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Psychiatric Comorbidities and Schizophrenia

Peter F. Buckley[1,2], Brian J. Miller[2], Douglas S. Lehrer[3], and David J. Castle[4]

[2]Department of Psychiatry, Medical College of Georgia, 997 St Sebastian Way, Augusta, GA 30912; [3]Wright State University Boonshoft School of Medicine and the Wallace-Kettering Neuroscience Institute; [4]ST. Vincent's Health and the University of Melbourne

Psychiatric comorbidities are common among patients with schizophrenia. Substance abuse comorbidity predominates. Anxiety and depressive symptoms are also very common throughout the course of illness, with an estimated prevalence of 15% for panic disorder, 29% for posttraumatic stress disorder, and 23% for obsessive-compulsive disorder. It is estimated that comorbid depression occurs in 50% of patients, and perhaps (conservatively) 47% of patients also have a lifetime diagnosis of comorbid substance abuse. This article chronicles these associations, examining whether these comorbidities are "more than chance" and might represent (distinct) phenotypes of schizophrenia. Among the anxiety disorders, the evidence at present is most abundant for an association with obsessive-compulsive disorder. Additional studies in newly diagnosed antipsychotic-naive patients and their first-degree relatives and searches for genetic and environmental risk factors are needed to replicate preliminary findings and further investigate these associations.

Key words: schizophrenia/comorbidity/substance abuse

The clinical heterogeneity of schizophrenia is indisputable. Virtually no 2 patients present with the same constellation of symptoms. Moreover, even in the same patient, symptoms can show dramatic change over time, and there is significant interplay between different sets of symptoms: eg, "secondary" negative symptoms might be ameliorated with resolution of positive symptoms, while core "deficit" negative symptoms are more enduring but can worsen over the longitudinal course of illness. Such observations give way to considerations that these may even constitute groups of diseases of generally common phenotypic expression but of different underlying etiopathology.[1]

Further complicating the clinical picture of schizophrenia as well as understanding the boundaries and etiology of this condition is the substantial psychiatric comorbidity.[2] Depression, anxiety, and substance abuse are common accompaniments of the schizophrenia condition, and they in turn perturb the clinical picture.[3] For example, depression can cause secondary negative symptoms, panic attacks can drive paranoia, and cannabis abuse can worsen positive and disorganization symptoms. Conversely, depressive symptoms seen in the context of a florid psychotic relapse often resolve with treatment of the positive symptoms but may remerge in the "post-psychotic" state and in turn worsen the longitudinal course of the illness.[4,5]

Nosologists have great difficulty dealing with complex sets of symptoms.[3,6,7] Generally, an implicit or explicit hierarchy is embraced, such that schizophrenia "trumps," depression, and anxiety. Or, if no primacy can be determined, resort is made to labels such as "schizoaffective disorder" or even "schizoobsessive" subtype of schizophrenia.[3,8] An alternative approach, reified in *Diagnostic and Statistical Manual of Mental Disorders*, is to consider these symptoms as part of another axis I diagnosis that is occurring alongside schizophrenia.[9] Under this scenario, the patient has 2 major conditions, and these have co-occurred (perhaps for some etiological reason common to both disorders). This is very much the model considered—and clinically endorsed—when a patient with schizophrenia also has an alcohol dependence or drug addiction problem.[10] Additionally, recent work on the potential biological vulnerability to cannabis abuse that might explain some variance in the risk of later developing schizophrenia raises again the proposition that the clinical associations that we commonly observe in schizophrenia may also have biological and potentially etiopathological significance. [11]

Bermanzohn et al[12] provocatively proposed that we "stake out the midground"; they suggest that psychiatric comorbidities are so common that they might be integral to schizophrenia. To a large extent, our current research in clinical trials and neurobiological studies is increasingly coming in line with this proposition because now such studies support broad inclusion criteria of "all comers" … the schizophrenia patients whom we see in everyday clinical practice, who have prominent anxiety

[1]To whom correspondence should be addressed; tel: 706-721-6719, e-mail: pbuckley@mcg.edu.

symptoms, or may also have depressive symptoms, and also abuse drugs and alcohol.

The purpose of this article is to "take stock" of these (anxiety, depression, and substance abuse) comorbidities and their relationship to schizophrenia. Reviewing the relevant epidemiological, genetic/familial, neurobiological, and therapeutic literature, we ask whether comorbidities should be considered:

- to have simply, by chance, co-occurred with schizophrenia;
- to have manifested "secondary" to the core disorder, schizophrenia;
- to have manifested because schizophrenia is more common in this core disorder; or
- are a consequence of some underlying shared liability to both sets of disorders.

Schizophrenia and Anxiety

There is an increased prevalence of anxiety disorders among patients with schizophrenia compared with the general population.[13] These include panic disorder, posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), generalized anxiety disorder, and social anxiety disorder. Prevalence estimates are influenced by heterogeneity among definitions of symptoms and rating instruments used for diagnosis. Other diagnostic issues complicating the study of anxiety in schizophrenia are that symptoms may occur spontaneously, intermittently, in direct response to psychotic symptoms, and/or as a side effect of antipsychotic medications. Here, we will focus on panic disorder, PTSD, and OCD, the 3 anxiety disorders that have been most extensively studied in patients with schizophrenia.

Panic Attacks and Panic Disorder

Two studies from the National Institute of Mental Health Epidemiologic Catchment Area survey found a 28%–63% (across the 5 study sites)[14] and 45%[15] prevalence, respectively, of panic attacks in patients with schizophrenia. Two other studies from the ECA survey[16,17] found a lifetime odds of $\geq$35 for having panic disorder in subjects with (compared with those without) a diagnosis of schizophrenia. In total, 27 published studies have investigated the epidemiology of panic symptoms among patients with schizophrenia.[12,14–39] (see Table 1) The prevalence of panic attacks (7.1%–63%) and panic disorder (3.3%–29.5%) vary widely across these studies. A weighted average of the available data from these (heterogeneous) studies crudely estimates a 25% prevalence of panic attacks and a 15% prevalence of panic disorder in patients with schizophrenia (data not shown). By comparison, the lifetime prevalence of panic disorder in the US general population ranges from 2.0%–5.1%.[17,40,41]

The majority of studies of panic attacks/disorder focused on patients with chronic schizophrenia. Two studies, however, investigated the prevalence of panic symptoms in patients with first-episode psychosis (FEP), which reduces confounding by medications and other factors. Strakowski et al[35] found that of 102 consecutive patients hospitalized FEP patients, 6% met *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*, criteria for panic disorder. The authors also found poorer initial outcomes in patients with comorbid panic disorder. In another study, Craig et al[24] examined panic symptoms in 225 patients with first-admission psychosis (schizophrenia or schizoaffective disorder) participating in the Suffolk County (NY) Mental Health Project. Panic symptoms were present at baseline in 11.2% of patients. Furthermore, patients with baseline panic symptoms were significantly more likely to exhibit positive symptoms of psychosis after 24 months.

Evidence from 3 studies[18,19,31] suggests that panic symptoms may be more common in patients with paranoid schizophrenia, compared with other schizophrenia subtypes or schizoaffective disorder. Furthermore, panic attacks were frequently related to paranoid ideations in these studies. Bermanzohn et al[43] described the potential for a relationship between panic attacks to paranoia. Comorbid panic symptoms may be associated with more severe psychopathology,[22,23,30,36,37] as well as increased risks of suicidal ideation and behavior,[26,45,46] and may also increase vulnerability to comorbid substance use.[28]

In a contrasting approach to the epidemiology of this association, another study from the ECA survey by Tien and Eaton[42] found that the presence of panic attacks was associated with a 2.28-fold increased risk of developing schizophrenia. The temporality of this association suggests that, for some patients, the presence of panic attacks may be part of the psychosis prodrome.

Weissman et al[47] reported on a potential syndrome with genetic linkage to chromosome 13q32 (marker D13S779) in 34 families segregating for panic disorder. In addition to panic disorder, these patients also had an excess of urologic problems, headaches, thyroid problems, and/or mitral valve prolapse. This region of chromosome 13 (13q32–34) encodes the G72/G30 gene complex (G72 is also known as D-amino acid oxidase activator or DAOA), which has been linked to schizophrenia in multiple studies, as reviewed in a recent meta-analysis.[48] Additional studies are needed to investigate potential shared genetic risk factors for schizophrenia and panic disorder.

Family and twin studies support the biological plausibility of an association between schizophrenia and panic disorder. Heun and Maier[29] reported on the only family study of panic disorder in schizophrenia. They assessed a total of 1068 first-degree relatives of 59 patients with

schizophrenia, 54 patients with panic disorder, 29 patients with panic disorder and schizophrenia, and 109 controls. They found a significantly increased prevalence of primary panic disorders among relatives of patients with schizophrenia (4.3%) compared with controls (0.9%) but not compared with subjects with panic disorder. Furthermore, there was not an increased risk of schizophrenia among relatives of patients with either panic disorder (0%) or control subjects (0.3%). In a sample of $N = 24$ twin pairs discordant for schizophrenia and $N = 3327$ twins without schizophrenia from the Vietnam Era Twin Registry, Lyons et al[32] found that the nonaffected co-twins of schizophrenia probands had a 3-fold increased odds of panic disorder compared with control twins. This finding did not reach statistical significance, but the results were limited by the small sample size of the study.

One large family study found an increased prevalence of panic disorder in first-degree relatives of patients with schizophrenia. However, the present evidence supporting the hypothesis that panic disorder is part of the syndrome of schizophrenia is limited, subject to confounding, and findings are in need of replication. Additional studies in drug-naive patients and their first-degree relatives, controlling for potential confounding factors are also needed to further investigate this association. Twin studies might also contribute to our knowledge base in this regard.

Posttraumatic Stress Disorder

Trauma histories are common in patients with schizophrenia, and childhood trauma is a risk factor for psychosis.[49] Patients with schizophrenia may be at increased risk for exposure to trauma, due to illness-related features, environmental influences, and/or comorbid substance use. Many factors complicate the diagnosis and investigation of co-occurring PTSD and schizophrenia, including the presence of psychotic symptoms within the context of PTSD, or PTSD symptoms—such as reexperiencing the trauma—that may mimic psychotic symptoms. Furthermore, psychotic symptoms (eg, hallucinations and delusions) or experiences (eg, involuntary hospitalization, seclusion, restraint, forced medications) may themselves be a traumatic event contributing to PTSD,[50–54] though they have not been uniformly considered as a potential precipitating stressor.

A total of 20 published studies have reported on the epidemiology of PTSD in schizophrenia. [32,34,36,39,51–66] (see Table 2) These samples, including those which considered psychosis-related symptoms or experiences, found a prevalence of PTSD among patients with psychosis 0%–67%. A weighted average of the available data from these (heterogeneous) studies crudely estimates a 29% prevalence of PTSD in patients with schizophrenia, compared with a 7.8% estimated lifetime prevalence of PTSD in the US general population.[67]

While the majority of these studies focused on patients with chronic schizophrenia, Strakowski et al[66] found that 4 of 18 (22%) patients with a schizophrenia-spectrum disorder met criteria for PTSD antecedent to their first psychotic episode. The diagnosis of PTSD predated the onset of the psychotic disorder by more than 1 year in 2 of these 4 patients. In a cohort of 170 patients with a FEP, Neria et al[62] found a 10% prevalence of PTSD.

The presence of PTSD has also been shown to be associated with more severe psychopathology (including cognitive impairments)[56,58,70,71], higher rates of suicidal ideation and suicidal behaviors,[68] and more frequent outpatient physical health visits and hospitalizations[69] in patients with schizophrenia.

Although a majority of studies found an increased prevalence of PTSD in excess of that in the general population, including inpatients with both FEP and chronic schizophrenia, there is little other evidence to support the hypothesis that PTSD is part of the illness of schizophrenia. The increased prevalence may be largely accounted for by environmental factors, particularly increased rates of exposure to childhood trauma or as the direct result of psychosis-related trauma. Factors, both clinical and neurobiological, that confer increased vulnerability to PTSD in patients with schizophrenia have been largely unexplored. We are aware of no published genetic or family studies of patients with schizophrenia and PTSD. In the twin study of Lyons et al,[32] nonaffected monozygotic cotwins of schizophrenia probands had a nonsignificant increased odds of PTSD compared with control twins.

Obsessive-Compulsive Disorder

Obsessive-compulsive symptoms (OCS) and OCD have been frequently studied in patients with schizophrenia (see Table 3), with the majority showing an increased rate of both OCS and OCD in schizophrenia. A study from the ECA survey[14] found a 12.5-fold increased odds of having OCD given a diagnosis of schizophrenia. By contrast, another study from this survey[42] found a 3.77-fold increased risk of schizophrenia among patients with OCD, suggesting that, for some patients, the presence of OCD may be part of the psychosis prodrome. A total of 36 studies have investigated the epidemiology of OCS/OCD among patients with schizophrenia.[12,15,16,19–21,23–25,28,34–36,38–40,65,66,72–87] (see Table 3) The prevalence of OCS (10%–64%) and OCD (0%–31.7%) vary widely across these studies and may have been overestimated due to difficulties in distinguishing clinically obsessions and delusions. It may be very difficult to determine whether the patient is experiencing an obsession or a delusion, especially when an obsession is held with firm conviction. A weighted average of the available data from these (heterogeneous) studies crudely estimates a 25% prevalence of OCS and a 23% prevalence of OCD in patients with

schizophrenia. OCS are present throughout the course of schizophrenia. Several studies have suggested that OCS manifest as part of the psychosis prodrome.[88–91] Two studies[72,91] found that the presence of OCS was associated wither earlier age of onset of psychosis. Additionally, 3 studies[35,66,84] have found an 11.0%–15.2% prevalence of OCD in patients with FEP.

Several studies have directly compared clinical features of schizophrenia with or without comorbid OCD. In a study of 22 adolescents with schizophrenia and OCD matched for age, gender, and number of hospitalizations with 22 adolescents with non-OCD schizophrenia, Poyurovsky et al[91] found that patients with schizophrenia and OCD had earlier age of onset of illness and more OCD-spectrum disorders, including primary tic disorders. There was no difference in the severity of schizophrenia symptoms based on the presence or absence of OCD. In a majority of patients in this study, OCS either preceded or co-occurred with the onset of schizophrenia. Poyurovsky et al[92] also compared 100 patients with schizophrenia and OCD, 100 patients with schizophrenia but no OCD, and 35 patients with OCD alone. They found an increased prevalence of OCD-spectrum disorders, including body dysmorphic disorder and tic disorder, among patients with schizophrenia and OCD vs non-OCD schizophrenia. There were no differences in affective, anxiety, and substance use disorders between these groups. The prevalence of OCD-spectrum disorders was similar between patients with schizophrenia and OCD and those with OCD. In a study of schizophrenia with and without OCD ($n = 50$ in each group), Rajkumar et al[93] found that comorbid OCD was associated with greater paranoia and first-rank psychotic symptoms, less anergia, increased rates of depression and comorbid personality disorder, and perhaps less disability. Several studies have found more severe neuropsychological impairments in patients with schizophrenia and OCD.[94,95] In comparison to patients with non-OCD schizophrenia and OCD, Whitney et al[95] found that patients with schizophrenia and OCD had greater impairments across several domains of executive function.

The presence of OCD also has prognostic significance in patients with schizophrenia. Parenthetically, obsessive symptoms—as was the case with affective symptoms—were originally considered to be of favorable prognostic value. This does not appear to be the case. Braga et al[39] found that patients with schizophrenia and comorbid OCD had greater disability as measured by Sheehan disability scale global scale, work subscale, and social life subscale scores. In a study of $N = 102$ patients with chronic schizophrenia, Berman et al[72] found that the presence of OCS was associated with earlier age of illness onset, increased rates of hospitalization in the previous 5 years, and a decreased likelihood of being employed or married. Sevincok et al[96] found that OCD was an independent risk factor for suicidal ideation and suicide attempts in patients with schizophrenia. OCD was also more prevalent among patients with (than those without) suicidal ideation. The authors also found that compulsions were a predictor of suicide attempts.

Poyurovsky et al.[97] completed an important family study of schizophrenia probands with ($n = 57$) and without ($n = 60$) OCD and 50 controls. Relatives of probands with combined schizophrenia and OCD ($n = 182$) had significantly increased rates of schizophrenia and OCD, as well as obsessive-compulsive personality disorder, than probands with non-OCD schizophrenia ($n = 210$). There was also a trend for an increased risk of OCD in relatives of probands with schizophrenia and OCD compared wiith non-OCD schizophrenia. Furthermore, relatives of probands with schizophrenia did not differ in risk of schizophrenia-spectrum, mood, or substance use disorders, based on the presence or absence of OCD. The authors argued that the differential aggregation of obsessive-compulsive-spectrum disorders in first-degree relatives supports the validity of a putative "schizoobsessive" schizophrenia subtype. In the only published genetic study of patients with schizophrenia and OCD, Poyurovsky et al[98] completed a case-control study of the COMT Val158 Met polymorphism. They found no differences in COMT allele and genotype distribution between patients with schizophrenia and OCD ($n = 113$), OCD ($n = 79$), and controls ($n = 171$).

Dopamine and serotonin are key neurotransmitters involved in the pathophysiology of both schizophrenia and OCD. While substantial overlap in neurobiology[87,99] may well contribute to the association between these disorders, a potential confounding factor in epidemiological studies of this association is that second-generation antipsychotics (SGAs) with serotonergic $5HT_2$ receptor blockade may exacerbate or produce de novo OCS in patients with schizophrenia.[100–103] By contrast, SGAs have also been effective as an adjunctive medication for treatment-refractory OCD.[104–107] Additional studies are needed to this investigate the neurobiology of this paradox, which has important treatment-related implications.

Taken together, several lines of evidence suggest that patients with both schizophrenia and OCD may represent a "schizoobsessive" subtype of schizophrenia, with differences in psychopathology, course of illness, and response to treatment, as opposed to comorbid syndromes. This literature supports the possibility that, in a subgroup of patients, OCD may be part of the illness of schizophrenia. Further studies in large samples from diverse population, including in newly diagnosed antipsychotic-naive patients, designed to control for potential confounding factors, are needed to replicate preliminary findings. The search for shared environmental risk factors, such as low birth weight or prenatal stress, for schizophrenia and OCD represents another area for future investigation. The presence of such factors would not

provide direct evidence for the relationship between these 2 conditions but would support the biological plausibility of their association. Additional family and genetic studies are needed to determine if schizophrenia and OCD constitute part of the heritable schizophrenia spectrum are accounted for by shared environmental risk factors or both.

Schizophrenia and Depression

The relationship between psychotic and affective symptoms has been central to the dilemma of psychiatric classification. Indeed, substantial evidence (not reviewed here) show that schizophrenia and bipolar disorder, in particular, may be distributed across a dimensional spectrum (or more apt, across multidimensional spectra).[108–112] Furthermore, there has been an ongoing and robust debate about the nosological status of "schizoaffective" disorder,[7,8,112] with varying definitions and approaches that make that literature very difficult to negotiate. These 2 aspects go way beyond the scope of this review yet are important aspects of nosology that are of relevance to the topic of psychiatric comorbidity. Here, we confine ourselves to reviewing studies of the co-occurrence of the symptoms of psychosis and unipolar depression, a phenomenon seen at some point in illness in the majority of schizophrenia sufferers, as well as in a substantial number of primary depressive patients. In this context, Möller poses the question: "whether these depressive symptoms are part of the rich psychopathological picture of schizophrenia, which, beside the core paranoid-hallucinatory syndrome, includes a negative syndrome, a cognitive syndrome and also a depressive syndrome, or whether depression and schizophrenia should be seen as separate conditions in terms of the concept of comorbidity."[113]

Bartels and Drake[114] suggested that depressive symptoms in schizophrenia be divided into 3 subtypes, including (1) depressive symptoms secondary to organic factors, (2) "nonorganic" depression intrinsic to the acute psychotic episode, and (3) depressive symptoms that are not temporally associated with the acute psychotic episode, such as symptoms associated with the prodrome, the postpsychotic interval, as well as those symptoms that resemble depression that may represent negative symptoms of schizophrenia. Such approaches offer a structure for considering the various relations of depressive symptoms in patients with schizophrenia and are addressed below.

Antipsychotic medications themselves produce neurological side effects like Parkinsonism (particularly bradykinesia, diminution of affective expression, masked facies, and verbal delays) and akathitic restlessness that may be confused with the psychomotor retardation or agitation of depression. Antipsychotic drugs may also produce a primary dysphoria, possibly due to dopamine blockade in reward pathways, and it has even been suggested that these drugs are innately depressogenic. People with schizophrenia are also prone to general medical morbidities[115] and substance use disorders,[116] some of which may also produce depressive symptoms. Certain negative symptoms, such as anhedonia, abulia, alogia, amotivational and avolitional states, and social withdrawal, can overlap with or spuriously suggest depression.[117] Demoralization,[118] disappointment, or loneliness[119] following a psychotic episode may create lingering feelings of dysphoria.

The classic construct of depression in schizophrenia is that of postpsychotic depression (PPD), defined in an appendix of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision,*[8] as a major depressive episode that is superimposed on, and occurs only during the residual phase of schizophrenia. PDD has traditionally been formulated as a psychological reaction to loss or to the psychological trauma of the psychotic episode. Roth wrote that the "depressive reaction that follows (a psychotic episode) is part and parcel of a total psychobiologic reaction to a failure of the patient in some area of human relationships."[120] The relationship of PPD to the psychotic episode itself remains unclear, including the question of whether the depression is a reaction to psychosis, or represents an unmasking effect of the depression as the psychosis remits.[121] This latter view is supported by observations that depressive symptoms are often associated with positive symptom scores[122] and decrease with effective neuroleptic treatment. There is a long-standing literature that depression is a common symptom found during psychotic decompensation.[123]

In contrast to early views that depression was associated with favorable prognosis in schizophrenia, the evidence speaks otherwise. Mandel et al[124] followed 211 schizophrenia patients in the community for a year after hospital discharge. The 25% of patients who suffered depression in the first few months after discharge had a notably greater burden of symptom chronicity. Johnson[125] reported that chronic patients who developed depression more than a year after acute recovery experienced more relapses than other patients. An older study by Tsuang and Coryell[126] and a more recent one by Sim et al[127] both failed to reveal better outcomes in schizoaffective disorder than schizophrenia.

Patients with schizophrenia are at increased risk of developing depression relative to the already high lifetime prevalence of depression in the general population. Many investigators have reported rates of depressive psychopathology in psychotic patients,[128–166] a summary of which is shown in table 4. As might be expected, the measured rates of depressive experience varied widely. There is methodological diversity in this literature due to varying definitions for schizophrenia (or psychotic illness), heterogenous study populations, and varying time intervals over which depressive occurrence was considered,

Table 1. Prevalence of Panic Attacks and Panic Disorder in Schizophrenia

Study	Sample	Criteria	N	Prevalence	Notes
Boyd et al[16]	Epidemiological Catchment Area	DSM-III/DIS		OR=37.9	
Robin and Regier[17]	Epidemiological Catchment Area	DSM-III/DIS		OR=35	
Tien and Eaton[42]	Epidemiological Catchment Area	DSM-III/DIS	40	OR=2.28	Attacks
Boyd[14]	Epidemiological Catchment Area	DSM-III/DIS		28-63%	Attacks
Bland et al[20]	Random community sample	DSM-III	20	29.5%	
Argyle[18]	Outpatients	DSM-III-R	20	35%	Attacks
				20%	Disorder
Lyons et al[32]	Affected co-twins		24	12.5%	
Moorey and Soni[33]	Outpatients	DSM-III-R	30	17%	Attacks
Cassano et al[21]	Inpatients (consecutive)	DSM-III-R/SCID-P	31	19.4%	
Chen et al[22]	Outpatients	SCID DSM-IV	32	25%	Attacks
Tibbo et al[36]	Outpatients	MINI DSM-IV	32	3.3%	
Bermanzohn et al[12]	Day hospital (consecutive)	SCID DSM-IV	37	10.8%	
Bayle et al. (2001)	Outpatients	DSM-III-R	40	36.8%	Attacks
Ciapparelli et al[23]	1-year cohort of patients in remission	DSM-IV	42	26.2%	
Cutler and Siris[26]	Outpatients (primarily) with post-psychotic depression	RDC	45	24.4%	
Labbate et al[31]	Inpatients (consecutive, veterans)	DSM-IV	49	43%	Attacks
				33%	Disorder
Ulas et al[37]		Bandelow Panic and	49	31%	Attacks
		Agoraphobia Rating Scale		14%	Disorder
Braga et al[39]	Outpatients	SCID DSM-IV	53	5.7%	
Zarate[38]	Outpatients (random sample)	DSM-IV	60	19.4%	
Cosoff and Hafner[25]	Inpatients (consecutive)	SCID DSM-III-R	60	6.3%	
Higuchi et al[30]	Outpatients	SCID DSM-III-R	45	20%	
Pallanti et al[34]	Outpatients	SCID DSM-IV	80	13.8%	
Heun and Maier[29]	Family study	DSM-III-R	88	33%	
Garvey et al[27]	Inpatients	DSM-III	95	17%	
Strakowski et al[35]	Inpatients with first-episode psychosis	SCID DSM-III-R	102	6%	
Goodwin et al[28]	Inpatients	DIGS DSM-III-R	184	7.1%	Attacks
Craig et al[24]	Inpatients with first-episode psychosis	SCID DSM-III-R	225	10-20%	Symptoms
Goodwin et al[15]	Epidemiological Catchment Area	DSM-III/DIS	260	45%	Attacks

DIGS = Diagnostic Interview for Genetic Studies RDC = Research Diagnostic Criteria
DIS = Diagnostic Interview Schedule SCID-P = Structured Clinical Interview for DSM-Patient Version
MINI = Mini International Neuropsychiatric Interview

ranging from point prevalence to many years. Nonetheless, as was noted in the outstanding review by Siris and Bench,[4] the above-cited studies have convincingly indicated that patients with schizophrenia were prone to elevated rates of depression, with a modal frequency of about 25%.

It is instructive to examine the likelihood that major depressive episodes will evolve into psychosis, and indeed, depressed patients are at high risk for developing psychotic symptoms during the course of affective illness. As a whole, however, this has been less thoroughly studied than the likelihood of depression in schizophrenic patients. Ohayon and Schatzberg[167]studied the point prevalence of depression in a general population sample of 18,980 people surveyed in a multinational European study. About 16.5% of all subjects endorsed at least one key depressive criterion, and of those, 12.5% reported delusions and/or hallucinations. Of the 454 subjects diagnosed with a full *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* major depressive episode, 18.6% experienced delusions and/or hallucinations. This is consistent

Table 2. Prevalence of Post-Traumatic Stress Disorder in Schizophrenia

Study	Sample	Criteria	N	Prevalence	Notes
Strakowski et al[66]	First-episode psychosis	SCID DSM-III-R	18	22%	
Lyons et al[32]	Affected co-twins		24	16.7%	
Kennedy et al[51]	Outpatients	DSM-IV/Penn PTSD Inventory	30	23.3%	
Kilcommons and Morrison[58]	Outpatient sample of convenience	DSM-IV	32	53%	
Tibbo et al[36]	Outpatients	MINI DSM-IV	32	0%	
McGorry et al. (2001)	Inpatients followed for one year	DSM-III	36	46%	At 4 months
				35%	At 11 months
Shaw et al. (1997)	Inpatients	CIDI/CAPS	42	52.4%	
Meyer et al. (1999)	Inpatients	CAPS	46	11%	
Resnick et al. (2003)	Outpatients	CAPS	47	13%	
Braga et al[39]	Outpatients	SCID DSM-IV	53	3.8%	
Gearon et al. (2003)	Outpatient females, comorbid substance use disorder	DSM-IV	54	46%	
Frame & Morrison (2001)	Inpatients	DSM-IV/ Davidson checklist	60	67%	At discharge
Seedat et al[65]	Inpatients	MINI	70	4.3%	
Pallanti et al[34]	Outpatients	SCID DSM-IV	80	1.3%	
Fan et al. (2008)	Outpatients	DSM-IV	87	17%	All with trauma history
Mueser et al. (1998)	Multicenter inpatients and outpatients	Chart records	94	30.9%	
Priebe et al. (1998)	Outpatients	DSM-III-R	105	51%	
Calhoun et al. (2007)	Inpatient male veterans	SCID/PTSD checklist	165	47%	
Neria et al. (2002)	Inpatients with first-episode psychosis	DSM-III-R	170	10.0%	
Mueser et al. (2004)	Multicenter inpatients and outpatients	PTSD checklist	526	31.6%	

CAPS = Clinician-Administered PTSD Scale
CIDI = Composite International Diagnostic Interview
MINI = Mini International Neuropsychiatric Interview

with findings that 14% of the ECA community sample diagnosed with major depression[168] and 16.9% of an independent first-admission major depression sample[169] experienced psychosis during the course of the depressive episode.

Studies of individuals at high risk and ultrahigh risk for developing schizophrenia have generally demonstrated a significant degree of depressive symptoms prior to and during the emergence of psychotic symptoms.[170–172] Cornblatt et al[173] identified affective disturbances and social isolation as part of an "underlying vulnerability core" in a group of 62 adolescents in various stages of emerging psychosis. Hafner et al[169] obtained comprehensive histories from 232 mostly previously untreated, first-admission adult, and teenaged patients diagnosed with schizophrenia, as well as 130 healthy controls and 130 demographically matched, first-admission patients with a diagnosis of depression. In comparing a subset of 130 patients with schizophrenia with the primary depression group, the authors generated lists of the 10 most frequent initial symptoms of illness for depressed and schizophrenia groups, resulting in a combined and highly overlapping list consisting of 13 symptoms. Eight of the 13 most common symptoms did not differ significantly in the frequency. Both diagnostic groups had suffered from both a depressive core syndrome and negative syndrome (difficulties in thinking and concentration, loss of energy, social withdrawal) in the early course of illness, with closely paralleling courses. Patients with schizophrenia were most distinguished, not surprisingly, by markedly escalating positive symptoms leading up to the index admission. The authors concluded that that the initial symptoms of illness reflected a core psychopathology common to the very

Table 3. Prevalence of Obsessive-Compulsive Disorder in Schizophrenia

Study	Sample	Criteria	N	Prevalence	Notes
Boyd et al[16]	Epidemiological Catchment Area	DSM-III/DIS		OR=12.5	
Tien and Eaton[42]	Epidemiological Catchment Area	DSM-III/DIS	40	OR=3.77	
Karno et al[77]	Epidemiological Catchment Area	DSM-III/DIS		12.2%	
Rae (unpublished)	Epidemiological Catchment Area reanalysis	DSM-III/DIS		23.7%	
Mohammadi et al[81]	Community sample		12	OR=1.3	Symptoms
Strakowski et al[66]	Inpatients with first-episode psychosis	SCID DSM-III-R	18	11%	
Bland et al[20]	Random community sample	DSM-III	20	59.2%	Symptoms
Cassano et al[21]	Inpatients (consecutive)	DSM-III-R/SCID-P	31	29%	
Tibbo et al[36]	Outpatients	MINI DSM-IV	32	0%	
Bermanzohn et al[12]	Day hospital (consecutive)	SCID DSM-IV	37	29.7%	
Nechmad et al[82]	Inpatients	DSM-IV	39	30.8%	Adolescents
Bayle et al. (2001)	Outpatients	DSM-III-R	40	35%	
Ciapparelli et al[23]	1-y cohort of patients in remission	DSM-IV	42	23.8%	
Fabisch et al[74]		DSM-IV	42	19%	
Poyurovsky et al[84]	Inpatients with first-episode psychosis	SCID	46	15.2%	Adolescents
Porto et al[83]	Day program	SCID DSM-IV	50	60%, 26%	Symptoms disorder
Tibbo et al[87]	Outpatients	SCID DISM-IV	52	25%	
Braga et al[39]	Outpatients	SCID DSM-IV	53	15.1%	
Tibbo et al[86]	Outpatients	SCID DISM-IV	56	25%	
Cosoff and Hafner[25]	Inpatients (consecutive)	SCID DSM-III-R	60	13.8%	
Zarate[38]	Outpatients (random sample)	DSM-IV	60	6.7%	
Poyurovsky et al[85]	Inpatients	SCID DSM-IV	68	23.5%	
Seedat et al[65]	Inpatients	MINI	70	4.3%	
Ohta et al. (2003)	Inpatients and outpatients	SCID DSM-IV	71	18.3%	
Kruger et al. (2000)	Inpatients	SCID DSM-III-R	76	15.8%	
Eisen et al[73]		SCID DSM-III-R	77	7.8%	
Pallanti et al[34]	Outpatients	SCID DSM-IV	80	22.5%	
Kayahan et al[78]	Inpatients and outpatients	SCID-P DSM-IV	100	64%, 30%	Symptoms disorder
Strakowski et al[35]	Inpatients with first-episode psychosis	SCID DSM-III-R	102	13.7%	
Berman et al[72]	Outpatients	Chart review	102	25%	Symptoms
Fabisch et al[75]	Inpatients	DSM-IV	150	10%	Symptoms
Fenton and McGlashan[76]	Inpatients followed for 15 y	DSM-III-R	163	12.9%	Symptoms
Goodwin et al[28]	Inpatients	DIGS DSM-III-R	184	5.4%	
Craig et al[24]	Inpatients with first-episode psychosis	SCID DSM-III-R	225	16.9%, 4%	Symptoms disorder
Meghani et al[80]	Outpatients	Unspecified	1458	31.7%	

DIS = Diagnostic Interview Schedule SCID-P = Structured Clinical Interview for DSM-Patient Version
MINI = Mini International Neuropsychiatric Interview

early stages of both illnesses. They also noted that the peak of depressive experience in patients with schizophrenia coincided with peak psychosis.

Concerning the neurobiology of schizophrenia and depression and evidence of etiologic and pathophysiologic coincidence or overlap, the majority of studies that might inform the topic utilize subjects with either depression or schizophrenia but rarely both. While functional imaging studies of depressed patients have shown decreased prefrontal metabolism or decreased regional cerebral blood flow (rCBF),[174,175] those that directly compared rCBF changes during working memory tasks in schizophrenia and depressed groups showed substantial intergroup differences in the direction of greater reduction of rCBF in

Table 4. Incidence of Prevalence of Secondary Depression in Schizophrenia (Modified From Siris and Bench)[4]

Study	N	Definition of Psychosis	Definition of "Postpsychotic" Interval	Definition of Depression	Percentage Depressed
McGlashan and Carpenter[128]	30	IPSS: more than 90% chance of schizophrenia	Cross-sectional at discharge and 1-year follow-up	'Depression' per PSE	Discharge: 43% 1-yr: 50%
Weissman et al[129]	50	Outpatients with New Haven Schizophrenia Index diagnosis of schizophrenia	Point prevalence	Raskin Scale score of 7 or more	28%
Van Putten and May[130]	94	Newly admitted patients; Feighner criteria for schizophrenia	Length of acute hospital stay	Increase in BPRS depression rating	38%
Knights et al[131]	37	CATEGO criteria: 87% = unequivocal schizophrenia	6 months or until relapse while on depot neuroleptic	PSE-based depression rating	54%
Roy (1980)[5]	100	DSM-III chronic paranoid schizophrenia	Chart review for mean of 6 years	DSM-III for major depressive disorder, secondary type	30%
Johnson[133]					
Cohort A:	41	Schizophrenia diagnosis based on Schneiderian first-rank symptoms	A: 2 months prospective prevalence study	A: HAM-D &/or BDI $\geq$ 15	A: 24%
Cohort B:	100	Outpatients free of acute symptoms for $\geq$ 3 months	B: Cross-sectional prevalence	B: Nurse & self-rating	B: 26%
Cohort C:	30	Patients maintained on depot neuroleptic	C: 2-year follow-up	C: HAM-D and/or BDI $\geq$ 15	C: 50% excluding episodes associated w/ psychotic relapse
Siris et al[134]	50	Acutely admitted inpatients diagnosed by RDC	Duration of hospitalization after resolution of flagrant psychotic symptoms	RDC for major or minor depression by chart review	6% major, 22% minor depression
Roy (1981)	100	DSM-III for schizophrenia	Chart review: 4-10 years	Treated for depression by antidepressants or ECT	39%
Moller and von Zerssen[136]	81	Inpatients with schizophrenia (77%) or paranoid psychosis (23%) by ICD criteria	Point prevalence at hospital discharge	3 consecutive Actual Mood Scores $\geq$ 21	23%
Guze et al[137]and Martin et al[138]	44	Feighner criteria for schizophrenia	Retrospective survey at 6-12 year follow-up point	Criteria close to Feighner criteria for depression	57%
Summers et al[139]		RDC schizophrenia:			
Cohort A:	161	Cohort A: chronic	A: admission to aftercare	A: SCL-90 scales	A: Schiz. more depressed vs. normals
Cohort B:	72	Cohort B: Acute	B: past month assessment (average 2.13 year post discharge)	B: 2 composite depression scales from KAS	B: 37% poor; 68% poor or equivocal
Watt and Shepherd (1983) (reported in Roy[140]	121	Chronic schizophrenia (PSE criteria)	PSE: Admission, 1 month, 1 year, & 5 years after discharge	PSE assessment of depression syndrome	40% at 1 mo., 1 yr. ('severe' in ¼ of these); 19% at 5 yrs
Munro et al[141]	100	Outpatients with DSM-III for schizophrenia	Clinic cross-sectional prevalence	Carroll Rating Scale	41% (10% severe, 18% moderate, 13% mild)

Table 4. Continued

Study	N	Definition of Psychosis	Definition of "Postpsychotic" Interval	Definition of Depression	Percentage Depressed
Elk et al[142]	56	CATEGO 'S' diagnosis	Point prevalence at hospital admission	PSE depressed mood + observed depression	30%
Leff et al[143]	31	Newly admitted patients with PSE/CATEGO schizophrenia	Until discharged or until 6 months	Depressed mood by PSE	45%
Johnson (1988)[17]	80	Feighner schizophrenia criteria;	Period began when patients were free of acute symptoms Period A: 0-12 months	Altered mood x $\geq$ 7 days with HAM-D & BDI each $>$ 15: DSM-III for depression	Period A: 13-30%
		Schneiderian first-rank symptoms	Period B: 12-36 months (ratings $\geq$ every 3 months)		Period B: 65%
Kulhara et al[145]	95	Outpatients with ICD-9 diagnosis of schizophrenia	Cross-sectional assessment	Depressed mood on PSE	32%
Hirsch et al (1989)[19]		DSM-III schizophrenia			
Cohort A:	46	Cohort A: Thought by nurses to be 'depressed'	A & B: Cross-sectional assessment	A: HAM-D & BDI	A: 7%
Cohort B: (also Barnes et al 1989)[20]	196	Cohort B: Long-stay inpatients		B: Depression item on PSE	B: 13%
Cohort C:	44	Cohort C: Outpatients with no florid symptoms in previous 6 months	Cohort C: Bimonthly assessments × 1 year while randomly assigned to depot neuroleptic or placebo	C: Manchester Scale depression item $\geq$ 2	C: 73% of psychotic relapses: prodrome included depression
Bandelow et al[148]	364	ICD-9 and RDC for schizophrenia	Point prevalence 3 months after discharge and acute stabilization on neuroleptic medication	BPRS anxious-depression scale $\geq$ 10	19.5%
Addington and Addington[149]	50	DSM-III Schizophrenia	Point prevalence	DSM-III depressive episode by PSE	24%
Breier et al[150]	58	RDC schizophrenia (N = 42) or schizoaffective disorder (N = 16; 12 depressed type)	Average follow-up = 6 + 3 years	RDC major depression	24%
Lindenmayer et al[151]	240	Mostly chronic inpatients with DSM-III schizophrenia	Point-prevalence	'Severe' PANSS depression component $>$ 19; 'mild to moderate' 11-18	5% severe depression 52% mild to moderate
Birchwood et al[152]	49	CATEGO class 's' for schizophrenia	Randomly selected from urban outpatient 'depot' treatment clinic	Score of at least 15 on the BDI	29%
Koreen et al[153]	70	'First break', RDC for schizophrenia (77%) or schizoaffective disorder (23%)	Repeated prospective assessment at weekly intervals during acute treatment, and monthly intervals thereafter up to 5 years	Syndromal depression &/or extracted HAM-D based on SADS interview	75% (met one criterion at some point); 22% (met both criteria concurrently)
Tapp et al[154]	91	DSM-IIIR & RDC for schizophrenia per SADS	Not stated	HAM-D rating (not specified)	37% (non-Kraepe- linian); 6% (Krae- linian)

Table 4. Continued

Study	N	Definition of Psychosis	Definition of "Postpsychotic" Interval	Definition of Depression	Percentage Depressed
Harrow et al[155]	54	RDC schizophrenia	Prevalence during 1 year before interview which was 4.5 years (avg) after hospital discharge of index psychotic episode	Full depressive RDC syndrome	37%
Mauri et al[156]	43	Chronic schizophrenic inpatients (DSM-IIIR) acute exacerbation	Prevalence at baseline and after 6 weeks of neuroleptic treatment	HAM-D & BPRS depression subscale	16.3%: moderate symptoms of depression (23.2%: mild sx)
Markou[157]	94	DSM-IIIR Schizophrenia; 50 inpatients & 44 chronic hospital outpatients	Point prevalence	'Significant depression' (HAM-D > 17) 'mild to moderate depression' (10- 17)	Inpatients: 10% significant 42% mild-moderate Outpatients: 4.5% significant 48% mild-moderate
Wassink et al[158]	62	Recent onset DSM-IIIR or DSM-IV schizophrenia	Point prevalence	DSM-IV major depressive disorder	35%
Muller and Wetzel[159]	132	Acute DSM-IIIR schizophrenia	Point prevalence	BRMES $\geq$ 14	42%
Sands and Harrow[160]	70	RDC schizophrenia	Assessed 7.5 years after discharge; covers the previous year	RDC depression, full syndrome vs. subsyndromal	36%: full syndrome 14%: subsyndromal
Zisook et al[161]	60	Outpatients with DSM-IIIR or DSM-IV schizophrenia, age 45-79	Point prevalence	HAM-D $\geq$ 17	Women: 20% Men: 7%
Baynes et al (2000)[35]	120	Stable outpatients, DSM-IIIR chronic schizophrenia	Point prevalence	BDI $\geq$ 17	13.3% (+ 24.2% with BDI = 10-16)
Bottlender et al[163]	998	First hospitalization, ICD-9 schizophrenia	Point prevalence	AMDP depression syndrome score $\geq$ 8	AMDP Dep$\geq$ 8: 21% "Clinically significant depression": 15.5%
Bressan et al[164]	80	Stable outpatients, DSM-V schizophrenia	Time since last psychosis; range = 2 mos-15 years	DSV-IV major depressive episode	16.3%
Serretti et al[165]	358	Inpatients/outpatients with various diagnoses (n=1351); 358 w/OPCRIT schizophrenia	Point prevalence	$\geq$4 OPCRIT depressive symptoms	26.8%
Hafner et al (2005)[39]	232	First-admission schizophrenics, age 12-59	Retrospective assessment of lifetime prevalence	Depressed mood for $\geq$ 2 weeks before first admission per IRAOS interview	83%

BDI = Beck Depression Inventory; BPRS = Brief Psychiatric Rating Scale; BRMES = Bech-Rafaelsen Melancholia Scale; DSM = Diagnositc & Statistical Manual; HAM-D = Hamilton Depression Rating Scale; ICD = International Classification of Diseases; IPSS = International Pilot Study or Schizophrenia; IRAOS = Interview for the Retrospective Assessment of the Onset of Schizophrenia; KAS = Katz Adjustment Scale; OPCRIT = Operational Criteria for Psychotic Illness; PANSS = Positive & Negative Syndrome Scale; PSE = Present State Examination; RDC = Research Diagnostic Criteria; SADS = Schedule for Affective Disorders & Schizophrenia; SCL-90 = Symptom Checklist, 90 item.

schizophrenia than depressed subjects.[176,177] Reduced hippocampal volume has been reported in depression and schizophrenia,[178–180] and a recent study examined the association between myelin related genes and the clinical characteristics of 280 schizophrenia subjects—specifically the presence or absence of depressive comorbidity.[181] The investigators demonstrated an association between the glycoprotein M6A gene (GPM6A)—a modulator of the influence of stress on the hippocampus in animals—with the subgroup of schizophrenia patients who showed the highest degree of depression.

In contrast, one of the most consistent functional imaging findings in depression concerns increased rCBF or glucose metabolism in the amygdala of ill subjects relative to healthy controls.[182] This finding is absent in patients with schizophrenia who, if anything, show diminished amygdalar activity relative to controls.[183] What is missing in the literature is direct comparison of neurobiological variables between patients with schizophrenia with and without comorbid depression.

Much has been written about the newer generation antipsychotic drugs and the potential advantage in psychotic patients with depression, including avoidance of dopamine blockade dysphoria and extrapyramidal side effects (EPS). The newer drugs' unique pharmacologic features, particular affinity at various serotonergic receptors, may well confer some direct and indirect advantages.[184]

Tollefson et al[185] raised the possibility that SGAs—in this instance olanzapine—may have a direct effect on a depressive symptom domain in patients with schizophrenia. In a path analysis of depression in schizophrenia and its treatment with either olanzapine or haloperidol, they reported superiority for olanzapine and that 56% of this effect on depressive symptoms was on "primary" symptoms rather than secondary to negative symptoms, relief of EPS, etc. Similar analyses have been conducted for other SGAs.[186,187] Moreover, clozapine's antisuicide effect did not appear to be related to (merely) better amelioration of symptoms because both clozapine and olanzapine fared equally well on positive, negative, and depressive symptom improvements.[188] Moreover, the now widespread use of SGAs in bipolar disorder is additional indirect evidence for some independence of effects on mood and not simply an "antipsychotic" effect (to reduce positive symptoms, thereby lessening depression) in schizophrenia.

From a different vantage point, the role of antidepressant therapy in schizophrenia has received relatively little attention, particularly given the frequency of depressive symptoms and the regular copharmacy (in approximately 30% of patients) of antidepressants and antipsychotics when treating patients with schizophrenia. Interestingly, Siris et al[189] showed that adjunctive imipramine improved depression and also resulted in fewer psychotic relapses. The information concerning adjunctive antidepressant therapy with SGAs is particularly scant. Whether, in view of their effect on neuroplasticity, these drugs might have broader clinical effects beyond treating comorbid depressive symptoms in schizophrenia is of interest. Cornblatt et al[190] found that prepsychotic adolescents who received antidepressants did just as well as prepsychotic patients who were treated with antipsychotics. Although a naturalistic study, the potential that antidepressants may impact the development of psychosis is intriguing and provocative.

Table 5. Consequences of Comorbid Substance Abuse in Patients With Schizophrenia

More positive symptoms
Relapse of psychosis
Heightened risk of violence
Heightened risk of suicide
More medical comorbidities
Legal complications, including heightened risk of incarceration
Greater propensity to antipsychotic-related side effects

In concluding this section, the following observations can be made: (1) depressive symptoms are common in patients with schizophrenia; (2) they add further to the disability of schizophrenia, including being associated with a heightened risk for psychotic relapses; (3) PPD may be a particular "forme fruste" of major depression in schizophrenia; (4) there is some evidence, far from conclusive, that medications might directly impact depressive, mood, and suicidality to some extent that is not simply "less depression because of less psychosis"; and (5) although intuitively appealing, there is insufficient evidence in the literature (including a dearth of neurobiological studies) to support the proposition that this represents a distinct subgroup of schizophrenia.

Substance Abuse Comorbidity

The abuse of alcohol and/or illicit drugs by patients with schizophrenia is a remarkably common phenomenon …"the rule rather than the exception.[10,191] In the ECA study, it was estimated that 47% of patients with schizophrenia also had a lifetime diagnosis of substance abuse disorder.[191] This is consistent with findings from a variety of other epidemiological and clinical studies, both in the United States and worldwide.[10,191–194] In general terms, substance abuse comorbidity is associated with a variety of negative consequences for the course of schizophrenia (see table 5), with medication nonadherence often appearing as a "final common pathway" for these effects. Description of the epidemiology and consequences of substance abuse and schizophrenia is beyond the scope of this article and is accounted well elsewhere.[8] Suffice it to say that substance abuse comorbidity is common and is deleterious to the course and outcome of schizophrenia. The investigation of this co-occurrence has been

(perhaps to a greater extent than the other comorbidities) hampered by a general effort to exclude patients with comorbid substance abuse when studying schizophrenia. Thus, sampling bias is an important consideration in evaluating this association.

Explanations for the common association of substance abuse with schizophrenia are highlighted. Firstly, one might consider this merely a chance co-occurrence, particularly because adolescents and young adults abuse drugs. Why should adolescents/young adults with schizophrenia be any less likely to do this? Epidemiological data and clinical experience suggest that this is not merely a "chance occurrence" and that it is frequent and beyond mere coincidence.[191–193] Furthermore, it seems that both patterns of use and motivations for use are very similar in individuals with schizophrenia, as in the nonschizophrenia population.

The second notion is that alcohol or drugs actually caused schizophrenia and that this explains the co-occurrence. Heavy and protracted abuse of alcohol has been causally associated with a discrete alcoholic hallucinosis, but this is relatively rare and the longitudinal course is usually not the same as schizophrenia, such that, eg, affect and personality are relatively preserved. Any strong causal association between alcohol and schizophrenia per se is difficult to envisage given the ubiquity of alcohol use and the fact that the vast majority of people who do use alcohol to excess do not develop schizophrenia. The evidence for illicit drugs being causally associated with schizophrenia is at best mixed but has been most compelling argued for cannabis. A number of cohort studies have now established a temporal relationship between cannabis exposure in adolescence or early adulthood, and later schizophrenia, with an odds ratio of just over 2.0 (2.09, with confidence intervals of 1.54–2.84) in a recent metaanalysis of these studies.[195] Additionally, some studies show a "dose-dependent" effect, such the more cannabis consumed the greater the likelihood of schizophrenia.[196] However, again the prevalence of schizophrenia is disproportionate to the ubiquitous smoking of cannabis, there is no clear association between rates of schizophrenia and rates of cannabis use in any given population, and most people who imbibe cannabis do not develop schizophrenia. Thus, it seems that cannabis can be conceptualized as a cumulative causal factor in some individuals, acting in concert with other vulnerability factors to promote the manifestation of the illness in some individuals who might otherwise have remained schizophrenia free. The effect is small, with a population attributable fraction of 5%–7%. Also, it does not appear that patients with schizophrenia and comorbid cannabis have any higher genetic loading for schizophrenia than patients with schizophrenia alone.[197]

Caton et al[198] examined the relationship between substance-induced psychosis and schizophrenia by longitudinally evaluating patients who presented acutely psychotic, all of whom had abused drugs or alcohol prior to this first ever presentation with psychosis. Forty-four percent of patients turned out over time to have had a drug-induced psychosis, while 56% of patients ultimately had schizophrenia as their primary diagnosis. Patients with a drug-related psychosis had marginally less positive and negative symptoms at initial presentation, they were more likely to have visual hallucinations, and their parents had a history of substance abuse. Caspi et al[11] examined this issue from a different, complementary perspective. As part of a large epidemiological study of schizophrenia in New Zealand, they found that those adolescents who possessed the "faulty" allele (val 158 met) polymorphism of the COMT (cathechol -O-methyl-transferase) gene were the people who had the vulnerability to cannabis abuse. This might help explain this association, which appears robust from epidemiological data but is still a small effect. There is a recent study of brain imaging in nonpsychotic cannabis abusers that shows progressive brain changes with heavy and chronic cannabis abuse.[199] The authors report some association between paranoid experiences in a subset of these patients and greater prominence of hippocampal changes. As a general observation, there have been few biological studies of this dual diagnosis patient population because substance abuse is more often than not an exclusionary criterion. On the other hand, there is a growing appreciation of potentially shared neurochemical vulnerability between substance abuse and schizophrenia.[200] Animal neurochemical and now human brain imaging studies point to the role of dopamine in the amygdala as being key to understanding drug craving and reward behaviors. In schizophrenia, pleasure and reward are blunted as part of negative symptoms. It is plausible that dopamine dysregulation might predispose patients with schizophrenia to abuse drugs.[194,200] It has also been explained that patients with schizophrenia who abuse drugs may actually have milder symptoms and that their poorer course is more attributable to the direct effect of drugs on worsening symptoms as well as the associated medication nonadherence. This is certainly intuitive in the sense that patients with more severe illness are less likely to have the opportunity and social context to acquire street drugs. It has also long been suggested that patients self medicate either to reduce their symptoms or to counteract the effects of antipsychotic medications.[201,202] Either association is plausible and in accord with clinical experience. However, the rate of substance abuse comorbidity has not seemed to diminish in an era of treatment with SGAs that have less motor and secondary negative symptom effects.[203] Regarding treatment of patients with substance abuse, these patients show similar responses to antipsychotic medications as nonabusing patients with schizophrenia—once they take their medication, a major challenge in this patient group.[20,204] In the clinical antipsychotic trials of intervention effectiveness (CATIE)

study, patients with comorbid substance abuse showed comparable responses with each SGA than patients without substance abuse.[205] There is some evidence that dual diagnosis patients might do better on clozapine, with less relapse into abuse of drugs or alcohol.[206]

Overall, while substance abuse comorbidity is remarkably common in schizophrenia, the evidence is lacking that this represents some distinct subgroup of etiopathological significance. While explanations toward a shared neurochemical, dopamine-mediated vulnerability to both schizophrenia and substance abuse are intuitively appealing, at present the evidence base is scant.[194] Moreover, the prevailing view in both the addiction field and in schizophrenia research is that this represents a co-occurrence of 2 conditions rather than some etiologically distinct subgroup of schizophrenia patients who are characterized by a proclivity to substance abuse.

Conclusions

There is clearly an increased prevalence of anxiety, depressive, and substance abuse disorders in patients with schizophrenia that occurs in excess of that in the general population. These comorbidities occur at all phases of the course of illness, including in the psychosis prodrome, FEP, and chronic schizophrenia. A limited body of evidence supports the plausibility of the hypothesis that anxiety disorders are part of the illness of schizophrenia, with the strongest evidence being for OCD. PTSD, and other anxiety symptoms, while common, do not appear to be etiologically linked to schizophrenia. Depressive symptoms are also intrinsic to the illness and import a poorer outcome, including more psychotic relapses. Understanding this relationship is important and is also additionally complicated by broader perspectives about the boundaries/overlap between psychosis and mood disorders. Substance abuse is particularly common and also worsens the course of illness, although here this effect is inextricably linked to treatment noncompliance. For each of these comorbidities, their presence is generally associated with more severe psychopathology and with poorer outcomes. What is conspicuous from this review is the relative lack of investigation toward a neurobiological basis of comorbidity among patients with schizophrenia. This is striking in view of how common and challenging these comorbidities are. There is a conspicuous absence of any ''smoking gun'' findings for etiological heterogeneity here. While there has been at least some headway in treatment studies of both pharmacology and nonpharmacology, it is rudimentary and in relation to OCD and schizophrenia there is the suggestion that antipsychotic medications might even aggravate these symptoms.[3] There is also, on the other hand, evidence that antidepressants can not just improve depressive symptoms but perhaps also impact favorably negative and general psychopathology as well.[5] These observations may contribute in part to the high rates of polypharmacy that are observed in the treatment of schizophrenia.[207] At present, the therapeutic implications of this clinical heterogeneity are poorly understood and are largely manifested in ''trial and error'' treatment choices. The most parsimonious conclusion at the present time is that these comorbidities are certainly more common than chance in schizophrenia, but their etiopathological significance and treatment implications thereupon are poorly understood at the present time.

References

1. Kirkpatrick B, Buchanan RW, Ross DE, Carpenter WT, Jr. A separate disease within the syndrome of schizophrenia. *Arch Gen Psychiatry*. 2001;58:165–171.
2. Pincus HA, Tew D, First MB. Psychiatric comorbidity: is more less? *World Psychiatry*. 2004;3:18–23.
3. Green AI, Canuso C, Brenner MJ, Wijcik JD. Detection and management of comorbidity in schizophrenia. *Psychiatr Clin N Am*. 2003;26:115–139.
4. Siris S, Bench C. Depression and schizophrenia. In: Hirsch S, Weinberger D, eds. Schizophrenia. 2nd ed. Oxford, UK: Blackwell; 2003:142–167.
5. Moller HJ. Drug treatment of depressive symptoms in schizophrenia. *Clin Schizophr Relat Psychoses*. 2007;1:328–340.
6. Kendell RE. The classification of depressions: a review of contemporary confusion. *Br J Psychiatry*. 1976;129:15–28.
7. Pierre JM. Deconstructing schizophrenia for DSM-V: challenges for clinical and research agendas. *Clin Schizophr Relat Psychoses*. 2008;2:166–174.
8. Wing J, Agrawal N. Concepts and classification of schizophrenia. In: Hirsch S, Weinberger D, eds. Schizophrenia. 2nd ed. Oxford, UJK: Blackwell; 2003:3–14.
9. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.*
10. Buckley PF. Prevalence and consequences of the dual diagnosis of substance abuse and severe mental illness. *J Clin Psychiatry*. 2006;67:5–9.
11. Caspi A, Moffitt TE, Cannon M, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-0-methyltransferase gene: longitudinal evidence of a gene x environment interaction. *Biol Psychiatry*. 2005;57:1117–1127.
12. Bermanzohn PC, Porto L, Arlow PB, Pollack S, Stronger R, Siris SG. Hierarchical diagnosis in chronic schizophrenia: a clinical study of co-occurring syndromes. *Schizophr Bull.* 2000;26:517–525.
13. Pokos V, Castle DJ. Prevalence of comorbid anxiety disorders in schizophrenia spectrum disorders: a literature review. *Curr Psychiatry Rev*. 2006;2:285–307.
14. Boyd JH. Use of mental health services for the treatment of panic disorder. *Am J Psychiatry*. 1986;143:1569–1574.
15. Goodwin R, Lyons JS, McNally RJ. Panic attacks in schizophrenia. *Schizophr Res*. 2002;58:213–220.
16. Boyd JH, Burke JD, Jr, Gruenberg E, et al. Exclusion criteria of DSM-III. A study of co-occurrence of hierarchy-free syndromes. *Arch Gen Psychiatry*. 1984;41:983–989.

17. Robins LN, Regier DA, eds. Psychiatric Disorders in America: the Epidemiological Catchment Area Study. New York, NY: The Free Press; 1991.
18. Argyle N. Panic attacks in chronic schizophrenia. *Br J Psychiatry*. 1990;157:430–433.
19. Baylé FJ, Krebs MO, Epelbaum C, Levy D, Hardy P. Clinical features of panic attacks in schizophrenia. *Eur Psychiatry*. 2001;16:349–353.
20. Bland RC, Newman SC, Orn H. Schizophrenia: lifetime comorbidity in a community sample. *Acta Psychiatr Scand*. 1987;75:383–391.
21. Cassano GB, Pini S, Saettoni M, Rucci P, Dell-Osso L. Occurrence and clinical correlates of psychiatric comorbidity in patients with psychotic disorders. *J Clin Psychiatry*. 1998;59:60–68.
22. Chen CY, Liu CY, Yang YY. Correlation of panic attacks and hostility in chronic schizophrenia. *Psychiatry Clin Neurosci*. 2001;55:383–387.
23. Ciapparelli A, Paggini R, Marazziti D, et al. Comorbidity with axis I anxiety disorders in remitted psychotic patients 1 year after hospitalization. *CNS Spectr*. 2007;12:913–919.
24. Craig T, Hwang MY, Bromet EJ. Obsessive-compulsive and panic symptoms in patients with first-admission psychosis. *Am J Psychiatry*. 2002;159:592–598.
25. Cosoff SJ, Hafner RJ. The prevalence of comorbid anxiety in schizophrenia, schizoaffective disorder and bipolar disorder. *Aust N Z J Psychiatry*. 1998;32:67–72.
26. Cutler JL, Siris SG. ''Panic-like'' symptomatology in schizophrenic and schizoaffective patients with postpsychotic depression: observations and implications. *Compr Psychiatry*. 1991;32:465–473.
27. Garvey M, Noyes R, Jr, Anderson D, Cook B. Examination of comorbid anxiety in psychiatric inpatients. *Compr Psychiatry*. 1991;32:277–282.
28. Goodwin RD, Amador XF, Malaspina D, Yale SA, Goetz RR, Gorman JM. Anxiety and substance use comorbidity among inpatients with schizophrenia. *Schizophr Res*. 2003;61:89–95.
29. Heun R, Maier W. Relation of schizophrenia and panic disorder: evidence from a controlled family study. *Am J Med Genet*. 1995;60:127–132.
30. Higuchi H, Kamata M, Yoshimoto M, Shimisu T, Hishikawa Y. Panic attacks in patients with chronic schizophrenia: a complication of long-term neuroleptic treatment. *Psychiatry Clin Neurosci*. 1999;53:91–94.
31. Labbate LA, Young PC, Arana GW. Panic disorder in schizophrenia. *Can J Psychiatry*. 1999;44:488–490.
32. Lyons MJ, Huppert J, Toomey R, et al. Lifetime prevalence of mood and anxiety disorders in twin pairs discordant for schizophrenia. *Twin Res*. 2000;3:28–32.
33. Moorey H, Soni SD. Anxiety symptoms in stable chronic schizophrenics. *J Ment Health*. 1994;3:257–262.
34. Pallanti S, Quercioli L, Hollander E. Social anxiety in outpatients with schizophrenia: a relevant cause of disability. *Am J Psychiatry*. 2004;161:53–58.
35. Strakowski SM, Tohen M, Stoll AL, et al. Comorbidity in psychosis at first hospitalization. *Am J Psychiatry*. 1993;150:752–757.
36. Tibbo P, Swainson J, Chue P, LeMelledo JM. Prevalence and relationship to delusions and hallucinations of anxiety disorders in schizophrenia. *Depress Anxiety*. 2003;17:65–72.
37. Ulas H, Alptekin K, Akdede BB, et al. Panic symptoms in schizophrenia: comorbidity and clinical correlates. *Psychiatry Clin Neurosci*. 2007;61:678–680.
38. Zarate R. The comorbidity between schizophrenia and anxiety disorders. Paper presented at: 31st Annual Meeting of the Association for Advancement of Behavior Therapy. Miami Beach: Fla; November 1997.
39. Braga RJ, Mendlowicz MV, Marrocos RP, Figueira IL. Anxiety disorders in outpatients with schizophrenia: prevalence and impact on the subjective quality of life. *J Psychiatr Res*. 2005;39:409–414.
40. Katerndahl DA, Realini JP. Lifetime prevalence of panic states. *Am J Psychiatry*. 1993;150:246–249.
41. Grant BF, Hasin DS, Stinson FS, et al. The epidemiology of DSM-IV panic disorder and agoraphobia in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2006;67:363–374.
42. Tien AY, Eaton WW. Psychopathologic precursors and sociodemographic risk factors for the schizophrenia syndrome. *Arch Gen Psychiatry*. 1992;49:37–46.
43. Bermanzohn PC, Arlow PB, Pitch RJ, Siris SG. Panic and paranoia. *J Clin Psychiatry*. 1997;58:325–326.
44. Hofmann SG. Relationship between panic and schizophrenia. *Depress Anxiety*. 1999;9:101–106.
45. Siris SG, Mason SE, Shuwall MA. Histories of substance abuse, panic and suicidal ideation in schizophrenic patients with histories of post-psychotic depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 1993;17:609–617.
46. Fialko L, Freeman D, Bebbington P, et al. Understanding suicidal ideation in psychosis: findings from the psychological prevention of relapse in psychosis (PRP) trial. *Acta Psychiatr Scand*. 2006;114:177–186.
47. Weissman MM, Fyer AJ, Haghighi F, et al. Potential panic disorder syndrome: clinical and genetic linkage evidence. *Am J Med Genet*. 2000;96:24–35.
48. Shi J, Badner JA, Gershon ES, Liu C. Allelic association of G72/G30 with schizophrenia and bipolar disorder: a comprehensive meta-analysis. *Schizophr Res*. 2008;98:89–97.
49. Morgan C, Fisher H. Environment and schizophrenia: environmental factors in schizophrenia: childhood trauma—a critical review. *Schizophr Bull*. 2007;33:3–10.
50. Shaw K, McFarlane AC, Bookless C, Air T. The etiology of postpsychotic posttraumatic stress disorder following a psychotic episode. *J Trauma Stress*. 2002;15:39–46.
51. Kennedy BL, Dhaliwal N, Pedley L, Sahner C, Greenberg R, Manshadi MS. Post-traumatic stress disorder in subjects with schizophrenia and bipolar disorder. *J Ky Med Assoc*. 2002;100:395–399.
52. Frame L, Morrison AP. Causes of posttraumatic stress disorder in psychotic patients. *Arch Gen Psychiatry*. 2001;58:305–306.
53. McGorry PD, Chanen A, McCarthy E, Van Riel R, McKenzie D, Singh BS. Posttraumatic stress disorder following recent-onset psychosis. An unrecognized postpsychotic syndrome. *J Nerv Ment Dis*. 1991;179:253–258.
54. Shaw K, McFarlane A, Bookless C. The phenomenology of traumatic reactions to psychotic illness. *J Nerv Ment Dis*. 1997;185:434–441.
55. Calhoun PS, Stechuchak KM, Strauss J, Bosworth HB, Marx CE, Butterfield MI. Interpersonal trauma, war zone exposure, and posttraumatic stress disorder among veterans with schizophrenia. *Schizophr Res*. 2007;91:210–216.

56. Fan X, Henderson DC, Nguyen DD, et al. Posttraumatic stress disorder, cognitive function and quality of life in patients with schizophrenia. *Psychiatry Res*. 2008;159:140–146.
57. Gearon JS, Kaltman SI, Brown C, Bellack AS. Traumatic life events and PTSD among women with substance use disorders and schizophrenia. *Psychiatr Serv*. 2003;54:523–528.
58. Kilcommons AM, Morrison AP. Relationships between trauma and psychosis: an exploration of cognitive and dissociative factors. *Acta Psychiatr Scand*. 2005;112:351–359.
59. Meyer H, Taiminen T, Vuori T, Aijälä A, Helenius H. Posttraumatic stress disorder symptoms related to psychosis and acute involuntary hospitalization in schizophrenic and delusional patients. *J Nerv Ment Dis*. 1999;187:343–352.
60. Mueser KT, Goodman LB, Trumbetta SL, et al. Trauma and posttraumatic stress disorder in severe mental illness. *J Consult Clin Psychol*. 1998;66:493–499.
61. Mueser KT, Salyers MP, Rosenberg SD, et al. 5 Site Health and Risk Study Research Committee. Interpersonal trauma and posttraumatic stress disorder in patients with severe mental illness: demographic, clinical, and health correlates. *Schizophr Bull.* 2004;30:45–57.
62. Neria Y, Bromet EJ, Sievers S, Lavelle J, Fochtmann LJ. Trauma exposure and posttraumatic stress disorder in psychosis: findings from a first-admission cohort. *J Consult Clin Psychol*. 2002;70:246–251.
63. Priebe S, Bröker M, Gunkel S. Involuntary admission and posttraumatic stress disorder symptoms in schizophrenia patients. *Compr Psychiatry*. 1998;39:220–224.
64. Resnick SG, Bond GR, Mueser KT. Trauma and posttraumatic stress disorder in people with schizophrenia. *J Abnorm Psychol*. 2003;112:415–423.
65. Seedat S, Fritelli V, Oosthuizen P, Emsley RA, Stein DJ. Measuring anxiety in patients with schizophrenia. *J Nerv Ment Dis*. 2007;195:320–324.
66. Strakowski SM, Keck PE, Jr, McElroy SL, Lonczak HS, West SA. Chronology of comorbid and principal syndromes in first-episode psychosis. *Compr Psychiatry*. 1995;36:106–112.
67. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1995;52:1048–1060.
68. Strauss JL, Calhoun PS, Marx CE, et al. Comorbid posttraumatic stress disorder is associated with suicidality in male veterans with schizophrenia or schizoaffective disorder. *Schizophr Res*. 2006;84:165–169.
69. Calhoun PS, Bosworth HB, Stechuchak KA, Strauss J, Butterfield MI. The impact of posttraumatic stress disorder on quality of life and health service utilization among veterans who have schizophrenia. *J Trauma Stress*. 2006;19:393–397.
70. Scheller-Gilkey G, Moynes K, Cooper I, Kant C, Miller AH. Early life stress and PTSD symptoms in patients with comorbid schizophrenia and substance abuse. *Schizophr Res*. 2004;69:167–174.
71. Goodman C, Finkel B, Naser M, et al. Neurocognitive deterioration in elderly chronic schizophrenia patients with and without PTSD. *J Nerv Ment Dis*. 2007;195:415–420.
72. Berman I, Kalinowski A, Berman SM, Lengua J, Gren AI. Obsessive and compulsive symptoms in chronic schizophrenia. *Compr Psychiatry*. 1995;36:6–10.
73. Eisen JL, Beer DA, Pato MT, Venditto TA, Rasmussen SA. Obsessive-compulsive disorder in patients with schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 1997;154: 271–273.
74. Fabisch K, Fabisch H, Langs G, Wieselmann G, Zapotoczky HG. Obsessive-compulsive symptoms in schizophrenia. *Schizophr Res*. 1997;24:15.
75. Fabisch K, Fabisch H, Langs G, Huber HP, Zapotoczky HG. Incidence of obsessive-compulsive phenomena in the course of acute schizophrenia and schizoaffective disorder. *Schizophr Res*. 2001;16:336–341.
76. Fenton WS, McGlashan TH. The prognostic significance of obsessive-compulsive symptoms in schizophrenia. *Am J Psychiatry*. 1986;143:437–441.
77. Karno M, Golding JM, Sorensen SB, Burnam MA. The epidemiology of obsessive-compulsive disorder in five US communities. *Arch Gen Psychiatry*. 1988;45:1094–1099.
78. Kayahan B, Ozturk O, Veznedaroglu B, Eraslan D. Obsessive-compulsive symptoms in schizophrenia: prevalence and clinical correlates. *Psychiatry Clin Neurosci*. 2005;59: 291–295.
79. Krüger S, Bräunig P, Höffler J, Shugar G, Börner I, Langkrär J. Prevalence of obsessive-compulsive disorder in schizophrenia and significance of motor symptoms. *J Neuropsychiatry Clin Neurosci*. 2000;12:16–24.
80. Meghani SR, Penick EC, Nickel EJ. Schizophrenia patients with and without OCD. *Paper presented at: 151st Annual Meeting of the American Psychiatric Association.* Toronto, ON; May, 1998.
81. Mohammadi MR, Ghanizadeh A, Moini R. Lifetime comorbidity of obsessive-compulsive disorder with psychiatric disorders in a community sample. *Depress Anxiety*. 2007;24:602–607.
82. Nechmad A, Ratzoni G, Poyurovsky M, et al. Obsessive-compulsive disorder in adolescent schizophrenia patients. *Am J Psychiatry*. 2003;160:1002–1004.
83. Porto L, Bermanzohn PC, Pollack S, Morrissey R, Siris SG. A profile of obsessive-compulsive symptoms in schizophrenia. *CNS Spectrum*. 1997;2:21–25.
84. Poyurovsky MD, Fuchs C, Weizman A. Obsessive-compulsive disorder in patients with first-episode schizophrenia. *Am J Psychiatry*. 1999;156:1998–2000.
85. Poyurovsky M, Hramenkov S, Isakov V. Obsessive-compulsive disorder in hospitalized patients with chronic schizophrenia. *Psychiatry Res*. 2001;102:49–57.
86. Tibbo P, Kroetsch M, Chue P, Warneke L. Obsessive-compulsive disorder in schizophrenia. *J Psychiatr Res.* 2000;34: 139–146.
87. Tibbo P, Warneke L. Obsessive-compulsive disorder in schizophrenia: epidemiologic and biologic overlap. *J Psychiatry Neurosci*. 1999;24:15–24.
88. Lucka I, Fryze M, Cebella A, Staszewsak E. Prodromal symptoms of schizophrenics syndrome in children and adolescents. *Psychiatr Pol*. 2002;36(suppl):283–286.
89. Iida J, Iwasaka H, Hirao F, et al. Clinical features of childhood-onset schizophrenia with obsessive-compulsive symptoms during the prodromal phase. *Psychiatry Clin Neurosci.* 1995;49:201–207.
90. Shioiri T, Shinada K, Kuwabara H, Someya T. Early prodromal symptoms and diagnoses before first psychotic episode in 219 inpatients with schizophrenia. *Psychiatry Clin Neurosci*. 2007;61:348–354.
91. Poyurovsky M, Faragian S, Shabeta A, Kosov A. Comparison of clinical characteristics, co-morbidity and pharmacotherapy in adolescent schizophrenia patients with and without obsessive-compulsive disorder. *Psychiatry Res.* 2008;159:133–139.

92. Poyurovsky M, Fuchs C, Faragian S, et al. Preferential aggregation of obsessive-compulsive spectrum disorders in schizophrenia patients with obsessive-compulsive disorder. *Can J Psychiatry*. 2006;51:746–754.
93. Rajkumar RP, Reddy YC, Kandavel T. Clinical profile of "schizo-obsessive" disorder: a comparative study. *Compr Psychiatry*. 2008;49:262–268.
94. Berman I, Merson A, Viegner B, Losonczy MF, Pappas D, Green AI. Obsessions and compulsions as a distinct cluster of symptoms in schizophrenia: a neuropsychological study. *J Nerv Ment Dis*. 1998;186:150–156.
95. Whitney KA, Fastenau PS, Evans JD, Lysaker PH. Comparative neuropsychological function in obsessive-compulsive disorder and schizophrenia with and without obsessive-compulsive symptoms. *Schizophr Res*. 2004;69: 75–83.
96. Sevincok L, Akoglu A, Kokcu F. Suicidality in schizophrenia patients with and without obsessive-compulsive disorder. *Schizophr Res*. 1002;90:198–202.
97. Poyurovsky M, Kriss V, Weisman G, et al. Familial aggregation of schizophrenia-spectrum disorders and obsessive-compulsive associated disorders in schizophrenia probands with and without OCD. *Am J Med Genet B Neuropsychiatr Genet*. 2005;133:31–36.
98. Poyurovsky M, Michaelovsky E, Frisch A, et al. COMT Val158Met polymorphism in schizophrenia with obsessive-compulsive disorder: a case-control study. *Neurosci Lett*. 2005;389:21–24.
99. Bottas A, Cooke RG, Richter MA. Comorbidity and pathophysiology of obsessive-compulsive disorder in schizophrenia: is there evidence for a schizo-obsessive subtype of schizophrenia? *J Psychiatry Neurosci*. 2005;30:187–193.
100. Mahendran R, Liew E, Subramaniam M. De novo emergence of obsessive-compulsive symptoms with atypical antipsychotics in asian patients with schizophrenia or schizoaffective disorder: a retrospective, cross-sectional study. *J Clin Psychiatry*. 2007;68:542–545.
101. Ertugrul A, Anil Yagcioglu AE, Eni N, Yazici KM. Obsessive-compulsive symptoms in clozapine-treated schizophrenic patients. *Psychiatry Clin Neurosci*. 2005;59(2):219–22.
102. Tranulis C, Potvin S, Gourgue M, Leblanc G, Mancini-Marie A, Stip E. The paradox of quetiapine in obsessive-compulsive disorder. *CNS Spectr*. 2005;10(5):356–61.
103. Lykouras L, Alevizos B, Michalopoulou P, Rabavilas A. Obsessive-compulsive symptoms induced by atypical antipsychotics. A review of the reported cases. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27(3):333–46.
104. Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry*. 2006;11(7):622–32.
105. Denys D, de Geus F, van Megen HJ, Westenberg HG. A double-blind, randomized, placebo-controlled trial of quetiapine addition in patients with obsessive-compulsive disorder refractory to serotonin reuptake inhibitors. *J Clin Psychiatry*. 2004;65(8):1040–8.
106. Bystritsky A, Ackerman DL, Rosen RM, Vapnik T, Gorbis E, Maidment KM, Saxena S. Augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder using adjunctive olanzapine: a placebo-controlled trial. *J Clin Psychiatry*. 2004;65(4):565–8.
107. Connor KM, Payne VM, Gadde KM, Zhang W, Davidson JR. The use of aripiprazole in obsessive-compulsive disorder: preliminary observations in 8 patients. *J Clin Psychiatry*. 2005;66(1):49–51.
108. Taylor MA. Are schizophrenia and affective disorder related? A selective literature review. *Am J Psychiatry*. 1992;149:22–32.
109. Walker J, Curtis V, Murray RM. Schizophrenia and bipolar disorder: similarities in pathogenic mechanisms but differences in neurodevelopment. *Int Clin Psychopharmacol*. 2002;17(Suppl. 3):S11–19.
110. Ketter TA, Wang PW, Becker OV, Nowakowska C, Yang Y. Psychotic bipolar disorders: dimensionally similar to or categorically different from schizophrenia? *J Psychiatr Res*. 2004;38:47–61.
111. Craddock N, O'Donovan MC, Owen MJ. Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. *Schizophr Bull*. 2006;32:9–16.
112. Raymond Lake C. Disorders of thought are severe mood disorders: the selective attention defect in mania challenges the Kraepelinian dichotomy a review. *Schizophr Bull*. 2008; 34:109–117.
113. Moller HJ. Occurrence and treatment of depressive comorbidity/cosyndromality in schizophrenic psychoses: conceptual and treatment issues. *World J Biol Psychiatry*. 2005;6: 247–263.
114. Bartels SJ, Drake RE. Depressive symptoms in schizophrenia: comprehensive differential diagnosis. *Compr Psychiatry*. 1988;29:467–483.
115. Osby U, Correia N, Brandt L, Ekbom A, Sparen P. Mortality and causes of death in schizophrenia in Stockholm county. *Sweden. Schizophr Res*. 2000;45:21–28.
116. Westermeyer J. Comorbid schizophrenia and substance abuse: a review of epidemiology and course. *Am J Addict*. 2006;15:345–355.
117. Siris SG, Adan F, Cohen M, Mandeli J, Aronson A, Casey E. Postpsychotic depression and negative symptoms: an investigation of syndromal overlap. *Am J Psychiatry*. 1988; 145:1532–1537.
118. Clarke DM, Kissane DW. Demoralization: its phenomenology and importance. *Aust N Z J Psychiatry*. 2002;36: 733–742.
119. Kudo J, Mori H, Gomibuchi T. Loneliness as expressed by schizophrenic patients in the early remission phase. *Nagoya J Med Sci*. 2002;65:115–126.
120. Roth S. The seemingly ubiquitous depression following acute schizophrenic episodes, a neglected area of clinical discussion. *Am J Psychiatry*. 1970;127:51–58.
121. Knights A, Hirsch SR. "Revealed" Depression and drug treatment for schizophrenia. *Arch Gen Psychiatry*. 1981;38: 806–811.
122. Baynes D, Mulholland C, Cooper SJ, Montgomery RC, et al. Depressive symptoms in stable chronic schizophrenia: prevalence and relationship to psychopathology and treatment. *Schizophr Res*. 2000;45:47–56.
123. Herz M. Prodromal symptoms and prevention of relapse in schizophrenia. *J Clin Psychiatry*. 1985;46:22–25.
124. Mandel MR, Severe JB, Schooler NR, Gelenberg AJ, Mieske M. Development and prediction of postpsychotic depression in neuroleptic-treated schizophrenics. *Arch Gen Psychiatry*. 1982;39:197–203.
125. Johnson DA. The significance of depression in the prediction of relapse in chronic schizophrenia. *Br J Psychiatry*. 1988;152:320–323.

126. Tsuang D, Coryell W. An 8-year follow-up of patients with DSM-III-R psychotic depression, schizoaffective disorder, and schizophrenia. *Am J Psychiatry*. 1993;150: 1182–1188.
127. Sim K, Chan YH, Chong SA, Siris SG. A 24-month prospective outcome study of first-episode schizophrenia and schizoaffective disorder within an early psychosis intervention program. *J Clin Psychiatry*. 2007;68:1368–1376.
128. McGlashan TH, Carpenter WT, Jr. An investigation of the postpsychotic depressive syndrome. *Am J Psychiatry*. 1976; 133:14–19.
129. Weissman MM, Pottenger M, Kleber H, Ruben HL, Williams D, Thompson WD. Symptom patterns in primary and secondary depression. A comparison of primary depressives with depressed opiate addicts, alcoholics, and schizophrenics. *Arch Gen Psychiatry*. 1977;34:854–862.
130. Van Putten T, May RP. "Akinetic depression" in schizophrenia. *Arch Gen Psychiatry*. 1978;35:1101–1107.
131. Knights A, Okasha MS, Salih MA, Hirsch SR. Depressive and extrapyramidal symptoms and clinical effects: a trial of fluphenazine versus flupenthixol in maintenance of schizophrenic out-patients. *Br J Psychiatry*. 1979;135:515–523.
133. Johnson DA. Studies of depressive symptoms in schizophrenia. *Br J Psychiatry*. 1981;139:89–101.
134. Siris SG, Harmon GK, Endicott J. Postpsychotic depressive symptoms in hospitalized schizophrenic patients. *Arch Gen Psychiatry*. 1981;38:1122–1123.
135. Roy A. Depression in the course of chronic undifferentiated schizophrenia. *Arch Gen Psychiatry*. 1981;38:296–297.
136. Moller HJ, von Zerssen D. Depressive states occurring during the neuroleptic treatment of schizophrenia. *Schizophr Bull*. 1982;8:109–117.
137. Guze SB, Cloninger CR, Martin RL, Clayton PJ. A follow-up and family study of schizophrenia. *Arch Gen Psychiatry*. 1983;40:1273–1276.
138. Martin RL, Cloninger CR, Guze SB, Clayton PJ. Frequency and differential diagnosis of depressive syndromes in schizophrenia. *J Clin Psychiatry*. 1985;46:9–13.
139. Summers F, Harrow M, Westermeyer J. Neurotic symptoms in the postacute phase of schizophrenia. *J Nerv Ment Dis*. 1983;171:216–221.
140. Roy A. Depression, attempted suicide, and suicide in patients with chronic schizophrenia. *Psychiatr Clin North Am*. 1986;9:193–206.
141. Munro JG, Hardiker TM, Leonard DP. The dexamethasone suppression test in residual schizophrenia with depression. *Am J Psychiatry*. 1984;141:250–252.
142. Elk R, Dickman BJ, Teggin AF. Depression in schizophrenia: a study of prevalence and treatment. *Br J Psychiatry*. 1986;149:228–229.
143. Leff J, Tress K, Edwards B. The clinical course of depressive symptoms in schizophrenia. *Schizophr Res*. 1988;1:25–30.
144. Johnson DA. The significance of depression in the prediction of relapse in chronic schizophrenia. *Br J Psychiatry*. 1988;152:320–323.
145. Kulhara P, Avasthi A, Chadda R, Chandiramani K, Mattoo SK, Kota SK, Joseph S. Negative and depressive symptoms in schizophrenia. *Br J Psychiatry*. 1989;154:207–211.
146. Hirsch SR, Jolley AG. The dysphoric syndrome in schizophrenia and its implications for relapse. *Br J Psychiatry*. 1989;(Suppl):46–50.
147. Barnes TR, Curson DA, Liddle PF, Patel M. The nature and prevalence of depression in chronic schizophrenic inpatients. *Br J Psychiatry*. 1989;154:486–491.
148. Bandelow B, Muller P, Gaebel W, Kopcke W, Linden M, Muller-Spahn F, Pietzcker A, Reischies FM, Tegeler J. Depressive syndromes in schizophrenic patients after discharge from hospital. ANI Study Group Berlin, Dusseldorf, Gottingen, Munich. *Eur Arch Psychiatry Clin Neurosci*. 1990; 240:113–120.
149. Addington D, Addington J. Depression dexamethasone nonsuppression and negative symptoms in schizophrenia. *Can J Psychiatry*. 1990;35:430–433.
150. Breier A, Schreiber JL, Dyer J, Pickar D. National Institute of Mental Health longitudinal study of chronic schizophrenia. Prognosis and predictors of outcome. *Arch Gen Psychiatry*. 1991;48:239–246.
151. Lindenmayer JP, Grochowski S, Kay SR. Schizophrenic patients with depression: psychopathological profiles and relationship with negative symptoms. *Compr Psychiatry*. 1991; 32:528–533.
152. Birchwood M, Mason R, MacMillan F, Healy J. Depression, demoralization and control over psychotic illness: a comparison of depressed and non-depressed patients with a chronic psychosis. *Psychol Med*. 1993;23: 387–395.
153. Koreen AR, Siris SG, Chakos M, Alvir J, Mayerhoff D, Lieberman J. Depression in first-episode schizophrenia. *Am J Psychiatry*. 1993;150:1643–1648.
154. Tapp A, Tandon R, Douglass A, Dudley E, Scholten R, Underwood M. Depression in severe chronic schizophrenia. *Biol Psychiatry*. 1994;35:667.
155. Harrow M, Yonan CA, Sands JR, Marengo J. Depression in schizophrenia: are neuroleptics, akinesia, or anhedonia involved? *Schizophr Bull*. 1994;20:327–338.
156. Mauri MC, Bravin S, Fabiano L, Vanni S, Boscati L, Invernizzi G. Depressive symptoms and schizophrenia a psychopharmacological approach. *Encephale*. 1995;21: 555–558.
157. Markou P. Depression in schizophrenia: a descriptive study. *Aust N Z J Psychiatry*. 1996;30:354–357.
158. Wassink TH, Flaum M, Nopoulos P, Andreasen NC. Prevalence of depressive symptoms early in the course of schizophrenia. *Am J Psychiatry*. 1999;156:315–316.
159. Muller MJ, Wetzel H. Dimensionality of depression in acute schizophrenia: a methodological study using the Bech-Rafaelsen Melancholia Scale (BRMES). *J Psychiatr Res*. 1998;32:369–378.
160. Sands JR, Harrow M. Depression during the longitudinal course of schizophrenia. *Schizophr Bull*. 1999;25: 157–171.
161. Zisook S, McAdams LA, Kuck J, Harris MJ, Bailey A, Patterson TL, Judd LL, Jeste DV. Depressive symptoms in schizophrenia. *Am J Psychiatry*. 1999;156:1736–1743.
162. Baynes D, Mulholland C, Cooper SJ, Montgomery RC, MacFlynn G, Lynch G, Kelly C, King DJ. Depressive symptoms in stable chronic schizophrenia: prevalence and relationship to psychopathology and treatment. *Schizophr Res*. 2000;45:47–56.
163. Bottlender R, Strauss A, Moller HJ. Impact of duration of symptoms prior to first hospitalization on acute outcome in 998 schizophrenic patients. *Schizophr Res*. 2000;44: 145–150.

164. Bressan RA, Chaves AC, Pilowsky LS, Shirakawa I, Mari JJ. Depressive episodes in stable schizophrenia: critical evaluation of the DSM-IV and ICD-10 diagnostic criteria. *Psychiatry Res*. 2003;117:47–56.
165. Serretti A, Mandelli L, Lattuada E, Smeraldi E. Depressive syndrome in major psychoses: a study on 1351 subjects. *Psychiatry Res*. 2004;127:85–99.
166. Hafner H, Maurer K, Trendler G, an der Heiden W, Schmidt M, Konnecke R. Schizophrenia and depression: challenging the paradigm of two separate diseases–a controlled study of schizophrenia, depression and healthy controls. *Schizophr Res*. 2005;77:11–24.
167. Ohayon MM, Schatzberg AF. Prevalence of depressive episodes with psychotic features in the general population. *Am J Psychiatry*. 2002;159:1855–1861.
168. Johnson J, Horwath E, Weissman MM. The validity of major depression with psychotic features based on a community study. *Arch Gen Psychiatry*. 1991;48: 1075–1081.
169. Hafner H, Maurer K, Trendler G, an der Heiden W, Schmidt M, Konnecke R. Schizophrenia and depression: challenging the paradigm of two separate diseases–a controlled study of schizophrenia, depression and healthy controls. *Schizophr Res*. 2005;77:11–24.
170. Hafner H, Loffler W, Maurer K, Hambrecht M, an der Heiden W. Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. *Acta Psychiatr Scand*. 1999;100:105–118.
171. Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, McGorry PD. Psychosis prediction: 12-month follow up of a high-risk (''prodromal'') group. *Schizophr Res*. 2003;60:21–32.
172. Schothorst PF, Emck C, van Engeland H. Characteristics of early psychosis. *Compr Psychiatry*. 2006;47:438–442.
173. Cornblatt BA, Lencz T, Smith CW, Correll CU, Auther AM, Nakayama E. The schizophrenia prodrome revisited: a neurodevelopmental perspective. *Schizophr Bull*. 2003;29: 633–651.
174. Baxter LR, Jr., Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, Gerner RH, Sumida RM. Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry*. 1989;46: 243–250.
175. Sackeim HA, Prohovnik I, Moeller JR, Brown RP, Apter S, Prudic J, Devanand DP, Mukherjee S. Regional cerebral blood flow in mood disorders. I. Comparison of major depressives and normal controls at rest. *Arch Gen Psychiatry*. 1990;47:60–70.
176. Berman KF, Doran AR, Pickar D, Weinberger DR. Is the mechanism of prefrontal hypofunction in depression the same as in schizophrenia? Regional cerebral blood flow during cognitive activation. *Br J Psychiatry*. 1993;162: 183–192.
177. Barch DM, Sheline YI, Csernansky JG, Snyder AZ. Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. *Biol Psychiatry*. 2003;53:376–384.
178. Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: a meta-analysis. *Am J Psychiatry*. 2004;161: 598–607.
179. Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry*. 2004; 161:1957–1966.
180. Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am J Psychiatry*. 2005;162:2233–2245.
181. Boks MP, Hoogendoorn M, Jungerius BJ, Bakker SC, Sommer IE, Sinke RJ, Ophoff RA, Kahn RS. Do mood symptoms subdivide the schizophrenia phenotype? association of the GMP6A gene with a depression subgroup. *Am J Med Genet B Neuropsychiatr Genet*. 2007.
182. Drevets WC. Neuroimaging abnormalities in the amygdala in mood disorders. *Ann N Y Acad Sci*. 2003;985:420–444.
183. Paradiso S, Andreasen NC, Crespo-Facorro B, O'Leary DS, Watkins GL, Boles Ponto LL, Hichwa RD. Emotions in unmedicated patients with schizophrenia during evaluation with positron emission tomography. *Am J Psychiatry*. 2003;160:1775–1783.
184. Siris SG. Depression in schizophrenia: perspective in the era of ''Atypical'' antipsychotic agents. *Am J Psychiatry*. 2000; 157:1379–1389.
185. Tollefson GD, Sanger Tm, Lu Y, Thieme ME. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. *Arch Gen Psychiatry*. 1998;55(3):250–258.
186. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry*. 1997;58(12):538–546.
187. Emsley R, Buckley PF, Jones AM, Greenwood MR. Differential effect of quetiapine on depressive symptoms in patients with partially responsive schizophrenia. *Journal of Psychopharmacology*. 2003;17(2):205–210.
188. Meltzer Hy, Alphs L, Green AI, Altamura C, ANad R, Bertoldi A, et al. International suicide prevention trial study group. Clozapine treatment for suicidality in schizophrenia: International suicide prevention trial (InterSePT). *Arch Gen Psychiatry*. 2003;60(1):82–91.
189. Siris SG, Morgan V, Fagerstrom R, Rifkin A, Cooper TB. Adjunctive imipramine in the treatment of postpsychotic depression. A controlled trial. *Arch Gen Psychiatry*. 1987;44(6): 533–539.
190. Cornblatt BA, Lencz T, Smith CW, Olsen R, Auther AM, Nakayama E, Lesser ML, Tai JY, Shah MR, Foley CA, Kane JM, Correll CU. Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective, naturalistic treatment study of adolescents. *J Clin Psychiatry*. 2007;68(4):546–57.
191. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. *JAMA*. 1990;264:2511–2518.
192. Kessler RC, Crum RM, Warner LA, et al. Lifetime co-occurrence of DSMIII-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Study. *Arch Gen Psychiatry*. 1997;54:313–321.
193. Merikangas KR, Ames M, Lui L. The impact of comorbidity of mental and physical conditions on sole disability in the US adult household population. *Arch Gen Psychiatry*. 2007;64(10):1180–1188.
194. O' Daly OG, Guillin, Tsapakis EM, et al. Schizophrenia and substance abuse comorbidity: a role for dopamine sensitization? *Journal of Dual Diagnosis*. 2005;1(2):11–40.
195 Moore TH, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health

outcomes: A systematic review. *Lancet*. 2007;370(95840): 319–328.

196. Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ*. 2002;325(7374):1199.
197. Boydell J, Dean K, Dutta R, et al. A comparison of symptoms and family history in schizophrenia with and without prior cannabis use: implications for the concept of cvannabis psychosis. *Schizophrenia Res*. 2007;93(1-3): 203–210.
198. Caton CL, Drake RE, Hasin DS, et al. Differences between early-phase primary psychotic disorders with concurrent substance use and substance-induced psychoses. *Arch Gen Psychiatry*. 2005;62(2):137–45.
199. Yucel M, Solowij N, Respondek C, et al. Regional brain abnormalities with long-term heavy cannabis use. *Arch Gen Psychiatry*. 2008;65(6):694–701.
200. Chambers RA, Bickel WK, Potenza MN. A scale-free systems theory of motivation and addiction. *Neuroscj Biobehav Rev*. 2007;31:1017–1045.
201. Dixon L, Haas G, Weiden PJ, et al. Acute effects of drug abuse in schizophrenic patients: clinical observations and patients' self-reports. *Schizophrenia Bulletin*. 1990;16: 69–79.
202. Voruganti LNP, Heslegrave RJ, Awad AG. Neuroleptic dysphoria may be the missing link between schizophrenia and substance abuse. *J Nerv Ment Dis*. 1997;185: 463–65.
203. Green AI, Noordsy DL, Burnette MF, et al. Substance abuse and schizophrenia: pharmacotherapeutic interventions. *J Subst Abuse Treat*. 2008;34:61–71.
204. Byerly MJ, Nakonezny PA, Lescouflair E. Antipsychotic medication adherence in schizophrenia. *Psych Clin North Am*. 2007;30(3):437–452.
205. Swartz MS, Wagner HR, Swanson JW, et al. The effectiveness of antipsychotic medications in patients who use or avoid illicit substances: Results from the CATIE study. *Schizophr Res*. 2008;100(1-3):39–35.
206. Drake RE, Xie H, McHugo GJ, et al. The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. *Schizophrenia Bulletin*. 2000;26(2):441–9.
207. Cascade E, Kalali A, Buckley PF. Current management of schizophrenia: antipsychotic monotherapy versus combination therapy. *Psychiatry*. 2008;5(5):28–30.