Anxiety in schizophrenia

AUTHORS: Samuel G Siris, MD, Raphael J Braga, MD
SECTION EDITOR: Stephen Marder, MD
DEPUTY EDITOR: Michael Friedman, MD

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INTRODUCTION

Anxiety is frequently observed among patients with schizophrenia. Anxiety may present as a component of schizophrenia (particularly during an acute psychotic episode), a result of an underlying organic condition, a medication side effect, or a symptom of a co-occurring anxiety disorder. A thorough psychiatric examination, including a medical history and physical examination, and possibly intervention trials, may be needed to arrive at an accurate diagnosis. Treatment is based on this determination.

The epidemiology, clinical manifestations, diagnosis, and treatment of anxiety and anxiety disorders (eg, posttraumatic stress disorder, obsessive-compulsive disorder, social anxiety disorder, generalized anxiety disorder) in patients with schizophrenia are discussed here. Anxiety disorders and schizophrenia as individual, noncomorbid conditions are discussed separately.

- (See "Schizophrenia in adults: Clinical features, assessment, and diagnosis".)
- (See "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)
- (See "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis".)
- (See "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis".)

- (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis".)

EPIDEMIOLOGY

Schizophrenia spectrum disorders include schizophrenia, schizoaffective, schizophreniform disorder, delusional disorders, and psychosis not otherwise specified. A meta-analysis of 52 studies with a total of 4032 patients with a schizophrenia spectrum disorder found that 38.3 percent suffered from a comorbid anxiety disorder [1]. Mean prevalence rates were as follows:

- Social anxiety disorder (social phobia) – 14.9 percent
- Posttraumatic stress disorder – 12.4 percent
- Obsessive-compulsive disorder (OCD) – 12.1 percent

Rates of anxiety disorder appear to be higher among individuals with schizoaffective disorder as compared with schizophrenia (30.1 versus 16.7 percent) [2].

Disorder rates across studies are markedly heterogeneous, largely due to use of different samples, diagnostic tools, and symptom-rating instruments. Mean rates are higher than those found for anxiety disorders in the general population. Additionally, studies suggest that individuals with an early age of schizophrenia onset have a higher prevalence of anxiety than individuals with later onset and the presence of anxiety disorders in patients with first episode psychosis has been associated with poorer initial outcomes [3,4].

Furthermore, an analysis of data from the Epidemiologic Catchment Area study found that the presence of OCD, social phobia, or panic attacks were associated with a 2.6 to 3.5 increased odds of developing schizophrenia [5].

PATHOGENESIS

Little is known regarding the pathophysiology of anxiety in schizophrenia.

Neurobiology — Imaging and postmortem studies suggest that dysregulation of the major neurotransmitters, such as dopamine, glutamate, and serotonin may contribute to the presence of anxiety symptoms in schizophrenia [6].

Some evidence suggests that the identification of neural abnormalities involved in anxiety, schizophrenia and schizophrenia with comorbid anxiety may lead to improved diagnosis and management of these conditions. In a magnetic resonance imaging (MRI) study, gray matter

volume changes in 80 subjects with schizophrenia, symptomatic anxiety, schizophrenia with comorbid anxiety, and healthy controls (n = 20 each group) were compared. Subjects with schizophrenia with comorbid anxiety had volumes comparable to control subject and showed less gray matter volume decreases in the dorsolateral prefrontal cortex and precentral gyrus than those with schizophrenia only. Subjects in the schizophrenia group showed reduced gray matter volumes in the dorsolateral prefrontal cortex, precentral gyrus, orbitofrontal cortex, temporal gyrus and inferior parietal gyrus as compared with subjects in the control group [7].

Genetics — Familial aggregation of obsessive-compulsive-associated disorders (ie, obsessive-compulsive disorder [OCD], obsessive-compulsive personality disorder, and schizophrenia with comorbid obsessive symptoms) has been reported, such that relatives of schizophrenia patients with OCD have higher rates of anxiety disorders than relatives of schizophrenia probands without OCD [8]. This provides support for the validity of the OCD as a discrete comorbid entity [9,10]. However, these findings are derived from small samples.

CLINICAL MANIFESTATIONS

Anxiety is theorized to perform the important signal function of alerting the individual to danger. An example is the anxiety that alerts a person to look both ways before crossing the street. When the anxiety is unduly severe, in the absence of sufficient cause, or lasts longer than reasonable it is considered a symptom. Symptoms of anxiety may include excessive or persistent worry, restlessness, hyperarousal, fatigue, irritability, poor concentration, sleep disturbance, and muscle tension. These symptoms may lead to distress and deficits in psychosocial functioning.

Symptoms of anxiety in patients with schizophrenia can be secondary to schizophrenia or independent of the psychotic disorder.

- Anxiety as a secondary symptom presents as an integral part of an active psychotic process. An example is a patient experiencing anxiety induced by terrifying hallucinations and delusions. Anxiety secondary to psychosis tends to improve as psychosis improves (eg, in response to antipsychotic treatment).

- Anxiety can persist in the form of a syndrome or disorder that co-occurs independently from schizophrenia. Specific anxiety disorders can present with different degrees of overlap with the psychotic symptoms of schizophrenia. As examples, panic and paranoia both involve extreme states of fear. It has been proposed that the affective storm of anxiety during a panic attack can spur a patient with schizophrenia to scan their

environment for danger that would justify the anxiety [11]. A paranoid individual may experience an exaggerated perception of danger in their environment as a complement to the extreme anxiety of the panic attack. Obsessions in obsessive-compulsive disorder (OCD) can overlap conceptually with delusions in schizophrenia. It can be the inability of a patient to get a delusional thought off their mind, rather than the incorrectness of the thought, which causes much of the patient's suffering and functional impairment [12].

Anxiety may be present prior to the occurrence of schizophrenia or may persist in the absence of psychosis. Anxiety is often a feature in the prodrome leading to schizophrenia [13]. Studies suggests that anxiety is more prevalent in individuals with an earlier rather than later age of schizophrenia onset. (See 'Epidemiology' above.)

Anxiety disorders including OCD, panic disorder, posttraumatic stress disorder, generalized anxiety disorder, specific phobias, and social anxiety disorder, and their distinguishing features [14] are discussed elsewhere.

- (See "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis" and "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis" and "Specific phobia in adults: Epidemiology, clinical manifestations, course, and diagnosis".)
- (See "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)
- (See "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis" and "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis" and "Specific phobia in adults: Epidemiology, clinical manifestations, course, and diagnosis".)
- (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis" and "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis" and "Specific phobia in adults: Epidemiology, clinical manifestations, course, and diagnosis".)
- (See "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis".)

COURSE

Patients with anxiety predating schizophrenia have been found to have worse outcomes compared with patients with anxiety that developed as part of the psychotic process [15,16]. High levels of anxiety symptoms or the presence of an anxiety disorder have been associated with more severe positive symptoms of schizophrenia, social withdrawal, depression, hopelessness, increased suicide rates, and poorer functioning [9,10]. Studies of patients with co-occurring schizophrenia and anxiety disorders have found that patients with anxiety disorders had increased service utilization and hospitalization rates compared with patients without an anxiety disorder [17].

ASSESSMENT

We find that the assessment of anxiety can be difficult when attempted in a single cross-sectional evaluation. We often find it is necessary to repeat the history and examination over an extended period of time to establish an accurate diagnosis. In patients with schizophrenia presenting with anxiety, the assessment and management of the anxiety are closely intertwined. The diagnosis of anxiety as a component of schizophrenia or an anxiety disorder is a diagnosis of exclusion. We rule out organic causes, including medication side effects as possible etiology of the symptoms.

History and examination — We take a detailed history and physical examination, review of medications and adherence. We typically send for laboratories including complete blood count and metabolic panel including calcium and thyroid function tests to assess for underlying causes of anxiety in patients with schizophrenia. If panic attacks are part of the differential diagnosis, concern about a potential pheochromocytoma or arrhythmia can prompt referral to a medical generalist or specialist.

Rating scale — The Staden Schizophrenia Anxiety Rating Scale, a validated tool for the assessment of anxiety in schizophrenia, is available for assessment of anxiety in individuals with schizophrenia [18].

Differential diagnosis — Assessment and management are guided by the differential diagnosis and determination of the likely source of anxiety or anxiety-like symptoms. We try to distinguish between anxiety as a symptom of schizophrenia and a distinct anxiety disorder. We consider the following as potential causes of anxiety in individuals with schizophrenia:

Anxiety as a symptom of schizophrenia — The presence of anxiety with an acute psychotic episode can increase the severity of the patient's clinical status and the difficulty of clinical management. The phenomenological distinction between symptoms of anxiety disorders and

psychotic symptoms can be often difficult to determine. We are vigilant to the temporal and clinical relationship between anxiety and psychotic symptoms. During acute psychotic breaks differentiating these relationships can be very difficult.

- In a patient presenting with panic attacks, untriggered attacks are suggestive of a panic disorder, while panic accompanying the persecutory delusions of schizophrenia does not suggest an independent anxiety disorder.

- The avoidance inherent in social anxiety can overlap phenomenologically with negative symptoms of schizophrenia (eg, a lack of interest in social activities). A patient avoiding social situations may have a comorbid social anxiety disorder, suggested by the presence of discomfort with social exposure, or may lack interest in social situations, a common negative symptom of schizophrenia. Social avoidance can also be due to active positive symptoms. As an example, a patient might avoid social interaction for delusional fear of persecution. Such cases should be distinguished from comorbid social anxiety disorder.

- Obsessions in obsessive-compulsive disorder can overlap with delusions in schizophrenia [12]. It can be the inability of a psychotic patient to get delusional thoughts off their mind, rather than the content of the thought itself, that causes much of the patient's suffering and functional impairment.

Side effect of antipsychotic or other medication — Medications taken may cause anxiety like symptoms. These are listed on the table (table 1). Antipsychotic medications can lead to akathisia or obsessive-compulsive symptoms.

- **Akathisia** – Akathisia is an extrapyramidal symptom that may present with fidgetiness, internal angst, motor restlessness, and inability to sit still. In milder cases the patient may describe a subjective feeling of restlessness but not show restless motor behavior. Akathisia and its treatments are discussed elsewhere. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Akathisia' and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)

- **Obsessive-compulsive symptoms** – De novo obsessive and compulsive symptoms can accompany initiation of a second-generation antipsychotic drug [19]. Data suggest that the symptoms increase with antipsychotic dose. A temporal association between medication initiation (or dose increase) and symptom onset can help to identify these side effects. However, the symptoms may develop weeks or months after medication initiation. The side effects are thought to be caused by the 5-HT2a antagonism of most second-

generation antipsychotics. Treatment of obsessional or compulsive symptoms in individuals treated with antipsychotic medications are discussed below. (See 'Anxiety related to medication effects' below.)

Co-occurring anxiety disorder — A co-occurring anxiety disorder can be diagnosed in patients with schizophrenia if the patient fully meets the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for the disorder and if the alternative possibilities, described above, have been ruled out [14]. While this may be clear cut in some cases, it may be more ambiguous in others. DSM-5 criteria require that the current anxiety symptoms are "not better accounted for by another mental disorder." This judgment is left to the individual clinician and may be less than obvious in some cases. Anxiety disorders are discussed elsewhere.

- (See "Specific phobia in adults: Epidemiology, clinical manifestations, course, and diagnosis" and "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis" and "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis".)
- (See "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)
- (See "Specific phobia in adults: Epidemiology, clinical manifestations, course, and diagnosis" and "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis" and "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis".)
- (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Specific phobia in adults: Epidemiology, clinical manifestations, course, and diagnosis" and "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis" and "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis".)
- (See "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis".)

Medically related causes — Many medical conditions can generate or mimic anxiety symptoms in patients with schizophrenia, including current medical illnesses and substance use disorders, including withdrawal. See table for medical conditions that can cause anxiety or symptoms that can be mistaken for anxiety (table 2). Individuals with schizophrenia have higher rates compared with the general population of such medical conditions, including cardiovascular and pulmonary disease [20] and substance use disorders [21,22]. (See "Co-

occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis".)

MANAGEMENT OF ANXIETY IN SCHIZOPHRENIA

Anxiety as a symptom of schizophrenia — Differentiating anxiety as a symptom of schizophrenia versus comorbid anxiety with schizophrenia can be difficult. Additionally, worsening anxiety has been described as a side effect of antipsychotic medications. In some cases, adjustment of the antipsychotic dose can be helpful in determining the diagnosis. In cases where the antipsychotic dose is increased and the anxiety and psychosis resolve, the response suggests that anxiety was a symptom of schizophrenia [23].

Anxiety related to medication effects

Obsessive-compulsive symptoms — In patients with anxiety (eg, obsessive-compulsive symptoms) secondary to second-generation medication, we individualize the treatment depending on the clinical presentation. When feasible (eg, low risk of exacerbation of psychosis), we decreased the antipsychotic medication by approximately 25 percent and monitor closely. If this is not feasible or does not result in improvement, we consider switching antipsychotics, possibly to one with less serotonin antagonism, such as haloperidol.

A change in antipsychotic medication may not be an option when the patient is taking clozapine, because this drug is typically used in patients with schizophrenic symptoms refractory to other antipsychotics. Case reports have suggested that selective serotonin reuptake inhibitors (SSRIs) may reduce clozapine-induced obsessive and compulsive symptoms [24-26]. However, it should be noted that controlled studies are lacking, and the risks of additional side effects should be weighed against potential benefits of adding an SSRI. Some SSRIs (especially fluvoxamine) interact with clozapine, leading to toxic clozapine levels in some individuals [27]. Fluvoxamine should be avoided in patients receiving clozapine. Other SSRIs should be used with caution and accompanied by monitoring of clozapine drug levels. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

Akathisia — Treatment of akathisia is discussed elsewhere. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Akathisia'.)

Co-occurring schizophrenia and anxiety disorder — Although not empirically tested in schizophrenia and varying by anxiety disorder, we often used a combined modality approach

with medication and cognitive-behavioral therapy (CBT). Combination therapy may be more effective than either of the individual modalities.

Pharmacotherapy — In most cases of co-occurring schizophrenia with anxiety disorder, our preference is pharmacologic management based on treatment recommendations for anxiety in the noncomorbid population. Minimal data (eg, small randomized trials, open trials, case reports) is available on treatment of comorbid anxiety and schizophrenia [28-36].

As examples:

- **Obsessive-compulsive disorder (OCD)** – Two small randomized trials have found the serotonergic antidepressants clomipramine and fluvoxamine to reduce OCD symptoms in patients with schizophrenia compared with placebo [28]. These findings have been supported by case reports suggesting efficacious treatment with fluoxetine, fluvoxamine, paroxetine, and sertraline. (See "Management of obsessive-compulsive disorder in adults".)

- **Panic disorder/attacks** – Case reports and open trials have reported reductions in panic attacks in patients with comorbid schizophrenia and panic disorder treated with alprazolam, diazepam, and imipramine [29-31]. A few case reports have suggested panic attacks respond to changes from a first- to second-generation antipsychotic [32,33]. No studies were found of SSRIs for panic in schizophrenia. (See "Management of panic disorder with or without agoraphobia in adults".)

- **Social anxiety disorder** – A small open trial suggested that aripiprazole may be effective for patients with schizophrenia and social phobia [34]. Sixteen patients had their existing antipsychotics cross titrated with aripiprazole and were then followed for two months. The change to aripiprazole was associated with a reduction of social anxiety after three weeks of treatment. These results have not been replicated. (See "Pharmacotherapy for social anxiety disorder in adults".)

- **Other anxiety or disorders** – No published trials or case reports are available to evaluate the efficacy of pharmacotherapy for posttraumatic stress disorder (PTSD), generalized anxiety disorder, or phobias other than social anxiety in patients with schizophrenia. (See "Generalized anxiety disorder in adults: Management" and "Posttraumatic stress disorder in adults: Treatment overview" and "Specific phobia in adults: Treatment overview".)

  Small trials or retrospective chart reviews have shown mixed results in the treatment of schizophrenia with anxiety [35,36].

Treatment of SSRIs in individuals on antipsychotic medications may result in changes in antipsychotic blood levels. Treatment of anxiety and specific anxiety disorders with SSRIs are discussed separately.

- (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis" and "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Drug-drug interactions'.)
- (See "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis".)
- (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis" and "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Drug-drug interactions'.)
- (See "Specific phobia in adults: Epidemiology, clinical manifestations, course, and diagnosis".)
- (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis" and "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Drug-drug interactions'.)
- (See "Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis".)

Cognitive-behavioral therapy — For patients with co-occurring panic disorder, social anxiety disorder, or PTSD who have not responded adequately to medication, we suggest a trial of adjunctive CBT. (See "Schizophrenia in adults: Psychosocial management".)

Limited evidence suggests that CBT may be efficacious in reducing symptoms of anxiety disorders in patients with co-occurring schizophrenia, including two small trials of patients with social anxiety disorder [37,38] and a small open trial of patients with panic disorder [39]. Stronger evidence supports the use of CBT for PTSD in patients with schizophrenia [40,41].

As an example, in a trial 155 subjects with co-occurring PTSD and a psychotic disorder (90 percent with schizophrenia or schizoaffective disorder) were randomly assigned to receive eight 90-minute sessions of one either prolonged exposure, eye movement desensitization and reprocessing therapy (EMDR), or waitlist (control) [41]. At the end of the treatment period and at six-month follow-up, groups who received exposure therapy or EDMR therapy experienced less

severe PTSD symptoms and had lower rates of participants continuing to meet PTSD diagnostic criteria compared with the control group (57 and 60 versus 27 percent). Additionally, participants receiving exposure therapy, but not those receiving EMDR, were more likely to meet criteria for full remission of PTSD compared with the control group (28.3 and 16.4 versus 6.4 percent). There were no differences in severe adverse events among groups.

In cases where specific situations or interpersonal interactions are identified as closely related to the onset of anxiety, the patient may benefit from supportive therapeutic techniques, building of the patient's coping skills, or family interventions [23]. (See "Schizophrenia in adults: Psychosocial management".)

Treatment of anxiety disorders with cognitive therapies are discussed elsewhere. (See "Generalized anxiety disorder in adults: Cognitive-behavioral therapy and other psychotherapies" and "Social anxiety disorder in adults: Psychotherapy" and "Psychotherapy for panic disorder with or without agoraphobia in adults" and "Specific phobia in adults: Cognitive-behavioral therapy" and "Posttraumatic stress disorder in adults: Psychotherapy and psychosocial interventions".)

Medical causes — We address medical causes, such as hyperthyroidism, which are thought to be causing anxiety in individuals with schizophrenia.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Psychotic disorders".)

SUMMARY AND RECOMMENDATIONS

- **Anxiety in schizophrenia** – Anxiety is frequently observed among patients with schizophrenia. The presence of anxiety with an acute psychotic episode can increase the severity of the patient's clinical status and the difficulty of clinical management. (See 'Introduction' above.)

- **Clinical manifestations** – Symptoms of anxiety may include excessive or persistent worry, restlessness, hyperarousal, fatigue, irritability, poor concentration, sleep disturbance, and muscle tension. These symptoms may lead to distress and deficits in psychosocial functioning. (See 'Clinical manifestations' above.)

- **Course** – High levels of anxiety symptoms or the presence of an anxiety disorder have been associated with more severe positive symptoms of schizophrenia, social withdrawal, depression, hopelessness, increased suicide rates, and poorer functioning. Additionally, increased service utilization and hospitalization rates are reported. (See 'Course' above.)

- **Differential diagnosis** – We consider the following as potential causes of anxiety in individuals with schizophrenia: (See 'Differential diagnosis' above.)

  - **Anxiety as a symptom of schizophrenia** – The phenomenological distinction between symptoms of anxiety disorders and psychotic symptoms can be often difficult to determine. We are vigilant to the temporal and clinical relationship between anxiety and psychotic symptoms. (See 'Anxiety as a symptom of schizophrenia' above.)

  - **Medication side effect** – Akathisia and obsessive compulsive symptoms may be cause by antipsychotic medications. (table 1). (See 'Anxiety related to medication effects' above.)

  - **Co-occurring schizophrenia with anxiety disorder** – In cases of co-occurring disorders, we cautiously typically treat the anxiety disorder pharmacologically, based on treatment recommendations for anxiety in the noncomorbid population. (See 'Co-occurring anxiety disorder' above.)

    We suggest a trial of adjunctive cognitive-behavioral therapy for patients with schizophrenia and co-occurring panic disorder, social anxiety disorder, or posttraumatic stress disorder who have not responded adequately to treatment with medication (**Grade 2C**).

  - **Medically related causes** – We use detailed history, examination and laboratory data including metabolic panel, thyroid functions, complete blood count to rule out medical causes of anxiety in schizophrenia (table 2). (See 'Medically related causes' above.)

- **Management of anxiety in schizophrenia** – Our management of anxiety in individuals with schizophrenia is guided by our use of the differential diagnosis to determine the most likely cause. The causes are addressed with pharmacologic changes, psychotherapy or addressing medical causes. (See 'Management of anxiety in schizophrenia' above.)

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