 percent had fewer than 90 days of lifetime neuroleptic exposure. All the patients were treated with relatively low doses of neuroleptics, usually of haloperidol or thioridazine, and were followed with clinical and instrumental assessments by "blind" raters for up to 3 years. Cumulative incidence of TD was 26, 52, and 60 percent after 1, 2, and 3 years, respectively. The incidence of TD was comparable in schizophrenia and non-schizophrenia subjects. Risk factors for the development of TD included cumulative amounts of neuroleptics (especially the high-potency ones) used, history of alcohol abuse or dependence, and presence of a subtle movement disorder at baseline.

Specific Management Considerations. To minimize the risk for development of TD and other iatrogenic complications in schizophrenia patients, high doses of neuroleptics should be avoided. Neuroleptic dose should be maintained at the lowest effective level. It is important to monitor for possible medication interactions and side effects. For example, among the elderly it would be important to assess the risk for falls due to postural hypotension.

Discussion

Research Implications. Clearly, better controlled studies on medical comorbidity in schizophrenia are needed. Traditionally, research on schizophrenia has excluded subjects with comorbid conditions. Because a majority of the patients with schizophrenia are affected by at least one type of comorbid condition, this exclusion has compromised the generalizability and ecological validity of research. Rather than continuing to view physical illnesses, substance abuse, and sensory deficits as "nuisance variables," these aspects should be studied in research protocols so that the interaction of schizophrenia and comorbid illnesses can be better understood, with the ultimate goal being more effective treatment of the patients.

Another research goal should be to study the interactions of more than one type of comorbid condition on the clinical course and treatment of schizophrenia. For example, alcohol abuse is a risk factor for certain physical illnesses, for cognitive impairment, and for TD, and all these are likely to complicate clinical management. Further research on medical conditions that seem to covary specifically with schizophrenia in either their presence or absence (e.g., polydipsia and rheumatoid arthritis, respectively) may help shed light on at least some aspects of the pathophysiology of schizophrenia.

Clinical Implications. To optimize treatment of patients with schizo-

phrenia, it is important to recognize comorbid physical conditions. Dissemination of findings to health-care professionals can raise awareness and help compensate for patients' deficits in reporting comorbid conditions. Information about risk factors can help direct assessment. Use of more systematic evaluations and use of multiple sources of information (e.g., caregivers, laboratory tests) would improve assessment of comorbid conditions. Finally, knowledge of comorbidity can aid in the clinical management of patients. For example, there is considerable evidence that schizophrenia patients are impaired in learning and that anticholinergic medications frequently used to treat neuroleptic side effects interfere with learning and memory. Integrating this information into patient management should influence how clinicians present instructions on how to use prescribed medication.

Targeted patient education regarding physical health, medication, and side effects may help to increase awareness of medical comorbidity in schizophrenia patients and help make them better advocates for themselves. By increasing clinicians' awareness of comorbid conditions and their effects, they may modify treatment to reduce the risks of polypharmacy. To reduce health-care costs and improve patients' quality of life, it may be important to increase outpatient monitoring to prevent exacerbations of conditions that would require more costly inpatient care to stabilize.

Medication noncompliance is a common and serious problem in the treatment of schizophrenia, with more than two-thirds of patients becoming noncompliant within 2 years after hospital discharge (Weiden et al. 1991). Noncompliance with medication regimens is associated with poor outcome, including increased risk of relapse, rehospitalization, and suicide (Weiden et al. 1995). Cognitive deficits and iatrogenic side effects play a role in decreasing compliance. Patients may not be able to manage complicated medication regimens, or they may simply forget to take their medicine. Many iatrogenic side effects are distressing to the patients and increase their resistance to taking medication. Increasing clinician awareness of comorbid conditions that may have an impact on patient compliance can lead to closer monitoring of patient characteristics that may signal noncompliance and ultimately will lead to improved care of schizophrenia patients.

In sum, both patient care and research could be improved considerably with increased attention to medical comorbidity in schizophrenia.

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