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Anxiety disorders in schizophrenia - the importance of differentiation and targeted treatment: a case report and literature review

Filip Grajnert,
4th Military Clinical Hospital, ul.Rudolfa Weigla 5, 50-981 Wrocław, Poland
https://orcid.org/0009-0003-0912-2557
f.grajnert@icloud.com

Wiktoria Bińczyk,
University Teaching Hospital, ul,Borowska 213, 50-556, Wrocław, Poland
https://orcid.org/0009-0004-6600-9259
Wiktoria.binczyk98@gmail.com

Olgierd Dróżdż,
University Teaching Hospital,, ul,Borowska 213, 50-556,Wrocław, Poland
https://orcid.org/0009-0006-6134-9101
Olgierd.drozdz@gmail.com

Bartosz Siudek,
A. Falkiewicz Specialist Hospital,ul.Warszawska 2, 52-114, Wrocław, Poland
https://orcid.org/0009-0002-4053-9724
Bartosz.siudek98@gmail.com

Jakub Plizga,
4th Military Clinical Hospital, ul. Rudolfa Weigla 5, 50-981 Wrocław, Poland
https://orcid.org/0009-0001-1172-9919
jakubplizga7@gmail.com

Agnieszka Głuszczyk,
4th Military Clinical Hospital, ul. Rudolfa Weigla 5, 50-981 Wrocław, Poland
https://orcid.org/0009-0003-5552-4186
gluszczyk.agnieszka@gmail.com

Mateusz Kamiński,
4th Military Clinical Hospital, ul. Rudolfa Weigla 5, 50-981 Wrocław, Poland
https://orcid.org/0009-0008-8559-7809
mattix141@gmail.com

Katarzyna Kuśmierczyk,
District Medical Center in Grójec, Piotra Skargi 10, 05-600 Grójec, Poland
https://orcid.org/0009-0005-2768-0362
kusmierczyk.kasia@gmail.com

Patrycja Karkos,
Lower Silesian Oncology Center in Wrocław, Plac Ludwika Hirszfelda 12, 53-413 Wrocław, Poland
https://orcid.org/0009-0005-7491-5638
karkos.patrycja@gmail.com

ABSTRACT

Schizophrenia is a chronic mental disorder characterized by severe cognitive and behavioral impairments. It often coexists with multiple and complex anxiety symptoms that exacerbate the clinical challenges associated with schizophrenia. This case report presents the history of a 32-year-old woman with a final diagnosis of both paranoid schizophrenia and mixed anxiety disorders. The patient presented with persistent auditory pseudohallucinations, severe anxiety together with occasional panic attacks, which were treated with a variety of antipsychotics. Treatment adjustments were necessitated by the emergence of side effects, including neutropenia, motor disturbances and the observation of major anxiety symptoms, including panic disorder. Ultimately, the successful use of quetiapine in monotherapy was achieved. This case study emphasizes the need for comprehensive treatment strategies to address the complex interplay of psychotic and anxiety symptoms. Increased clinical awareness and targeted treatment of comorbid anxiety can significantly improve the quality of life of patients with schizophrenia.

KEYWORDS:

schizophrenia, comorbid anxiety disorders, paranoid schizophrenia, cognitive-behavioral therapy (CBT), antipsychotic medication, panic disorder

INTRODUCTION

Schizophrenia is a chronic and debilitating mental disorder that is characterized by significant impairments in thought processes, perceptions, emotional responsiveness, and social interactions. Some of the core symptoms of schizophrenia are hallucinations, delusions, and disorganized thinking. Concurrently, anxiety disorders are prevalent among individuals with schizophrenia, with studies indicating that up to 65% of schizophrenic patients also suffer from at least one anxiety disorder (Braga et al., 2013; Buckley et al., 2009).

Schizophrenia is co-occurring with the whole spectrum of anxiety disorders, with the most prevalent comorbidity being social anxiety disorder (SAD), and others diagnoses

including obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), panic disorder (PD), generalized anxiety disorder (GAD), simple phobia (SP) and agoraphobia (AP) (Temmingh et al., 2015). Anxiety disorders commonly precede the onset of schizophrenia as part of the prodrome of the illness in most cases, but they can also occur concurrently or follow the diagnosis (Kiran, Chaudhury, 2016).

The etiology of anxiety in schizophrenic patients is complex, encompassing various factors related to the primary schizophrenic pathology, reactions to the diagnosis, side effects of antipsychotic medications, and independent comorbid conditions (Temmingh et al., 2015). It is noteworthy that childhood trauma has been linked to schizophrenia. However, recent studies have indicated that the association is not with schizophrenia itself, but rather with specific mental symptoms such as psychosis and anxiety. These symptoms, in turn, have been found to have long-term consequences contributing to the development of various psychiatric disorders, including schizophrenia and anxiety disorders suggesting that there may be a common underlying factor (Nierop et al., 2014).

The effective management of anxiety in schizophrenia necessitates a dual approach involving pharmacotherapy and psychotherapy. Most of the antipsychotic medications, while essential for controlling psychotic symptoms, fail to adequately address anxiety. In contrast, selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT) have demonstrated efficacy in treating anxiety within this population (Hofmann, Smits, 2008).

It is of the utmost importance to distinguish anxiety disorders from the symptoms of schizophrenia as a distinct clinical diagnosis to improve the clinical outcome. The coexistence of anxiety disorders with schizophrenia exacerbates the clinical challenges faced by patients and healthcare providers alike, contributing to increased subjective distress, a higher risk of suicide, diminished social functioning, and a more severe progression of schizophrenia (Achim et al., 2011). Enhanced awareness and implementation of targeted treatment strategies for these comorbid conditions can facilitate more effective management and improve the quality of life for those patients.

CASE DESCRIPTION

Patient information and psychiatric history:

A 32-year-old woman with a secondary vocational education in confectionery. She has no children, lives with her parents, and is currently unemployed. The patient has a history of somatic conditions including status post-cardiac surgery for atrial septal defect (ASD), left-

sided hearing loss, strabismus with progressive vision impairment in the left eye, and obesity. There is no family history of psychiatric disorders, and she denies substance use.

The patient's first psychotic episode most likely occurred in 2013; her parents reported perceptual disturbances and delusional beliefs. She was not examined by a psychiatrist until her first hospitalization in 2017, during which she was diagnosed with acute polymorphic psychotic disorder with symptoms of schizophrenia. (ICD-10: F23.1). According to her medical records, symptoms included a complex delusional system, persecutory and poisoning delusions, auditory hallucinations (commenting and imperative), and auditory verbal hallucinations. She displayed no suicidal tendencies but exhibited dissimulating behavior, anxiety, and a sense of threat. Treatment included risperidone, extended-release quetiapine, and as-needed quetiapine. Upon discharge, she was in partial remission with a stabilized mood.

Since her first hospitalization, she has reported persistent auditory pseudohallucinations of varying intensity, often becoming imperative and suicidal during exacerbations. During this time, she received outpatient care at a private psychiatric facility, where her diagnosis was changed to paranoid schizophrenia. (ICD-10: F20.0). The patient also experienced a variety of symptoms including generalized anxiety, social phobia, and panic attacks, particularly premenstrual. During this time, the treatment regimen included risperidone (up to 4 mg/day), quetiapine (up to 125 mg/day), olanzapine (up to 20 mg/day), aripiprazole (up to 30 mg/day), escitalopram (up to 10 mg/day), fluoxetine (up to 60 mg/day), lorazepam (1 mg as needed), and propranolol (up to 80 mg/day). In 2022, she was re-hospitalized due to exacerbated pseudohallucinations, anxiety, and suicidal ideation. Her medication was adjusted to include clozapine and pregabalin due to the ineffectiveness of her previous treatment with olanzapine in combination with aripiprazole. The change resulted in significant symptom improvement. However, attempts to increase pregabalin led to balance issues and falls, accompanied by tremors and muscle stiffness. These symptoms necessitated further medication adjustments.

Current Hospitalization:

The patient was admitted again due to worsening auditory pseudohallucinations, including threatening and imperative voices, escalating anxiety, depressive mood, and suicidal thoughts. She exhibited avoidance behavior, social withdrawal, weight gain, and limb tremor.

Clinical Findings and Treatment:

- Slow and gradual increase of clozapine up to 225mg/day provided moderate improvement in auditory pseudohallucinations and sleep regulation.

- Persistent balance disturbances and tremor prompted neurological consultation and EEG testing, which didn't reveal any epileptic activity.
- Clozapine had to be reduced and eventually discontinued due to moderate neutropenia detected during upper respiratory tract infection.
- Pregabalin was discontinued, alleviating motor symptoms and anxiety.
- Extended-release quetiapine was gradually introduced and increased up to 800mg/day, resulting in significant symptomatic relief, with the patient reporting improvement at a dose of 300-400mg/day

Panic Attack Incident:

During the premenstrual period, the patient experienced a severe panic attack characterized by hyperventilation, dyspnea, and fear of dying. This episode intensified her psychotic symptoms, with an increase in auditory hallucinations and delusional interpretations. The patient expressed past traumatic experiences, including a sexual assault in 2013, but it was not factually verifiable. Lorazepam was administered for a short time, and her quetiapine dose was subsequently increased. After the episode, the patient's behavior has changed from withdrawn and polite to irritable and demanding. Her psychological state slowly stabilized over two days after the attack, with a gradual improvement in mood and social interaction.

Discharge Condition:

Upon discharge, the patient exhibited spontaneous and coherent speech, with no observable signs of anxiety or depressive symptoms. She acknowledged experiencing benign pseudohallucinations, denied any delusional thoughts or suicidal ideation, and demonstrated normal sleep patterns and appetite. However, she expressed apprehension about the potential cessation of the pseudohallucinations. She plans to initiate outpatient psychotherapy with the support of her family.

DISCUSSION

Anxiety symptoms frequently co-occur with schizophrenia and have a significant impact on the course of the disease. The experience of anxiety is associated with increased self-awareness of the disease, although it has a negative impact on morbidity and increases the risk of suicide (Temmingh et al., 2015). Additionally, these patients experience death anxiety, the level of which increases correlating with the severity of their psychopathology (Özturk, 2021).

Furthermore, anxiety disorders have a detrimental impact on the quality of life of patients with schizophrenia, with the most significant impact observed in those with comorbid SAD and PD. Additionally, it was observed that these patients required significantly more medical, psychological, and mental health services. Furthermore, cognitive impairment was more prevalent in these patients (Temmingh et al., 2015).

Psychotic symptoms in schizophrenia are dependent upon alterations in the dopaminergic system, specifically increased dopamine activity in the associative striatum which plays the main role in the occurrence of psychotic symptoms (Kesby et al., 2018). However, dopamine is also crucial for mediating anxiety to amygdala (Zarrindast, Khakpai, 2015) indicating that both anxiety and psychotic symptoms share the dopaminergic system. This could potentially explain the link between increased anxiety and exacerbation of psychotic symptoms in the patient.

In this case, schizophrenia was the primary diagnosis of the patient, nonetheless anxiety symptoms affecting the patient were not less severe than psychotic symptoms. It is therefore of high importance to be aware of comorbid anxiety disorders in schizophrenia and to refrain from assigning anxiety to schizophrenia, but rather to treat it as a separate disorder. (Tibbo, 2003). Prior to admission to the hospital, the patient exhibited symptoms of GAD. Subsequently, while hospitalized, the patient developed symptoms of panic disorder that coincided with an exacerbation of her psychotic symptoms. The patient had experienced episodes of panic disorder in the past, but they had been dismisse15d by her family, who believed that “their daughter was hysterical”.

Clinicians should not hesitate to assign a secondary diagnosis in addition to schizophrenia (Tibbo, 2003). Oftentimes anxiety is unrecognized or treated ineffectively, in turn leading to suboptimal symptom management and thus a lower quality of life. Therefore, it is crucial to underline the role of correctly identifying anxiety in psychotic patients. Moreover, an understanding of the correlation between anxiety and functional status in schizophrenia may be applicable in research, enabling the prediction of patients’ outcomes, the cost of primary care and medical utilization (Wetherell et al., 2003).

The diagnosis of anxiety in patients with schizophrenia might pose a challenge due to an ‘emotional paradox’. From one perspective, negative symptoms are characterized by a lack of emotional expression and withdrawal; whilst from the other perspective, there is increased experience of anxiety due to positive symptoms such as delusions and hallucinations (Temmingh et al., 2015).

Another challenge contributing to the underdiagnosis of anxiety disorders in individuals with schizophrenia is that the symptoms of acute psychosis often overshadow anxiety symptoms in the assessment of clinicians. However, considering that anxiety disorders have a scientifically proven negative impact on the quality of life of patients with schizophrenia, it is worth reconsidering whether focusing primarily on psychotic symptoms is beneficial for the patient. Anxiety among patients with schizophrenia is associated with lower quality of life, impaired social functioning, reduced overall well-being and impediment to role functioning. Moreover, this correlation remained significant after the exclusion of depressive symptoms (Wetherell et al., 2003).

It is noteworthy that there are treatments for comorbid anxiety disorders which are responsive to treatment in general, providing significant benefit to the patient. Pharmacotherapy encompasses medicines from various groups, including second-generation antipsychotics such as aripiprazole, risperidone, olanzapine and quetiapine; first-generation antipsychotic (trifluoperazine); selective serotonin reuptake inhibitors (e.g. fluvoxamine, fluoxetine and escitalopram); alpha-2-delta-ligands (e.g. pregabalin); and benzodiazepines.

The patient was initially treated with clozapine, which was subsequently discontinued due to neutropenia. The patient then received granulocyte colony-stimulating factor, which improved blood morphology. Pregabalin, on the other hand, was discontinued due to emergence of neurological side effects in this patient. The medication is used to relieve anxiety in schizophrenia, although it should be noted that caution is required due to the risk of increasing serum levels of clozapine. Consequently, the patient started treatment with extended-release quetiapine, which is an appropriate choice for patients susceptible to extrapyramidal symptoms, as evidenced by this case.

Furthermore, quetiapine has an anxiolytic effect in schizophrenia at doses exceeding 300 mg/day, eventually reaching an antipsychotic effect in high doses, up to 800 mg/day. During hospitalization, the doses were gradually increased up to 800 mg/day, with a favorable effect observed at doses exceeding 300 mg/day, which is the required dose to achieve desired initial mood-stabilizing effect. Olanzapine, despite its efficacy in the treatment of anxiety in schizophrenia, was not selected due to its higher potential to induce weight gain, which is particularly detrimental in the context of the patient's high BMI, and its previous lack of effectiveness (even in combination with aripiprazole). Eventually quetiapine was chosen as it has a moderate potential for weight gain, which is lower than that of olanzapine (Temmingh et al., 2015).

Noteworthy, clozapine is associated with treatment-emergent social anxiety. Although the serum levels of clozapine in this patient were not measurable. During the phase of acute panic, the patient was administered lorazepam with satisfactory effect. In general, guidelines advise against use of benzodiazepines, as they offer minimal benefit in treatment of psychotic symptoms. However, they are useful in acute stages of anxiety and have a strong potential for reducing panic attacks. Nevertheless, a history of substance abuse must be taken into consideration, as it is a contradiction for benzodiazepines (Temmingh et al., 2015). However, this was not the case in this patient.

This patient planned to begin a therapeutic process of psychotherapy after her discharge from the hospital. It has been demonstrated that CBT is an effective treatment for patients with comorbid anxiety and schizophrenia. However, studies that focus on the therapeutic outcomes of improvements in both anxiety and psychotic symptoms are valuable. Future investigations should also examine whether addressing anxiety symptoms in this population leads to improvements in quality of life and functioning (Wetherell et al., 2003).

In contrast, the hypothesis may be that as psychotic features intensify, anxiety symptoms may partially diminish. Prior to discharge, the patient expressed fear of letting go of the auditory pseudohallucinations. The underlying theory is that the inner voices provide a kind of emotional support, sometimes described as "gentle and kind" and help reduce anxiety by allowing the patient to reorganize their perception of reality. By attributing their fears to a deceptive environment, the patient finds it less frightening than facing incoherent chaos, which may explain their reluctance to relinquish delusions (Grillo, 2018).

CONCLUSION

This case study highlights the complexity of managing comorbid anxiety and panic disorders in the context of paranoid schizophrenia. It underscores the importance of comprehensive treatment approaches, including careful medication adjustments and psychological support, to address both psychotic and anxiety symptoms. Special attention should be paid to the history of trauma, including that related to the psychotic episode itself (Nierop et al., 2014). Given that anxiety symptoms are potentially treatable and exert a significant impact on the quality of life for individuals with schizophrenia, clinicians should raise their awareness of comorbid anxiety disorders in this population. This heightened awareness can result in more accurate diagnoses and facilitate the provision of appropriate treatment (Wetherell et al., 2003).

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Author's contribution:

Conceptualization, Bartosz Siudek, Mateusz Kamiński, Katarzyna Kuśmierczyk; **Methodology**, Jakub Plizga, Olgierd Dróżdż, Agnieszka Głuszczyk; **Software**, Patrycja Karkos, Wiktoria Bińczyk; **Check**, Katarzyna Kuśmierczyk, Olgierd Dróżdż; **Formal analysis**,; **Investigation**,; **Resources**, Wiktoria Bińczyk, Bartosz Siudek; **Data curation**, Agnieszka Głuszczyk, Filip Grajnert, Bartosz Siudek; **Writing - rough preparation**, Filip Grajnert, Jakub Plizga, Patrycja Karkos; **Writing - review and editing**, Filip Grajnert, Wiktoria Bińczyk, Olgierd Dróżdż, Bartosz Siudek, Jakub Plizga, Agnieszka Głuszczyk, Mateusz Kamiński, Katarzyna Kuśmierczyk, Patrycja Karkos; **Visualization**, Jakub Plizga, Wiktoria Bińczyk, Filip Grajnert; **Supervision**, Olgierd Dróżdż, Mateusz Kamiński, Katarzyna Kuśmierczyk; **Project administration**, Agnieszka Głuszczyk, Patrycja Karkos, Mateusz Kamiński; **Receiving funding**, not applicable;

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