

ORIGINAL ARTICLE

Comorbid anxiety disorders in patients with schizophrenia

Kristýna VRBOVÁ¹, Ján PRAŠKO¹, Dana KAMARÁDOVÁ¹, Monika ČERNÁ¹,
Marie OCISKOVÁ^{1,2}, Klára LÁTALOVÁ¹, Zuzana SEDLÁČKOVÁ²

¹ Department of Psychiatry, Faculty of Medicine and Dentistry, Palacky University Olomouc, University Hospital Olomouc, Czech Republic; ² Department of Psychology, Philosophical Faculty, Palacky University Olomouc, Czech Republic.

Correspondence to: Jan Prasko, Department of Psychiatry, Faculty of Medicine and Dentistry, Palacky University Olomouc, University Hospital Olomouc, Czech Republic; E-MAIL: prasko@fnol.cz

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Abstract

BACKGROUND: According to recent research, it is still more evident that patients with schizophrenia also suffer from anxiety disorders. Although there is a significant clinical relevance, the impact of anxiety disorders in patients with schizophrenia remains poorly understood.

METHOD: A literature search was conducted via Medline and Web of Science using key words relating to schizophrenia and all diagnoses of anxiety disorders. This article reviews the epidemiology and phenomenology of comorbid anxiety symptoms and disorders in schizophrenia.

RESULTS: The literature review shows that anxiety and comorbidity with panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder and/or posttraumatic stress disorder are all more common in schizophrenia than in the population. Higher levels of anxiety or comorbid diagnosis of anxiety disorder are associated with lower quality of life, impaired functioning, increased incidence of suicide attempts and increased relapse risk. This comorbidity negatively affects treatment efficacy and outcome of the disorder. Comorbidity of anxiety disorder may also play a role in processes that underpin the development of psychotic symptoms. The conventional treatment for anxiety disorder can help alleviate anxiety symptoms in those patients.

CONCLUSION: The data support the importance of correct evaluating and treatment of comorbid anxiety disorders and symptoms in schizophrenia patients.

INTRODUCTION

Both schizophrenia and anxiety disorders are psychiatric diagnoses that may occur separately, or may co-occur as comorbidity (Young *et al* 2013). Prevalence of comorbidity of schizophrenia and anxiety disorders differs from diagnosis to diagnosis (Achim *et al* 2011) and is associated with lower social functioning (Blanchard *et al* 1998). Patients with schizophrenia suffer from a variety of symptoms that may change from early to late stage. Closer attention is cur-

rently paid to warning signs that may precede onset or relapse of psychosis. Anxiety may be one of the symptoms indicating progression towards psychotic decompensation (Argyle 1990). Anxiety can also differ between patients with different diagnoses. Psychotic anxiety is more intense and has more psychomotor symptoms (Baylé *et al* 2011). In spite of recent progress in research of both anxiety disorders and schizophrenia, there are still not enough data on their relationship. Hierarchical assumptions built in diagnostic systems and difficulties in methodology interfere with

the development of studies on accessory symptoms outside of the core positive-negative-disorganized features (Braga *et al* 2004). Findings from the latest studies have repeatedly challenged these beliefs by presenting data on comorbid disorders in schizophrenic patients. Comorbid anxiety disorders or symptoms such as obsessive-compulsive disorder (OCD), panic disorder, social phobia, generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) can develop in schizophrenia in the same way as in patients with anxiety disorder only (Dernovsek & Sprah 2009).

METHOD

A computerized search of the literature published from 1966 to December 2012 was conducted on Medline and Web of Science. Only studies encompassing the diagnosis of schizophrenia were included. The relevant review articles, papers and abstracts were identified using the word “schizophrenia” and the words from the names of each anxiety disorder mentioned in 10th revision of the International Classification of Diseases (ICD-10). The databases were searched for articles containing the combinations of the following keywords: schizophrenia, panic disorder, social phobia, generalized anxiety disorder, agoraphobia, specific phobia, posttraumatic stress disorder and OCD. No language-specific constraints were applied. After computer search, the list of references was examined manually to find supplementary articles.

RESULTS

In schizophrenia, different types of anxiety disorders may occur (Baylé *et al* 2011). Another question is whether prevalence of anxiety disorders also differs in the group of psychotic illnesses (schizophrenia, schizoaffective disorder). In their study, Cosoff and Hafner (1998) examined 100 inpatients with DMS-IV diagnoses of schizophrenia or schizoaffective disorder and they also involved patients with bipolar disorder, whose Kraepelinian separation from schizophrenia is being questioned (Craddock & Owen 2005). The proportion of patients with anxiety disorder (43–45%) was almost identical across these three diagnoses. Also the level of anxiety did not differ statistically between schizophrenic patients and those with schizoaffective disorder (Ndetei *et al* 2013). The prevalence rates of social phobia (17%), OCD (13%) and generalized anxiety disorder in patients with schizophrenia were relatively high. The prevalence of OCD (30%) and panic disorder (15%) were higher in patients with bipolar disorder (Cosoff & Hafner 1998). In contrast to this study, Young *et al* (2013) found statistically significant differences in prevalence of anxiety disorder between these three groups of patients. Anxiety disorders were most frequent in patients with schizoaffective disorder (30.1%), as compared with bipolar patients (22.4%)

and patients with schizophrenia (16.7%). Seedat *et al* (2007a) focused on hospitalized schizophrenic patients. Their results suggest that 25% of schizophrenic patients suffer from anxiety disorder. In case of comorbidity of schizophrenia and anxiety or affective disorder, 44.9% of patients were affected (Karatzias *et al* 2007). GAD and social phobia were the most frequent ones. They also found a wide discrepancy between diagnosis made by a structured interview (Mini International Neuropsychiatric Interview) and by clinical symptom status measures (face-to-face diagnostic interview, the Hospital Anxiety and Depression Scale, the Hamilton Anxiety Scale, the Spielberg Anxiety Inventory and the Stein Generalized Anxiety Disorder Scale). Patients suffering from psychosis or bipolar disorder may also suffer from more than one anxiety disorder. In their study, Ciapparelli *et al* (2007) investigated 98 patients with schizophrenia, schizoaffective disorder or bipolar disorder. Multiple anxiety diagnoses were observed in 32.6% of patients.

Level of anxiety is associated with clinical symptomatology and quality of life in patients with schizophrenia and schizoaffective disorder (Lysaker & Salyers 2007; Wetherell *et al* 2003; Huppert & Smith 2005). Higher level of anxiety is connected to more severe hallucinations, less hope and lower psychosocial function (Lysaker & Salyers 2007). Thus, according to other authors, the presence of comorbidity of anxiety disorder does not make differences in level of psychotic symptoms (Achim *et al* 2011).

There is increasing evidence for the significant connection between child trauma and schizophrenia (Benouna-Greene *et al* 2011; Larsson *et al* 2013, Lysaker *et al* 2005, Lysaker & Salyers 2007; Matheson *et al* 2013; Outcalt & Lysaker 2012; Sideli *et al* 2012). The influence of childhood adversity in development of schizophrenia was studied in a meta-analysis by Matheson *et al* (2013). They found moderate- to high-quality evidence of association with childhood adversities in patients with schizophrenia compared to healthy controls. Lysaker *et al* (2005) studied the relation between sexual abuse and anxiety in patients with schizophrenia. In their group of 40 patients, twenty-one had been sexually abused in childhood. Sexual abuse in schizophrenia patients was associated with higher level of dissociation and intrusive experiences. Sexual trauma is also associated with higher level of anxiety (Lysaker *et al* 2005; Lysaker & Salyers 2007). Sexual trauma is also associated with higher social withdrawal due to stigmatization and greater levels of discrimination experience and alienations (Outcalt & Lysaker 2012). Thus, childhood abuse itself is not sufficient for development of psychosis, also genetic liability and later environmental risk play role in development of psychosis (Sideli *et al* 2012). Connection of anxiety disorders and schizophrenia also suggest an association between presence of schizophrenia in first-degree relatives and increase risk for anxiety disorders (DeVylder & Lukens 2013).

There are some studies that investigate self-esteem and anxiety in patients with schizophrenia (Karatzias *et al* 2007; Lysaker *et al* 2008). Patients with comorbid anxiety of affective disorders have lower self-esteem (Karatzias *et al* 2007).

Panic disorder and/or agoraphobia

Occurrence of panic disorder with or without agoraphobia and panic attacks is common in persons suffering from schizophrenia or schizoaffective disorder. Panic disorder is typically characterized by paroxysmal presence of symptoms, as compared to schizophrenia, the symptoms of which are often chronic and thus it can be easily overlooked. The mechanism of association between these two disorders is not known. It is possible that psychotic symptomatology leads to panic attacks or vice-versa, i.e. that panic attacks lead to higher vulnerability to psychotic disorder (Goodwin *et al* 2004).

Labbate *et al* (1999) carried out a study to find out the frequency of panic disorder and panic attacks in 53 male outpatients with chronic schizophrenia or schizoaffective disorder. Appearance of panic disorder differs between different types of psychosis. Comorbidity of panic disorder was present in 10% of patients with schizoaffective disorder or undifferentiated schizophrenia compared to 47% of patients with paranoid schizophrenia. Also panic attacks were more frequently present in patients with paranoid schizophrenia (57%) as compared with schizoaffective or undifferentiated schizophrenia patients (20%).

Influence of comorbid panic on clinical symptoms in patients with schizophrenia was studied by Ulas *et al* (2007). In their study, forty-nine patients suffering from schizophrenia were rated using the Positive and Negative Syndrome scale (PANSS), Clinical Global Impression (CGI), Hamilton Depression Rating Scale (HDRS), Extrapyramidal Symptom Rating Scale (ESRS), and Bandelow Panic and Agoraphobia Rating Scale. Seven (14.3%) patients fulfilled the panic disorder criteria and fifteen (30.6%) patients met the criteria for panic attacks. Patients with panic symptoms had higher scores in the PANSS, HDRS, CGI and ESRS. Higher scores in the HDRS in schizophrenic patients were also found by Chen *et al* (2001). Schizophrenic patients with panic disorder also report higher level of dysthymia when compared with schizophrenic patients without comorbidity (Rapp *et al* 2012). As far as positive symptoms of schizophrenia are concerned, panic disorder is related to psychotic symptoms (Cassano *et al* 1998) mostly to paranoia (Huppert & Smith 2005; Bermanzohn *et al* 1999). In their 24-month follow-up study, Craig *et al* (2002) examined schizophrenia/schizoaffective patients (n=225), patients with bipolar disorder with psychosis (n=138) and with major depression with psychosis (n=87). Presence of panic disorder was investigated with the Structured Clinical Interview for DSM-III-R. After 24 months, patients with baseline panic symptoms showed statistically

significantly higher probability of positive symptoms exhibition. Another important topic is hostility that may occur in both patients with panic (Fava *et al* 1993) and psychotic patients (Bartels *et al* 1991; Reagu *et al* 2013). Patients with comorbid schizophrenia and panic had higher levels of hostility as compared to patients with schizophrenia only (Chen *et al* 2001).

Relationship with negative symptomatology is less obvious. Huppert and Smith (2005) found no relationship between presence of panic and negative symptoms. According to other authors, comorbidity with panic disorder and schizophrenia negatively affects level of cognitive functioning as compared to patients with schizophrenia only (Rapp *et al* 2012). Comorbidity with panic affects not just the clinical symptoms, but also global functioning of patients. Chan *et al* (2001) measured level of functioning with the Global Assessment of Functioning Rating Scale (GAF) in a group of 32 patients. Eight patients met the DSM-IV criteria for panic attacks. Scores in the GAF scale were significantly lower than in those without panic attacks. Comorbidity of schizophrenia and panic is associated with a decrease in the psychological domain of the World Health Organization Quality of Life Instrument –Short Form (Ulas *et al* 2010). These results show that panic symptoms in schizophrenia may be related to level of depression, extrapyramidal side-effects and positive and negative symptoms, and may influence the quality of life.

Social phobia

Social anxiety is a frequent comorbidity of schizophrenia but often remains unrecognized and is thus associated with a high level of disability. Social anxiety is linked with heightened symptoms and lower self-esteem (Lysaker *et al* 2008). Diagnosing social anxiety may be especially valuable in management of patients with schizophrenia, because of exaggerated social isolation in patients with such comorbidity. Social anxiety is a disabling condition in outpatients with schizophrenia. Lower self-esteem can be a risk factor for the development of social anxiety in individuals with schizophrenia (Lysaker *et al* 2008).

Comorbidity of social phobia with schizophrenia is reported in 11% to 36% (Mazeh *et al* 2009; Cosoff & Hafner 1998; Braga *et al* 2005; Pallanti *et al* 2004; Voges & Addington 2005). Thus, the prevalence is higher than in healthy population (12.1%) (Kessler *et al* 2005). The main cause of higher prevalence of social phobia in patients with schizophrenia has not been clarified yet. Changes in functioning are probably present before the clinical onset of the disease. It was found that severe social anxiety in patients with first episode of psychosis is associated with worse premorbid functioning (Romm *et al* 2012). Also negative beliefs about psychosis and self may play a role in the development of social anxiety disorder (Gumley *et al* 2004).

There is a question whether presence of social phobia has an impact on clinical symptoms of schizo-

phrenia. The PANSS for schizophrenia is useful in measuring positive and negative symptoms of schizophrenia (Kay *et al* 1987). Patients with comorbid social phobia had higher severity PANSS total score (Mazeh *et al* 2009). Schizophrenia patients with social anxiety disorder comorbidity have significantly higher scores on the Liebowitz Social Anxiety Scale (LSAS) (Pallanti *et al* 2004). The score of the PANSS positive subscale significantly correlated with the score of the LSAS "fear" scale (Mazeh *et al* 2009). Specific behavior that is related with social anxiety seems to be associated with negative symptoms (Penn *et al* 1994). Avoidance scores are higher among patients with negative signs (Mazeh *et al* 2009). On the other hand, scores of social anxiety in schizophrenia patients with comorbidity of social anxiety and scores of patients with social anxiety as a primary diagnosis do not differ (Pallanti *et al* 2004).

Posttraumatic stress disorder

Dissociation is often related to psychological trauma and is also commonly correlated with PTSD. Both dissociation and trauma are frequent in patients with schizophrenia. In patients with schizophrenia who might not develop PTSD posttraumatic symptomatology may reflect dissociation and Schneiderian symptoms. Vogel *et al* (2009) in their study of 71 patients suffering from schizophrenia, depression, PTSD and dissociative disorder used the PANSS, Montgomery-Åsberg Depression Rating Scale (MADRS), Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie scale for dissociation and Structured Clinical Interview for DSM-IV (SCID). Based on their findings, trauma and dissociation were connected with more severe symptoms of schizophrenia. Particularly high levels of dissociation were associated with an increase in symptom burden while criterion A and PTSD had little or no such effect.

Higher risk of development of psychosis in patients with child trauma was demonstrated in a meta-analysis by Varese *et al* (2012). The prevalence of PTSD in patients with schizophrenia ranges from 28% to 51% (TARRIER & PICKEN 2011; MCGORRY *et al* 1991; PRIEBE *et al* 1998). There is a question of genetic vulnerability to development of psychosis after trauma. Collip *et al* (2013) studied twins to investigate the influence of FK506 binding protein 5 in development of psychosis after trauma. The FK506 gene is an important regulator of the stress hormone system. They found an interaction between child trauma and FK506 gene polymorphism on psychotic symptoms and cortisol. Their findings suggest that trauma increases the risk of psychosis by persisting changes in the cortisol feedback loop.

Schäfer and Fisher (2011) reviewed the current literature on childhood trauma and emerging treatments for PTSD, one of its most common consequences, in patients with psychotic disorders. Between 40% and 50% of patients with psychosis reported either childhood sexual abuse or childhood physical abuse. The

diagnostic criteria for PTSD were fulfilled in 11% to 46% of patients. The authors proved a positive connection between clinical profile, outcome and presence of a history of PTSD and/or child trauma. In a cross-sectional study of Beattie *et al* (2009), 45% of psychotic patients had moderate to severe PTSD symptoms related to psychosis and 31% to admission. The most distressing aspects of psychosis and admission were for most subjects' positive symptoms and the first admission. Physical and childhood sexual traumas were significant predictors of some PTSD symptoms.

Obsessive-compulsive disorder

The presence of obsessive-compulsive symptoms in schizophrenia patients was recognized at the very beginning of the descriptions of the illness. The prevalence of obsessive-compulsive symptoms in schizophrenia (OCSs) seems to be higher than would be expected on the basis of comorbidity rates. The association between schizophrenia and OCD is complex. Although obsessive-compulsive symptoms in schizophrenia patients are conceptually controversial, recent findings suggest that schizophrenia with OCSs may constitute a distinct schizophrenic subgroup. Several studies investigated the association between OCSs and schizophrenia. These studies defined their co-occurrence in terms of comorbidity and compared schizophrenia patients separated into groups according to whether OCSs in schizophrenia were present or not.

Review of brain abnormalities in schizophrenia and OCD detected the involvement of similar regions, namely the frontal lobe, basal ganglia, thalamus and cerebellum, in both schizophrenia and OCD (Venkatasubramanian *et al* 2009). Neurodevelopmental etiopathogenesis has been designed to explain schizophrenia as well as OCD (Hwang *et al* 2009). There is also a significant overlap in neurotransmitter system dysfunction, especially in the serotonin and dopamine system (Tibbo & Warneke 1999).

The rates of occurrence of OCSs and OCD were studied by Kayahan *et al* (2005). They examined 100 subjects with the DSM-IV diagnosis of schizophrenia with the SCID-P, PANSS, Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and Calgary Depression Rating Scale for Schizophrenia. A total of 30% of patients met the criteria for OCD and OCSs occurred in 64% of patients. In a 5-year study by de Haan *et al* (2013), 48.9% of schizophrenic patients reported OCSs. And the rates of subjects with comorbid OCD varied between 7.3% and 11.8% during the follow-up. When comparing groups with and without OCSs schizophrenic patients with OCSs were found to have an earlier onset of schizophrenia, lower socio-economic status and more severe psychiatric symptoms. Also earlier hospitalization of schizophrenia patients, positive family history of schizophrenia and more severe schizophrenic symptoms are associated with OCS comorbidity. In patients with chronic schizophrenia, negative symptoms were

associated with OCD comorbidity (Owashi *et al* 2010). Lower age of onset in a group of OCD comorbidity with schizophrenia was also found in a study by Üçok *et al* (2011).

Psychotic symptoms may also occur in patients with OCD. In a study by Eisen and Rasmussen (1993) of 475 OCD patients diagnosed according to the DSM-III-R and/or treated as OCD patients in outpatient clinics, 67% of patients were identified as having psychotic symptoms (delusions, hallucinations and/or thought disorder). Six percent of subjects had only lack of insight and high conviction about the reasonableness of the obsession. This is referred to as OCD without insight. In their group, only 4% of OCD patient met the criteria for schizophrenia.

Poyurovsky *et al* (2003) provided phenomenological characterization of a schizophrenia subgroup with OCD. A coherent sample of 55 subjects who met the DSM-IV criteria for both OCD and schizophrenia matched for age and number of hospitalization was examined with the SCID-I, Scales for the Assessment of Positive and Negative Symptoms, Y-BOCS, CGI and HDRS. Patients with schizophrenia with OCD had lower positive dimension scores. They identified two subgroups of schizo-obsessive patients, OCD independent of schizophrenia symptoms and OCD partially overlapping positive symptoms. In their group, schizophrenia patient with OCD were treated with add-on SSRIs or clozapine more than schizophrenia patients without OCD.

Guillem *et al* (2009) examined the relationship between schizophrenia symptoms and OCSs in schizophrenia by correlation with a dimensional perspective in 59 patients with schizophrenia. The goal of their study was to determine how OCSs contribute to symptom expression in schizophrenia. Patients were rated with the Schedule for the Assessment of Positive/Negative Symptoms (SAPS/SANS) and Y-BOCS. The results showed a significant positive relationship between delusions and obsessions. These findings are in accordance with the view that they reflect demonstration of the similar mechanisms. Similar results denote an association between auditory hallucinations and compulsions. Inverse relationship was found between somatic obsession and disorganization and between holding-collecting compulsion and delusion or auditory hallucinations. Thus, OCSs may have protective effects against disorganization and psychotic symptoms.

There is also a question how comorbid OCD or OCSs influence severity and demographic features of patients with schizophrenia. Schizophrenic patients may be divided into three groups: without comorbid OCSs, with OCD but not meeting the criteria for OCD, and with OCD comorbidity and diagnosed by the DSM-IV criteria. According to the results of a review and meta-analysis by Cunill *et al* (2009), the presence of OCSs was significantly related to greater severity of global psychotic symptoms, positive psy-

chotic symptoms and negative psychotic symptoms. Surprisingly, there were no differences in the severity of global psychotic, positive psychotic symptoms or negative psychotic symptoms between the group with OCD and non-OCD group. Patients with OCD comorbidity and schizophrenia showed higher scores in the MADRS as compare to schizophrenic patients only or those with OCS comorbidity. Patients with OCSs had lower mean PANSS negative subscale scores than the two other groups (de Haan *et al* 2005). Patients with OCS comorbidity have higher rates of occupation, lower prevalence of other psychiatric disorder, lower numbers of hospitalizations, higher GAF score and longer duration of education as compared to patients without OCSs, as shown by Üçok *et al* (2011). Patients with schizophrenia and OCD or OCSs showed greater severity of schizophrenia symptoms measured by the Y-BOCS and PANSS, when compared to those with schizophrenia without OCD and OCSs, claimed Sa *et al* (2009).

The etiopathogenesis of OCSs or OCD in patients with schizophrenia may be also influenced by drugs used in treatment of schizophrenia. The new-onset OCSs have been reported with the use of atypical, antiserotonergic second-generation antipsychotics (de Haan *et al* 2002; Sa *et al* 2009; Mukhopadhaya *et al* 2009; Schirmbeck *et al* 2011). The glutamatergic and serotonergic systems are suspected to be involved in the development OCSs in patients treated with atypical antipsychotics (Mahendran *et al* 2007). A beneficial role of antipsychotics in the treatment of OCD may be played by dopamine. Several clinical and epidemiological studies showed that the subgroup of obsessive-compulsive schizophrenia is associated with poor outcome and is more frequent than previously realized (Seedat *et al* 2007b; Hwang *et al* 2009, Cunill *et al* 2009; Owashi *et al* 2010; Üçok *et al* 2011). Two controlled trials focused on influence of accessory SSRIs to standard antipsychotic treatment in patients with schizophrenia. Their clinical condition either improved or worsened (Reznik & Sirota 2000).

A few studies investigated the role of clozapine. Patients using clozapine had significantly higher severity scores in both obsessive-compulsive and schizophrenia rating scales (Sa *et al* 2009; Schirmbeck *et al* 2011; Mukhopadhaya *et al* 2009). There are some reports showing de novo appearance or reappearance of pre-existing OCSs under clozapine therapy. However, there are also reports of a positive effect of clozapine therapy in obsessive-compulsive schizophrenic patients (Reznik *et al* 2004). It seems that comorbid OCSs are common among clozapine-treated refractory schizophrenic patients.

An individual treatment approach is necessary in treatment of patients with schizophrenia that should be based on the pathogeneses and clinical status of the patient (Hwang *et al* 2009).

CONCLUSIONS

In most cases, patients with comorbid anxiety disorders were not treated for them, primarily due to the fact that their psychotic symptoms required full diagnostic and therapeutic attention. Anxiety symptoms were associated with poorer outcomes and negative impact on the quality of life of patients with schizophrenia. Schizophrenic patients with severe anxiety create an identifiable subgroup of patients. In some schizophrenia patients, a history of childhood sexual abuse may be a predisposing factor for significant levels of persistent anxiety. Clinicians treating patients with schizophrenia should focus on anxiety disorder comorbidity, especially because patients may not report anxiety symptoms at the first presentation. Whereas the treatment of anxiety disorders is successful, more attention should be paid to their comorbidity with psychosis and possibilities of their treatment. Larger and methodologically superior studies are necessary to clarify the relationship between schizophrenia and anxiety disorders.

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