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Anxiety as a Core Aspect of Schizophrenia

Stefano Pallanti · Andrea Cantisani · Giacomo Grassi

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Abstract The clinical relevance of anxiety disorders in schizophrenia has been neglected for a long time and has only recently become the subject of a systematic investigation, although its consequences may have a very negative impact on the outcome and considerably worsen the trajectory of the disease. This could be originally related to the hierarchical organization of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and to the lack of assessment instruments. In this article, we will review the most recent literature concerning two of the most impairing anxiety disorders in comorbidity with schizophrenia, such as panic disorder and social anxiety disorder, briefly analyze the role of anxiety in the prodromal phase of psychosis and provide suggestions for the clinical assessment.

Keywords Schizophrenia · Psychosis · Anxiety · Panic disorder · Social anxiety · Comorbidity · Prodromal symptoms · Psychiatry

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S. Pallanti (✉) · A. Cantisani · G. Grassi
Department of Psychiatry, University of Florence,
via delle Gore 2H,
50141 Florence, Italy
e-mail: stefano.pallanti@unifi.it

A. Cantisani
e-mail: andre.canti@gmail.com

G. Grassi
e-mail: giacomograssimd@gmail.com

S. Pallanti
Department of Psychiatry, Mount Sinai School
of Medicine, 1 Gustave Levy Place,
New York, NY 10029, USA

Introduction

Until the early 1980s psychiatry research had focused on psychotic disorders, whereas psychology research had focused on anxiety disorders and neurosis, maintaining a clear separation between these research fields. Although the relationship between anxiety disorders (AD) and schizophrenia (SZ) was recognized long ago, it remains a substantial matter of debate. Even if the presence of anxiety in psychotic disorders has been associated with a greater risk of suicide [1], poorer social functioning [2] and an increased risk of relapse [3], the clinical significance of this problem has often been under-recognized or even neglected. This could be originally related to the hierarchical organization of the Diagnostic and Statistic Manual of Mental Disorders (DSM). For example, the Third Edition allowed a diagnosis of an AD only if it were not evidently caused by another axis I disorder such as SZ. Nowadays the scenario has changed, as this criterion became less restrictive and evolved gradually along with subsequent editions of the manual, arriving at the current DSM-IV TR definition that allows the diagnosis of an AD if the symptoms are "not better accounted" or "not restricted" to schizophrenia. In fact, recent epidemiological studies showed that anxiety disorders are highly prevalent in schizophrenia spectrum disorders and that these prevalence rates are higher than those reported for the general population [4].

Considering the fact that evidence suggests comorbid anxiety disorders may worsen patients' functioning [5] and that benzodiazepine use is associated with a marked increase in mortality among patients with schizophrenia (whereas the use of an antidepressant is not) [6••], the prompt recognition and the consequent search for a more specific treatment of the symptoms of AD could be of potential benefit for schizophrenia patients.

In this article, we will review the most recent literature concerning some of the most frequently comorbid ADs in schizophrenia, such as panic disorder (PD) and social

anxiety disorder (SAD). We will also briefly focus on anxiety symptoms in the prodromal phase of schizophrenia. However, for a review of the current literature on two other important comorbid conditions in schizophrenic patients such as obsessive-compulsive disorder and post-traumatic stress disorder, we refer the reader to other papers.

Panic Disorder in Schizophrenia

The prevalence rates of comorbid panic disorder in schizophrenia vary considerably across studies; therefore, it is difficult to obtain an exact estimate of the frequency of this phenomenon in both clinical and research settings.

In 2009, Buckley and colleagues reviewed a considerable amount of data regarding the more relevant disorders in comorbidity with schizophrenia and found that the prevalence of PD ranged from 3.3 %–29.5 %, whereas the prevalence in the US general population ranges from 2.0 %–5.1 % [7, 8]. This variability in prevalence percentages may be due to the fact that the diagnostic criteria used in these studies are not always the same, which may relate to the aforementioned changes in the different editions of the DSM.

A more recent meta-analysis [4], published in 2011 by Achim et al., combined the data of 23 different studies, for a total of 1,393 patients, and reported prevalence ranging from 0.0 % to 35 %, with a mean rate of 9.8 %. The various instruments used to detect symptoms and different sample characteristics may have accounted for this great variance.

The latest evidence is represented by a study that investigated anxiety disorder comorbidity in a sample of 631 patients primarily diagnosed with bipolar disorder, schizophrenia or schizoaffective disorder [9]. The authors found that PD rates were significantly higher in participants with schizoaffective disorders (15.7 %) as compared to patients with schizophrenia (6.9 %) or bipolar disorder (6.9 %).

The current literature showed that many patients with comorbid schizophrenia and panic symptoms/disorder appear to have a distinct pattern of clinical symptoms, comorbidities, neuropsychological performances and treatment responses, suggesting the existence of a panic-psychosis subtype of schizophrenia [10]. From one perspective, there are a few reports showing a worsening or a de-novo onset of panic symptoms in schizophrenic patients following the administration of typical antipsychotics [11]. On the other hand, several authors reported that panic disorder may begin before the onset of psychosis, particularly during the prodromal phase, describing a temporal association of paroxysmal panic symptoms with an abrupt onset of auditory hallucinations or paranoid thinking, suggesting that panic could represent a distinct pathogenic primary causation for the development of a psychotic syndrome [11]. This hypothesis is also supported by studies showing a higher rate of positive symptoms in schizophrenia patients who present comorbid panic symptoms [10]. Furthermore, panic-schizophrenia patients showed some clinical characteristics distinct from those without co-morbid panic symptoms such as a higher rate of depression, suicidal ideation, lifetime substance abuse and hostility [10, 12, 13].

In addition to the issue noted above, the neurocognitive performance of schizophrenia patients with and without panic symptoms/disorder seems to be different [10]. In a recent study, schizophrenia patients with panic disorder reported a better global neurocognitive performance, showing higher verbal IQ, better problem solving, set switching, delayed recall, attention and verbal fluency than schizophrenia patients without comorbid panic symptoms/disorder [10]. Finally, a common genetic vulnerability to both panic and psychosis could explain the high rate of comorbidity between the two disorders. Such a relationship has been suggested by studies reporting a higher risk for panic among first-degree relatives and monozygotic twins of schizophrenic patients [14].

The presence of panic and depressive symptoms is correlated to a lower global quality of life in schizophrenia patients [15•]. Thus, the recognition and treatment of panic symptoms/disorder represents an important goal for the management of these patients. However, an evidence-based approach for the recognition, assessment and treatment of panic attacks in SZ is still difficult because there are few data addressing this issue in the current literature.

Panic diagnosis represents a clinical challenge in schizophrenia. In fact, psychotic symptoms and cognitive impairment represent two main limitations in identifying panic symptoms. Concurrent hallucinations and delusions may mask panic symptoms, and the cognitive impairment may limit the clinical interview. Therefore, panic is often misdiagnosed as a physical illness [16•]. Unfortunately, there are no specific diagnostic interviews designed to address the particular issues of comorbid panic and schizophrenia. Savitz and colleagues, in a recent study, developed a clinical interview for the assessment of panic symptoms in schizophrenia, but this scale has still not been validated [16•]. However, in our opinion, several aspects of the patient story could help in identifying the presence of panic symptoms.

First of all, the clinician has to pay attention to the coping style of the patient. If the patient reacts to hallucinations with an agoraphobic-like response, both passive (e.g., escaping from a situation) and active (e.g., becoming hostile or aggressive), it is plausible to suspect a panic attack and appropriate treatment should follow. The few data on this topic suggest that alprazolam and clonazepam could be helpful for treating panic symptoms, considering also that many schizophrenia patients report panic attacks that have a longer duration than panic attacks in non-schizophrenic patients, persisting up to hours (e.g., up to 3 h). Some authors reported that the improvement in panic symptoms is then followed by an improvement of positive and negative symptoms [11].

Social Anxiety in Schizophrenia

Social anxiety is one of the most frequent psychiatric disorders in the general population and is a cause of functional disability. Moreover, subjects with this diagnosis are more prone to develop substance or alcohol abuse, increasing the social and working disability. In patients with schizophrenia, this particular pattern of additional problematic conditions may lead to even more harmful consequences, seriously worsening the already poor outcome of the disorder [17]. Social phobia in schizophrenia has been associated with an increased risk of suicide, poorer quality of life [4], poorer social functioning [18] and lower self-esteem [19]. Nevertheless, compared to other anxiety disorders such as panic disorder or obsessive-compulsive disorder, social anxiety has not been intensively and widely investigated. In 1994, Penn et al. suggested that social anxiety was more frequent in schizophrenia patients than in the general population [20], and epidemiological studies found prevalence rates ranging from 13 % to 39 % [5]. These percentages are confirmed by a recent meta-analysis [4] that reports a range of social anxiety comorbidity in schizophrenia patients from 3.6 % to 39.5 %, making it one of the most frequent anxiety disorders. However, schizophrenia and social anxiety have some superficial similarities in symptom presentation that could confuse a clinician. Both may result in social withdrawal, isolation or the feeling of being judged negatively by others, but in the former these symptoms are phenomenologically related to detachment, while in the latter they are mainly caused by interpersonal sensitivity. In line with this, a study of outpatients with schizophrenia found a correlation between the increase in negative symptoms and the decrease in insight and avoidance-related behaviors [5]. This may be interpreted as an expression of the detachment secondary to negative symptoms of schizophrenia that could easily be confounded with social phobia. Moreover, the same study found that schizophrenia patients with comorbid social anxiety disorder show higher levels of insight and avoidance behaviors, supporting the hypothesis that awareness of illness could result in an increase of social phobia. As hypothesized, the same group of patients showed lower scores on quality of life measures and lower indexes of social adjustment [5].

From a clinical point of view, it is important to underline some peculiar subgroup characteristics that may be helpful in the detection of social phobia in schizophrenia. This kind of patient usually has a tendency to anxiety disorder, and frequently the clinical presentation is complicated by substance abuse. Moreover, and maybe even more specifically, a very low social adaptation with low subjective well-being co-occurs with a good family adaptation, suggesting that the patient may feel distressed only during unfamiliar social circumstances involving interaction with strangers. The assessment can be done with the Liebowitz Social Anxiety Scale (LSAS), as its use has been found to be adequate and reliable even in this subgroup of patients [5].

In a study published in 2010 [21], Lysaker and colleagues focused on a wider set of potential correlates of social anxiety in schizophrenia, such as negative and positive symptoms, affect recognition, self-esteem and internalized stigma. One of the interesting hypotheses that the authors posed was that these last two variables could lead to social anxiety symptoms given the fact that self-esteem has been associated with social competence [22] and stress resistance [23], making the patients more vulnerable, and that that awareness of stigma among persons with schizophrenia may result in social avoidance [24]. The results indicated that self-esteem, self-stigma, negative symptoms and emotional discomfort were significantly related to social anxiety assessed concurrently and 5 months later. Moreover, negative symptoms and discrimination experiences at baseline continued to predict social anxiety at 5 months, also controlling for initial levels of social anxiety.

More recently, a follow-up study of deinstitutionalized schizophrenia patients showed that after 5 years social anxiety symptoms were very common among this group and that the development of these was not associated with psychotic symptoms or social functioning, but with subjective quality of life. At both baseline and follow-up, lower measures of subjective quality of life were correlated with higher symptoms of social phobia, highlighting again the correlation between these factors, but suggesting a more complex relationship [25]. This recent evidence highlights the impact that social anxiety has on schizophrenia patients and has important clinical implications, as it could be of help in developing more person-centered interventions, taking into account many aspects of the illness that are often neglected, such as the influence of stigma and discrimination, the role of self-esteem and the relationship with quality of life and severity of disease.

Non-Psychotic Psychosis Prodrome

The spectrum of psychopathological symptoms in the schizophrenia prodromal phase is very large, including different manifestations preceding the psychosis onset, ranging from mood symptoms to attenuated psychotic symptoms. However, since the 1930s, many authors have noted that "neurotic symptoms" or anxiety symptoms often precede the onset of psychotic symptoms. In a 1996 review on the prodromal manifestations of psychosis, Yung and McGorry

reported that several authors showed the presence of anxiety symptoms, obsessive-compulsive symptoms and somatic concerns as typical schizophrenic prodromal symptoms [26].

Recently we studied the prevalence and the clinical impact of obsessive-compulsive (OC) and OC spectrum symptoms, such as hypochondriasis, in schizophrenic patients treated with atypical antipsychotics [27]. We found a higher prevalence of obsessive-compulsive disorder and hypochondriasis than in the general population. Of interest for this article is that examining the onset of the OC spectrum symptoms retrospectively, nearly one half of patients reported the presence of these symptoms before the onset of psychotic symptoms. The retrospective examination is surely a main limitation, and we cannot rule out inaccuracies in the retrieval of information.

In our opinion, anxiety symptoms, somatic concerns and obsessive-compulsive symptoms are very important in the assessment of a putative prodromal phase. In particular, when assessing a patient showing anxiety symptoms, somatic concerns and impairments in cognitive or social functioning, special attention should be given to the potential for a prodromal syndrome. However, there is currently no strong evidence to accurately predict the trajectory of the onset of anxiety symptoms, and further research is needed.

Conclusions

Anxiety spectrum disorders are a frequent comorbidity in schizophrenia. Current data suggest that schizophrenia patients with comorbid anxiety disorders may have different clinical features and functioning than those without. Further research is needed in order to better define this clinical phenotype and to clarify the existence of a specific endophenotype, namely the emotional endophenotype.

Conflict of Interest No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Taiminen T, Huttunen J, Heila H, et al. The Schizophrenia Suicide Risk Scale (SSRS): development and initial validation. Schizophr Res. 2001;47:199–213.
2. Blanchard JJ, Mueser KT, Bellack AS. Anhedonia, positive and negative affect, and social functioning in schizophrenia. Schizophr Bull. 1998;24:413–24.
3. Bayle FJ, Krebs MO, Epelbaum C, et al. Clinical features of panic attacks in schizophrenia. Eur Psychiatr. 2001;16:349–53.
4. Achim AM, Maziade M, Raymond E, et al. How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. Schizophr Bull. 2011;37:811–21.
5. Pallanti S, Quercioli L, Hollander E. Social anxiety in outpatients with schizophrenia: a relevant cause of disability. Am J Psychiatry. 2004;161:53–8.
6. •• Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P. Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. Arch Gen Psychiatry. 2012;69:476–83. *This interesting paper, based on the data of a large cohort of patients, highlights the association between benzodiazepine use and increased mortality in schizophrenia*.
7. Buckley PF, Miller BJ, Lehrer DS, et al. Psychiatric comorbidities and schizophrenia. Schizophr Bull. 2009;35:383–402.
8. 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 Psychiatr. 2006;67:363–74.
9. Young S, Pfaff D, Lewandowski KE, Ravichandran C. Anxiety disorder comorbidity in bipolar disorder, schizophrenia and schizoaffective disorder. Psychopathology. 2012 Aug 16. [Epub ahead of print].
10. Rapp EK, White-Ajmani ML, Antonius D. Schizophrenia comorbid with panic disorder: evidence for distinct cognitive profiles. Psychiatr Res. 2012;197:206–2011.
11. Kahn JP, Meyers JR. Treatment of comorbid panic disorder and schizophrenia: evidence for a panic psychosis. Psychiatr Ann. 2000;30:29–33.
12. Chen CY, Liu CY, Yang YY. Correlation of panic attacks and hostility in chronic schizophrenia. Psychiatr Clin Neurosci. 2001;55:383–7.
13. Goodwin RD, Amador XF, Malaspina D, et al. Anxiety and substance use comorbidity among inpatients with schizophrenia. Schizophr Res. 2003;61:89–95.
14. 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.
15. • Ulas H, Polat S, Akdele BB, et al. Impact of panic attacks on quality of life among patients with schizophrenia. Progr Neuro Psychopharmacol Biol Psychiatr. 2010;34:1300–5. *This paper highlights the importance of recognizing and treating panic symptoms in schizophrenic patients in order to improve the patient's quality of life*.
16. • Savitz AJ, Kahn TA, McGovern KE, Kahn JP. Carbon dioxide induction of panic anxiety in schizophrenia with auditory hallucinations. Psychiatr Res. 2011;189:38–42. *This paper highlights the importance of recognizing panic symptoms in schizophrenia and their relevant role in the development of psychotic symptoms*.
17. Green AI, Brown ES. Comorbid schizophrenia and substance abuse. J Clin Psychiatr. 2006;67(9):e08.
18. Blanchard JJ, Mueser KT, Bellack AS. Anhedonia, positive and negative affect, and social functioning in schizophrenia. Schizophr Bull. 1998;24(3):413–24.
19. Gumley A, O'Grady M, Power K, Schwannauer M. Negative beliefs about self and illness: a comparison of individuals with psychosis with or without comorbid social anxiety disorder. Aust N Z J Psychiatr. 2004;38(11):960–4.
20. Penn DL, Hope DA, Spaulding W, Kucera J. Social anxiety in schizophrenia. Schizophr Res. 1994;11(3):277–84.
21. Lysaker PH, Yanos PT, Outcalt J, et al. Association of stigma, self-esteem, and symptoms with concurrent and prospective assessment of social anxiety in schizophrenia. Clin Schizophr Relat Psychoses. 2010;4(1):41–8.

22. Hansson L. Determinants of quality of life in people with severe mental illness. Acta Psychiatr Scand. 2006;429:46–50.
23. Hobfoll SE, Walfish S. Coping with a threat to life: a longitudinal study of self concept, social support, and psychological distress. J Soc Clin Psychol. 1984;12(1):87–100.
24. Birchwood M, Trower P, Brunet K, et al. Social anxiety and the shame of psychosis: a study in first episode psychosis. Behav Res Ther. 2007;45(5):1025–37.
25. Kumazaki H, Kobayashi H, Niimura H, et al. Lower subjective quality of life and the development of social anxiety symptoms after the discharge of elderly patients with remitted schizophrenia: a 5-year longitudinal study. Compr Psychiatr. 2012;53(7):946–51.
26. Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. Schizophr Bull. 1996;22(2):353–70.
27. Grassi G, Pellegrini M, Poli L, et al. Obsessive-compulsive disorder and hypochondriasis in schizophrenic patients treated with clozapine versus other atypical antipsychotics. European Neuropsychopharmacology. J Eur Coll Neuropsychopharmacology. 2012;22(Supplement 2):S328.