



Detection and management of comorbidity in patients with schizophrenia

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Schizophrenia is associated with substantial psychiatric and medical comorbidity [1–3]; approximately 50% of patients with schizophrenia have at least one comorbid psychiatric or medical condition [3–6]. Comorbid psychiatric disorders, such as substance use disorder, often have a deleterious effect on the course of schizophrenia, and comorbid medical conditions, such as diabetes, may contribute to a decreased life span in patients with schizophrenia. As the overall ability to treat schizophrenia has improved with the introduction of the novel antipsychotic drugs, negative effects of comorbidity seem to have become more obvious [7]. The detection and management of comorbid conditions in this patient population are essential if the general outcome of patients is to be optimized.

Some comorbid conditions may have a genetic link to schizophrenia itself, and establishing whether patients with schizophrenia are at increased risk for certain genetic disorders may further understanding of psychosis. Preliminary evidence indicates an increased prevalence of schizophrenia and bipolar disorder in adults with velocardiofacial syndrome, a condition associated with small deletions of chromosome 22q11 [8]. Chromosome 22q11 contains the gene for catechol-*O*-methyltransferase, an enzyme involved in the degradation of dopamine [9]. Dysregulated dopamine transmission has long been thought to play an important role in the pathophysiology of

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psychosis [10], and recent studies suggest that polymorphisms at the catechol-*O*-methyltransferase gene may impair prefrontal cognitive function and increase the risk of psychotic symptoms [11].

Other comorbid conditions may provide clues about the neurobiology of schizophrenia itself. Green and colleagues [12] proposed a neurobiologic hypothesis suggesting that the high rates of substance use disorders observed in patients with schizophrenia may be related to dysfunctional dopamine-mediated mesocorticolimbic brain reward pathways in these individuals. Despite the presence of physiologic alterations in endocrine and immune function in psychotic patients that seem to result in reduced resistance to certain diseases [13], patients with schizophrenia also seem to be relatively protected against rheumatoid arthritis [14].

Some comorbid illnesses are likely based on lifestyle factors (eg, poor diet, lack of exercise, and cigarette smoking) [15]; others may be partly iatrogenic and linked to treatment, such as tardive dyskinesia, hyperprolactinemia, and weight gain, with their associated medical illnesses. Although psychiatry is becoming increasingly able to control the symptoms of schizophrenia and improve some of the cognitive deficits seen in these patients, identifying and managing the associated comorbidities remain major challenges. This article addresses many important comorbid conditions: depression, obsessive-compulsive (OC) symptoms, substance use disorder, suicide, hyperprolactinemia, weight gain, and diabetes.

Detecting and managing psychiatric comorbidity in patients with schizophrenia

Although the hierarchical system for psychiatric diagnosis tends to limit the concurrent diagnosis of Axis I disorders, such as depression and OC disorder, in patients with schizophrenia [6], studies suggest that co-occurring psychiatric syndromes are seen in up to one half of these patients [3,6,16]. Although it is unclear whether these coexisting syndromes represent distinct comorbidity or additional symptom dimensions of a heterogeneous disorder, evidence suggests that these syndromes are useful predictors of outcome and are potentially treatable [17].

Depressive disorders

Although schizophrenia is conceptualized as a nonaffective psychotic syndrome, it is often associated with a variety of depressive states, ranging from dysphoria to major depression. According to the Epidemiological Catchment Area study, people with schizophrenia have a 14 times greater risk of having a depressive disorder than the general population [16]; the National Comorbidity Study found an 81% lifetime risk of depression in patients with schizophrenia [16] compared with a risk of 7% to 25% in the general population [18]. Some have viewed depression as a part of schizophrenia

per se [19,20]; others have suggested it can be an expression of or response to severe psychosis [20] and likely to improve with treatment of psychosis [21,22]; still others have ascribed it to a postpsychotic state, occurring after the resolution of psychotic symptoms [23].

The literature is divided over the prognostic significance of depressive symptoms in patients with schizophrenia. Some studies suggest that they are predictive of a good outcome [19], whereas others suggest the opposite [24,25]. Depression in chronic schizophrenia has been associated with a risk of relapse [25] and suicide [26]. Koreen and colleagues [21] found, however, that although up to 75% of patients with first-episode schizophrenia had depressive symptoms at baseline, nearly all of these depressive symptoms resolved as the psychosis remitted.

Detection and management of depressive disorders

Detecting depression in patients with schizophrenia requires an understanding of the range of depressive states that these patients are likely to experience and of the common conditions (eg, negative symptoms or medication side effects) that may be confused with depression. Determining the temporal appearance, duration, and severity of depressive symptoms is important in formulating an appropriate treatment plan.

Several authors noted that depressive symptoms occurring during exacerbations of schizophrenia improve as the psychosis remits [21–23]. Nonetheless, enduring symptoms meeting criteria for major depression are thought to occur at some point in the lifetime of 60% of patients with schizophrenia [27]. Approximately 10% to 30% of patients with schizophrenia-spectrum illness meet criteria for schizoaffective disorder [28]; in patients with schizoaffective, depressed type, symptoms of depression are present for a substantial proportion of the total duration of the psychotic illness. Postpsychotic depression, meeting criteria for major depression, is reported to occur in approximately 30% to 50% of patients [23,29]; it classically emerges after the resolution of psychotic symptoms and is seen most commonly after the first episode of schizophrenia [21,23]. According to Iqbal and colleagues [29], patients who have postpsychotic depression feel a greater sense of loss, are more self-critical, have a lower self-esteem, and have better insight into their illness than patients without it.

Other clinically significant depressive phenomena, such as dysphoria and demoralization, frequently occur in patients with schizophrenia [29,30]. Dysphoria, which includes symptoms of depression and anxiety, may occur at any point in the illness and seems to be associated with psychosocial stress [31] and positive symptoms [32]. Demoralization, which occurs as patients struggle with their illness and its effect on their functioning [30], seems to be associated with high performance expectations and insight into the illness and with hopelessness, low self-esteem, and suicidal thoughts [33]. Classic vegetative symptoms of depression may not be present in patients with demoralization and dysphoria [33].

The negative symptoms of schizophrenia, including affective flattening, avolition, apathy, anhedonia, and asociality, easily can be mistaken for depression [20,23,30]; in addition, antipsychotic side effects, such as sedation and akinesia (or other extrapyramidal system effects), may mimic depression [34]. Although some authors suggest that depression may overlap with or worsen negative symptoms [35], others do not [36,37]. In distinguishing depression from negative symptoms, the diagnosis should be based on the presence of a core depressed mood and related neurovegetative symptoms and not on symptoms of flatness and anhedonic indifference without mood changes [19].

The management of depressive symptoms within schizophrenia depends on when they appear during the course of the disorder and their persistence. Treatment may include pharmacologic and psychosocial interventions [38]. Because depressive symptoms may herald psychotic relapse, emergence of depressive symptoms should alert the clinician to the need to assess symptoms of psychosis. As reviewed by Levinson and colleagues [39], most treatment studies of depressive symptoms during an acute schizophrenic episode show that typical antipsychotics alone are as effective as when they are combined with antidepressants or lithium. More recent evidence suggests that compared with typical antipsychotics, atypical agents may be more efficacious in acutely psychotic patients with a comorbid mood disorder, including patients with schizoaffective disorder [40–42]. The treatment of major depression that occurs after the remission of psychosis may rely, however, on combinations of antipsychotics and antidepressants or mood stabilizers or both [39]. Although antidepressants seem to be of little value in treating depression with acute psychosis, tricyclics and serotonin reuptake inhibitors may have a role in the treatment of postpsychotic depression meeting criteria for major depression [43–45]. There is little support in the literature, however, for the routine use of antidepressants in the treatment of subsyndromal depressive symptoms or demoralization [29,39]; psychosocial interventions, including stress reduction, problem-solving skills, job training, cognitive therapy, and support, may be more effective interventions for such symptoms [38].

Obsessive-compulsive symptoms

Obsessive compulsive (OC) symptoms in patients with schizophrenia have been documented in several well-designed studies with an estimated prevalence of 3.5% to 46% [3,17,46,47]. Although the wide range in prevalence is likely to reflect inconsistent definitions for these symptoms, most contemporary studies report rates between 10% and 25% [3,48]. OC symptoms in patients with schizophrenia are important to identify because they seem to have prognostic significance, and they may be differentially responsive to conventional versus specialized treatments.

Distinguishing between delusions, obsessions, ruminations, and preoccupations can be difficult in patients with thought disorder [46]. Classic teaching describes delusions as ego-syntonic and actively embraced by the patient, whereas obsessions are typically ego-dystonic and recognized as pathologic intrusions [49]. This distinction does not always hold true in clinical interviews of patients with psychosis. Obsessions and delusions seem to lie on a continuum of insight [46], and in patients with schizophrenia, delusions and obsessions may be overlapping [50]. Hwang and Opler [49] identified three patterns of OC symptoms in patients with schizophrenia: patients with long-standing OC symptoms preceding the onset of psychosis, patients with new-onset OC symptoms developing at or after the onset of schizophrenia, and patients with transient OC symptoms over the course of schizophrenic illness.

Although some authors have considered OC symptoms in these patients a defense against “personality disintegration” and a positive prognostic indicator [51], several more recent studies suggest that OC symptoms in schizophrenia are associated with greater psychopathology and worse outcome. Patients with OC symptoms tend to be more socially isolated, have longer hospitalizations, and be less treatment responsive than patients without this symptom complex [17,49]. Some [52,53], but not all [54], authors found that patients with schizophrenia and OC symptoms have more positive and negative symptoms than patients without OC symptoms. Several authors suggested an association between OC symptoms and neurocognitive dysfunction in schizophrenia [49,53,54]. In a study of 30 patients with schizophrenia, Berman and coworkers [54] found that patients with OC symptoms performed worse than patients without OC symptoms on measures of visuospatial skills, delayed verbal memory, and cognitive shifting abilities; the severity of OC symptoms correlated with poor performance on these cognitive tasks. Patients with OC disorder show deficits in similar cognitive tasks [55]. Nonetheless, it is unclear whether OC symptoms are related causally to OC disorder or whether they represent characteristics of a distinct subtype of schizophrenia [56].

Detection and management of obsessive-compulsive symptoms

The types of obsessions and compulsions experienced by patients with schizophrenia are similar to those found in classic OC disorder—contamination obsessions, hand-washing rituals, and counting and checking compulsions [47]. Several contemporary studies reliably used the Yale-Brown Obsessive-Compulsive Scale [57] to detect OC symptoms in patients with schizophrenia.

Typical antipsychotic medications seem to be of limited value in the treatment of OC symptoms in schizophrenia [58]. Emerging data suggest, however, that serotonin reuptake inhibitors added to typical antipsychotics can be used successfully in patients with schizophrenia and OC symptoms [59]. A review [60] of several small (and mostly open) trials using adjunctive clomipramine,

imipramine, or fluoxetine found that 67.2% of patients showed improvement in OC symptoms with no worsening of psychosis, whereas 19% showed worsening of psychosis. In a small double-blind, crossover study of adjunctive clomipramine and placebo, Berman and colleagues [59] showed clomipramine was superior to placebo when added to typical anti psychotics in the treatment of obsessions and compulsions, and improved overall schizophrenic symptoms. Clinicians considering such an augmentation strategy should be aware that some serotonin reuptake inhibitors can increase some antipsychotic blood levels and should be used carefully.

The data regarding the role of atypical antipsychotics in patients with schizophrenia and OC symptoms are contradictory and still limited [16]. Several case reports indicate that atypical antipsychotics, with their combined dopamine D₂ and serotonin 5-HT₂ antagonism, may exacerbate or cause OC symptoms in patients with schizophrenia [61–63], although this phenomenon has not been shown in a controlled trial [64]. Case reports also suggest that serotonin reuptake inhibitors may be added effectively to an atypical antipsychotic to target OC symptoms in patients with schizophrenia [65]. A report suggests that the atypical antipsychotic risperidone may enhance treatment response in some patients with OC disorder [66].

Although cognitive behavioral therapy has a role in the treatment of OC disorder [67], to the authors' knowledge nonpharmacologic approaches to OC symptoms in schizophrenia have not been studied systematically. The potential value of cognitive behavioral therapy in this patient population may be influenced by a patient's level of cognitive function and degree of insight [68]. Given the frequency of OC symptoms in schizophrenia, more work is necessary to clarify their clinical correlates and prognostic significance and optimal treatment strategies.

Comorbid substance abuse

The lifetime prevalence of alcohol or substance use disorder (abuse or dependence) in patients with schizophrenia ranges from 10% to 60% [69]. The Epidemiologic Catchment Area study reported that 47% of patients with schizophrenia have a serious problem with substance use during their lifetime compared with 16% of the general population [70]. Rates of nicotine use in these patients have been reported to range from 58% to 90% [71]. Excluding nicotine, alcohol use disorder is the most frequent co-occurring disorder in schizophrenia [72]. Of illicit substances, patients with schizophrenia preferentially use cannabis [73], although cocaine abuse is also common, especially in the inner cities [74]. Similar to the general population, men are disproportionately represented among patients who use substances [75].

The use of drugs and/or alcohol complicates the course of illness and the treatment for patients with schizophrenia. For these individuals, even regular use of fairly small amounts of alcohol can have negative effects [76]. Patients who are comorbid for schizophrenia and substance use are at

increased risk for infectious diseases, such as HIV, hepatitis B, and hepatitis C [77]. The use of alcohol and drugs is associated with treatment noncompliance, clinical exacerbations and poorer global functioning, relapse, an increased rate of hospitalizations, and higher rates of homelessness [72,78–81]. Comorbid alcohol and drug use worsens the course of illness for all patients with schizophrenia, including patients in their first episode [82]. Cannabis use disorder is reported in more than 50% of first-episode patients [83], and the use of cannabis in this population may cloud the diagnosis of a psychotic disorder and lengthen the time before treatment is initiated [84]. The financial and emotional toll of an already devastating illness is compounded by a comorbid alcohol or drug use disorder [85].

Several authors have proposed a “self-medication” hypothesis to explain the use of alcohol and other substances by patients with schizophrenia—to lessen negative symptoms and extrapyramidal system side effects of antipsychotic medications [86,87]. Although nicotine and substances of abuse may decrease negative symptoms and extrapyramidal system effects [88], these apparent beneficial effects may not be *causally* related to the substance use. Two groups reported that patients with fewer negative symptoms use substances more frequently [89,90]; in addition, first-episode patients, who have not yet had exposure to antipsychotic treatment, are likely to use substances.

As an extension of the self-medication hypothesis, based on findings from animal studies [91], Green and colleagues [12] proposed a neurobiologic formulation, suggesting that the high rates of comorbid alcohol and substance use disorders in these patients may relate to a deficiency in their dopamine-mediated mesocorticolimbic brain reward circuits and to the ability of alcohol and substances of abuse to ameliorate this deficiency. A related formulation regarding the vulnerability to substance abuse in patients with schizophrenia has been proposed by Chambers and colleagues [92]. In patients with schizophrenia, alcohol and drugs may reduce negative symptoms and extrapyramidal effects, while enhancing the brain reward systems by acting to improve the “signal detection” capability of dopamine-rich systems [12,93,94].

Detection and management of substance abuse

Substance abuse is often neither detected nor addressed in mental health settings [95]. In part, this situation may be due to the traditional separation between mental health and substance abuse services. Clinicians should ask patients about use of drugs and alcohol, understanding that use may be denied. Screening can be assisted through the use of standardized measures, especially instruments specifically developed for patients with mental illness (eg, the Dartmouth Assessment of Lifestyle Instrument [96]). When possible, clinicians also should pursue collateral reports from family members, case managers, and others involved in the delivery of services to the patient.

Patients with schizophrenia and a comorbid alcohol or substance use disorder require specialized treatment for both disorders [97]. This can be

accomplished in a number of ways: sequential treatment, parallel treatment, or integrated treatment of the disorders [98]. Integrated treatment programs generally are accepted as the preferred method of treatment by patients and clinicians [76]. Such programs deliver psychosocial treatment and substance abuse services and provide medication management [99]. Drake and associates [100] noted that the effective treatment of these patients involves (1) staged interventions (tailored to the patient's degree of willingness to engage in treatment), (2) assertive outreach [101], (3) motivational interviewing [102], (4) comprehensive services (including medication management) [98,100], (5) social support intervention, and (6) a long-term perspective (eg, an understanding that treatment takes place over months and years).

Pharmacotherapy for patients is still evolving, and there is no standardized treatment approach that meets the needs of all patients [103,104]. Pharmacologic agents can be used to decrease symptoms of schizophrenia and improve overall functioning; a few agents may lead to a decrease in substance use (see later). Optimally, medications serve to potentiate psychosocial treatments, and psychosocial treatments can serve to increase medication compliance.

Patients with comorbid substance abuse tend to respond poorly to typical antipsychotics. Although these medications are effective for the underlying psychosis, their side effects may cause patients to use drugs and alcohol in an attempt to diminish these effects [87]. The novel antipsychotics may have important advantages for these patients however because they produce fewer extrapyramidal symptoms, are more effective in reducing at least some negative symptoms, and may improve cognitive dysfunction [105,106]. The medication that has received the most attention for its utility in patients with comorbid substance use is the novel antipsychotic clozapine.

Several anecdotal reports suggesting that clozapine may limit drug and alcohol use in patients have appeared in the literature. These case reports have described clozapine's apparent ability to reduce alcohol use [107], substance use [108], cocaine craving [109], and cigarette smoking [110]. Two preliminary studies from the authors' group, one naturalistic [111] and the other retrospective [112], showed greater than 70% reduction in alcohol use in patients taking clozapine to treat schizophrenia; striking reductions in use of cannabis (67–80%) and cocaine (80%) also were noted. The findings from the case reports and the studies of our group regarding the beneficial effects of clozapine have been supported further by reports from Buckley and colleagues [113] and Lee and associates [114].

Fewer data exist on the effects of other atypical antipsychotics in these patients. A retrospective study from the authors' group suggested that risperidone is less likely than clozapine to reduce alcohol and cannabis use [115]. Smelson and colleagues [116] reported, however, that risperidone seemed to help schizophrenic patients who used cocaine remain in treatment, reduce relapse, and have lower craving scores than patients treated with a typical neuroleptic. A report by Albanese [117] on bipolar patients with comorbid substance use

disorders suggested that risperidone use was associated with maintenance of abstinence in these patients and a report by Brown and associates [118] suggested that, in a group of psychiatric patients with comorbid stimulant abuse, quetiapine was associated with decreased craving for cocaine. To the authors' knowledge, there are no data available on whether olanzapine, ziprasidone, or aripiprazole limit alcohol or substance use in these patients.

Although many studies are under way to investigate the potential role of pharmacotherapy in people with alcohol or other substance use disorders (but who do not have schizophrenia), few agents have been studied in patients with schizophrenia and comorbid alcohol and substance use disorders. Disulfiram has been used with safety and some success in this patient population [119], although it must be used with caution because of its potential ability to increase psychosis [120]. Three groups [121–123] have reported that naltrexone may have some value in decreasing alcohol in comorbid patients. Lastly the tricyclic antidepressants, desipramine or imipramine, have been shown in preliminary studies to have a potential role in comorbid patients, especially patients with comorbid cocaine disorder [124,125].

Suicide

Although suicide is a problem for the general population (the ninth leading cause of death in the United States), among people with schizophrenia it is the leading cause of premature death [126]. Nearly 50% of patients with schizophrenia attempt suicide, and their lifetime risk of suicide is 10% [127], a risk 10-fold higher than in the general population, as high as patients with affective disorders [128].

Suicide in patients with schizophrenia has been associated with hopelessness and a sense of disappointment over failure to meet high expectations [129]. It has been suggested that suicide by patients with schizophrenia can be a “nonpsychotic reaction to a severe illness” [130]. This notion is supported by data suggesting that patients with higher levels of awareness of their illness are at increased risk for suicide [131].

One of the strongest predictors of suicide in these patients is having a history of previous suicide attempts [132,133]. As in the general population, male gender also seems to be a risk factor [133]; men with schizophrenia commit suicide at an earlier age than women [132]. Drake and Cotton [134] found that patients with schizophrenia who succeed in a suicide attempt are more depressed and isolated than those who do not. The risk of suicide risk is elevated after discharge from a psychiatric hospitalization [133] and can remain elevated for the first 3 months after discharge [132]. Patients who kill themselves have been found to have been more “improved” on discharge from the hospital, although they tended to have returned to more isolated living arrangements [26].

An early age of onset of schizophrenia has been found to be a risk factor for suicide [135], and the early phase of illness is a time of increased risk [130]. Suicide most often occurs during the active phase of the illness

[136]. Patients with prominent negative symptoms may have a reduced risk for suicide compared with patients with positive symptoms, especially suspiciousness and delusions [137]. Although substance abuse is an established risk factor for suicide in the general population [138], to date, it has not been clearly shown to be a risk factor among patients with schizophrenia [135]. Kaplan and Harrow [139] found that poor overall functioning is a risk factor for suicide in patients with schizophrenia.

Detection and management of suicidality

The detection of suicidal ideation in patients with schizophrenia can be difficult. Suicide in schizophrenia can be an impulsive act, which makes prediction difficult [140]. Schizophrenic patients who kill themselves may not disclose their intentions in advance [141], and they tend to choose highly lethal methods for suicide [136]. Studies of this population found that 49% to 96% of patients had been seen by a health care professional within 3 months of committing suicide [136], and at least half had been seen the week before their suicide [132].

Harkavy-Friedman and Nelson [142] suggested that psychosocial and biologic issues be addressed carefully when working with schizophrenic patients presenting with suicidal behavior. Because discharge from the hospital can lead to social isolation [26], follow-up treatment is essential. Services should be set up before discharge. When the patient is discharged, intensive outreach often is required to engage patients in treatment and to prevent the social isolation that can occur. Referral and engagement in day treatment can help address this isolation.

Psychopharmacologic interventions also need to be assessed. In a study of 88 patients with schizophrenia who died by suicide, Heilae and coworkers [143] found that more than half of the patients who committed suicide either were prescribed inadequate doses of neuroleptic treatment or were not compliant with treatment; an additional 23% were considered to be not responsive to treatment. Obviously, optimal treatment for psychosis and affective symptoms is essential, as is an attempt to limit alcohol and substance abuse.

Studies suggest that clozapine, an atypical antipsychotic, may decrease rates of suicide. Meltzer and Okayli [144] followed 88 treatment-resistant patients for 7 years and found that the number of patients with *no suicidality* increased with clozapine treatment (from 53% of the group before clozapine to 88% during treatment with clozapine). Moreover, a review of current and former users of clozapine found that clozapine reduced mortality, mostly through a decrease in the suicide rate [145]. Reid and associates [146], in a review of suicide rates in more than 30,000 patients, concluded that patients with schizophrenia or schizoaffective disorder who were treated with clozapine showed a substantially reduced risk of suicide. Lastly, in a study of over 900 patients with schizophrenia, Meltzer and colleagues [147] found that clozapine was more likely than olanzapine to decrease suicidality in patients at risk for suicide.

Psychoeducation may increase compliance with treatment, although there may be an increased risk for suicide in patients who have more awareness and understanding of their illness [131]. Listening to patient reports and subjective experience of their distress is crucial because it has been shown to be a predictor of suicide [148]. Optimal treatment for patients with schizophrenia who are at risk of suicide includes careful assessment of risk factors for suicide, the use of active outreach to engage patients, referral to day programs after discharge to address social isolation, and effective pharmacotherapy.

Detection and management of medical comorbidity

The rate of physical disease among patients with serious mental illness is increased compared with the general population [2,149,150]. Goldman [5] estimated that nearly 50% of patients with schizophrenia suffer from at least one comorbid medical condition; Allebeck and Wistedt [151] found a nearly twofold increase in overall mortality compared with the general population. Although patients with schizophrenia are at particular risk for suicide and accidental death, they also are at risk for premature death from comorbid medical conditions [7].

Increased incidence of cardiovascular, pulmonary, and infectious disorders has been reported in patients with schizophrenia compared with psychiatric and normal controls [152]. These patients also seem to be at risk for psychogenic polydipsia [153] and osteoporosis [154]. In a study surveying more than 700 patients with schizophrenia, Dixon and colleagues [4] described self-reported problems with “eyesight, teeth, high blood pressure, and bowels” to be the most commonly noted lifetime medical conditions. Of particular concern within this study was the finding that lifetime and current rates of diabetes mellitus were far greater than those seen in the general population. Patients with schizophrenia seem to be at increased risk for contracting HIV and hepatitis B and C [155]. Several studies report higher than expected death rates from cardiovascular, pulmonary, infectious, gastrointestinal, and endocrine disorders in patients with schizophrenia [150,152,156–159].

Co-occurring illnesses in patients with schizophrenia often are undiagnosed or come to clinical attention at acute, or advanced, phases when the disease is severe, painful, or life-threatening [150,160]. Patients with schizophrenia are less likely to receive adequate health care as a result of barriers that are related to the health care system (eg, lack of health insurance and stigmatization by health care providers) and to the patients themselves (eg, poor communication skills and nonadherence with treatment) [5]. Additionally, patients with schizophrenia may have increased pain tolerance compared with the general population [161]. This sensory deficit may lead to reduced reporting of physical problems and contribute to morbidity in these patients [2].

In addition to the systemic barriers to health care access and the intrinsic patient factors that may lead to increased medical comorbidity, certain

lifestyle factors and the use of antipsychotic medications (with their attendant side effects) place patients at considerable risk for serious, at times life-threatening conditions. Fortunately, some of the unhealthy habits and medication side effects may be modified successfully with clinical intervention. It is important for the clinician to recognize and minimize these factors to improve the long-term health status of these vulnerable patients.

Detecting and managing lifestyle factors

Lifestyle factors, such as cigarette smoking, substance abuse, poor nutrition, and lack of exercise, may place patients with schizophrenia at increased risk for certain physical disorders [162]. Although some lifestyle factors may be secondary to isolation and poverty [163] and more difficult to impact, others may be altered with appropriate health promotion intervention.

Cigarette smoking

Cigarette smoking is the most preventable cause of death in society [164] and the prevalence of cigarette smoking in patients with schizophrenia is up to three times that found in the general population [15]. Not surprisingly, smoking-related disease seems to be more prominent among these patients than in the general population [156]. Some studies have suggested, however, that patients with schizophrenia have lower than expected cancer rates, particularly lung cancer [152]. Although this counterintuitive finding has led some investigators to speculate that schizophrenia may confer a selective advantage against cancer [165], this hypothesis is not yet substantiated [166]. Nonetheless, cardiovascular and pulmonary diseases, which typically are associated with cigarette smoking, consistently are reported to be the most frequent causes of medical comorbidity and mortality in patients with schizophrenia [151,157,158].

Although smoking cessation may be more difficult for people with schizophrenia than for others [167], clinicians still should discuss the hazards of smoking and encourage patients to reduce their cigarette consumption. Some evidence suggests that group therapy combined with a nicotine patch may be effective in helping patients with schizophrenia reduce smoking [168]. Cigarette smoking among these patients may be more than just a “bad habit,” however. One small study showed that haloperidol was associated with an increase in smoking and nicotine levels [169], whereas others suggest that switching treatment from typical antipsychotics to clozapine may lead to a decrease in smoking [110,170]. A controlled study [168] suggested that atypical antipsychotic medications may facilitate smoking cessation more than typical agents. Data also are emerging about the beneficial effects of bupropion combined with psychotherapy on nicotine addiction in this patient population [171]. Pharmacologic and psychosocial interventions may be useful in assisting patients to reduce smoking and ultimately, it is hoped, smoking-related disease and mortality.

HIV and hepatitis risks

Although alcohol and substance abuse were discussed earlier, they may contribute independently to the increased rates of certain medical disorders in patients with schizophrenia, in particular HIV and hepatitis B and C [77,172,173]. Other behavioral factors, such as having multiple partners and engaging in unsafe sexual practices, may place patients with schizophrenia at increased risk for sexually transmitted diseases [174]. Clinicians should obtain information about patients' sexual practices, provide education about safe sex, and when indicated test for HIV and hepatitis. The psychiatric care of patients with schizophrenia and HIV/AIDS or hepatitis should occur in close collaboration with infectious disease or gastroenterology specialists.

Exercise and diet

Compared with the general population, patients with schizophrenia seem to exercise less and to eat a diet higher in fat and lower in fiber [162]. Data from the 1989 National Health Interview Survey (NHIS) indicated that individuals with schizophrenia have body mass index distributions similar to or higher than the general population [175]. Allison and colleagues [176] found that although there may be a small subpopulation of underweight patients with schizophrenia, as a whole, this population is as obese or more obese than people without schizophrenia; the prevalence of overweight and obesity in patients with schizophrenia is 40% to 62% and may be particularly high in women [176,177]. Obesity may contribute to the increased rates of cardiovascular disease, type 2 diabetes, hypertension, dyslipidemia, and sleep apnea reported in patients with schizophrenia [178–180]. Although atypical antipsychotics produce clinically significant weight gain [181,182] (see later), earlier studies (such as the NHIS) suggested that obesity among patients with schizophrenia was common before the widespread use of these medications. In addition to medication effects and patient-based endogenous factors, lifestyle factors, such as poor diet and lack of exercise, may play an important role in the development of obesity in these patients.

Detecting and managing antipsychotic medication side effects

Adverse effects of antipsychotic medications can increase medical morbidity. Waddington and coworkers [183] found that treatment with more than one antipsychotic concurrently was associated with reduced survival, although the causal link is not known. Although typical antipsychotics can cause extrapyramidal effects, tardive dyskinesia, and hyperprolactinemia, some atypical antipsychotics seem to cause medically significant weight gain and altered glucose and lipid metabolism [179,181,184,185]. Additionally, some typical and atypical antipsychotics, such as thioridazine and ziprasidone, may prolong the QTc interval of the electrocardiogram, potentially increasing the risk of arrhythmia [186]. Although clozapine is the most effective treatment for schizophrenia, it carries the risk of causing agranulocytosis

(0.4%) [187] and a risk that is greater than other antipsychotics of producing seizure (5% at moderate doses) [188]. Clozapine seems also to be associated with a rare (but increased) risk of myocarditis [189,190].

Common antipsychotic medication side effects, including extrapyramidal effects and tardive dyskinesia, are well described in the literature [191], and a detailed discussion of them is beyond the scope of this article. Because the common endocrine and metabolic effects of these medications may contribute to the increased medical morbidity in patients with schizophrenia, however, further discussion of their detection and management is warranted here.

Hyperprolactinemia

Typical antipsychotics and risperidone have the potential to elevate serum prolactin levels, whereas several atypical antipsychotics are less likely to do so [192]. Although early studies of the long-term effects of antipsychotic-induced hyperprolactinemia reported few negative consequences of prolactin elevation [193], it is a topic that has received limited investigation. Hyperprolactinemia resulting from medical illness is known to produce galactorrhea, hypogonadism (evidenced by sexual and menstrual dysfunction and diminished gonadal hormone levels), and osteoporosis, all of which also have been reported in patients with schizophrenia [154,194–197]. With the exception of studies on galactorrhea [194], few investigations directly assessed the relationship between actual prolactin levels and these conditions in patients with antipsychotic-induced hyperprolactinemia. Interestingly, a few reports have failed to find a close relationship between prolactin levels and sexual and menstrual dysfunction [195,198,199] or between prolactin and gonadal hormone levels [200].

Although the potential long-term health consequences of chronic antipsychotic-induced hyperprolactinemia have not been established firmly, clinicians should inquire about the possible adverse effects of hyperprolactinemia and aim to diminish them. Galactorrhea and sexual and menstrual dysfunction, associated with prolactin elevation, may be minimized by dose reduction or by a medication change to an antipsychotic with less prolactin-elevating potential [192,201]. Moreover, case reports suggest that dopamine agonists (eg, bromocriptine and cabergoline), although they have the potential to worsen psychosis, may alleviate hyperprolactinemia and associated hypogonadism if added to typical antipsychotics or risperidone [202,203]. Lastly, since sustained hyperprolactinemia can increase the risk for osteoporosis [154], patients who require long-term treatment with antipsychotics and have shown continued hyperprolactinemia may be appropriate candidates for screening with bone densitometry.

Weight gain, diabetes, and hyperlipidemia

Studies suggest that 50% of patients taking antipsychotic medication experience clinically significant weight gain [204]. As a class, atypical antipsychotics consistently have been shown to cause more weight gain than the typical agents [181,205]. In a large meta-analysis comparing weight gain

associated with a variety of atypical and typical antipsychotics, Allison and co-workers [181] found, after 10 weeks of treatment, a mean weight gain of 9.8 lb with clozapine, 9.1 lb with olanzapine, and 4.6 lb with risperidone compared with 2.4 lb with haloperidol. The authors found the atypical antipsychotic ziprasidone to be associated with less than a 1 lb weight gain and the typical agent molindone to be associated with a small weight loss. Antipsychotic-induced weight gain is usually most rapid in the acute phase of treatment, then tends to plateau after 1 to 2 years [206]. Younger patients and patients with a low baseline body mass index may be more susceptible to atypical antipsychotic-induced weight gain [207]. This noticeable and often unacceptable side effect may threaten medication compliance and increase obesity-related comorbidities, such as diabetes and serum lipid abnormalities [178,181].

In addition to causing clinically significant weight gain, the atypical antipsychotics (especially clozapine and olanzapine) have been implicated in rare cases of ketoacidosis and in an increased risk of type 2 diabetes mellitus, a condition that is estimated to be twice as prevalent in patients with schizophrenia compared with the general population [179,182,208,209]. Although clozapine is the most effective treatment for refractory schizophrenia, the cumulative incidence of diabetes among long-term clozapine patients may be as high as 35% [179]. It must be recognized, however, that although antipsychotics may result in impaired glucose tolerance and type 2 diabetes, especially in patients with other risk factors (eg, family history) [182], schizophrenia itself may be a risk factor for diabetes [209].

Obesity, including antipsychotic-induced obesity, also is associated with serum lipid abnormalities. Studies suggest that clozapine and olanzapine are associated with hypertriglyceridemia [179,185]. The novel antipsychotic ziprasidone may be associated with a reduction of cholesterol and triglycerides, independent of changes in weight [210].

Detecting and managing weight gain and obesity-related conditions associated with atypical antipsychotic medications are essential to ensure optimal treatment outcome and to minimize iatrogenic medical comorbidity. Patients should be educated about the potential for weight gain, counseled about dietary choices, encouraged to exercise, and weighed frequently. Although data are limited, there is some suggestion that behavioral weight reduction programs that teach problem-solving skills and that use reinforcement (to compensate for cognitive deficits) and incremental approaches to behavioral change may be successful in patients with schizophrenia [178,211,212]. In a small study evaluating a Weight Watcher's program for patients with olanzapine-related weight gain, however, only the men experienced significant weight loss [213].

Use of some centrally acting weight loss drugs in this population theoretically is limited by their potential to increase biogenic amine activity and possibly to exacerbate symptoms of psychosis. An open trial of amantadine, used in 12 patients with olanzapine-associated weight gain, was well tolerated,

however, and resulted in a 3.5-kg average weight loss [214]. Additionally, case reports described the successful use of nizatidine [215] and topiramate [216] in reducing weight gain associated with olanzapine and clozapine. Lastly, although there have been no clinical trials, there may be a potential role for the non-centrally acting weight control drug orlistat [178].

Because atypical antipsychotics seem to increase weight and potentially alter glucose and lipid metabolism, they should be administered with care in patients with risk factors for diabetes and cardiovascular disease. These patients may benefit from a baseline fasting glucose and lipid panel assessment, with follow-up monitoring and, if indicated, measurement of glycohemoglobin and glucose tolerance testing [179]. Patients who develop glucose intolerance or diabetes may require treatment with hypoglycemic agents, and patients with hyperlipidemia may require lipid-lowering agents. These simple interventions, which seem to be overlooked frequently by psychiatrists [179], may be important in minimizing the overall morbidity of patients with schizophrenia.

Summary

Approximately half of patients with schizophrenia have at least one comorbid psychiatric or medical condition, worsening prognosis and contributing to the high rate of morbidity and mortality. Depression is associated with suicide, the leading cause of premature death in patients with schizophrenia; obsessive-compulsive symptoms may worsen prognosis; alcohol and substance use disorders are associated with a poor outcome; and comorbid medical conditions, including cardiac and pulmonary disease, infectious diseases, diabetes, hyperlipidemia, hypogonadism, and osteoporosis, are often underrecognized and undertreated. The new generation of antipsychotic medications has improved the potential outcome of patients with schizophrenia. Providing optimal treatment for patients and fully realizing the potential of these new agents require focused attention on detection, recognition, and treatment of comorbid psychiatric and medical conditions in patients with schizophrenia.

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