Treatment of Comorbid Panic Disorder and Schizophrenia: Evidence for a Panic Psychosis

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Why is it important to consider comorbid panic disorder in schizophrenia? After all, schizophrenia wreaks such devastation on patients' lives that panic disorder would seem trivial in comparison. However, clinical experience and a growing literature suggest that comorbid panic disorder may be a major determinant of distress and dysfunction across many psychiatric disorders, including schizophrenia.1,3 The recognition of panic disorder in patients with schizophrenia is crucial for designing effective treatment. In addition, panic disorder may play a significant pathogenetic role in some schizophrenic illness.

During the past 30 years, the diagnosis of psychiatric disorders has become increasingly precise. Symptoms that were once lumped together under one diagnosis are now accurately distinguished from one another, with disorders such as psychotic mania, delusional depression, and paranoid delusional disorder being properly differentiated.4 These more specific diagnoses came into common use as psychiatry better understood their symptom clusters, natural history, and treatment response. For example, the discovery of lithium made the distinction between psychotic mania and schizophrenia far more clinically pressing.

As a result of recent interest in psychiatric comorbidity, illnesses once thought to be distinct from one another, such as obsessive-compulsive disorder and schizophrenia, are now known to have important areas of overlap. Some clinicians use the term “schizo-obsessive disorder” to describe this condition.5,9 Similarly, social phobia has been suggested as an etiologic factor for schizophrenia.9 This article considers the treatment of comorbid panic disorder and schizophrenia and, in light of these new perspectives, the possibility of a distinct “panic psychosis.”4,12 Although this article is based on a growing body of research, it includes a substantial amount of clinical impression.

CoMorbidity of Panic Disorder and Schizophrenia

Many studies have examined the prevalence of panic disorder in patients with schizophrenia. Reported rates range from 16% to 63%.13-20 There are several explanations for this broad range. First, the prevalence of panic disorder may differ among subtypes of schizophrenia. For example, panic is less frequent in undifferentiated schizophrenia.20 Second, because schizophrenic subtypes may not be distributed uniformly across treatment sites, the panic rate found by a particular investigator may be skewed. Third, different treatment sites could also have different levels of treatment response, study participation, and patient articulation of symptoms. Finally, the tools used by investigators to assess panic differ in their effectiveness (eg, SCID vs SCID-UP and

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SADS vs SADS-LA). None of these instruments is a substitute for a skillful interview, especially in view of the confusing concurrence of panic symptoms with psychotic exacerbation. Thus, the adequacy or inadequacy of the interview may also contribute to the difference in prevalence.

Beyond studies of comorbidity, Heun and Maier's data suggest a familial aggregation of panic disorder and schizophrenia, raising the possibility of a panic-related etiology for at least some cases of schizophrenia.

**CLINICAL PERSPECTIVES ON NATURAL HISTORY**

Impressionistically, the rate of panic disorder among patients with schizophrenia in state hospital wards, emergency rooms, outpatient clinics, and the private office is closer to the higher end of the epidemiologic estimates. Moreover, patients often report retrospectively that panic anxiety was part of a prodromal phase before their psychosis. For example, after a few months or years of panic attacks, the episodes begin to take on new symptoms of confusion, fearfulness, or paranoia. Soon after, abrupt auditory hallucinations are coincident with panic attacks. Not surprisingly, patients quickly become more attentive to the voices than to the other symptoms of panic disorder. Commonly, the symptoms of panic disorder, although continuing, are attributed to the voices or to another psychotic causality. Other psychotic thoughts and paranoid fears may also be acutely exacerbated during a panic attack. One patient believed she was actually being stabbed by someone and that this was causing her chest pain. Another described a "mind virus" that made her feel claustrophobic on buses.

Patients with this kind of panic psychosis typically appear to have classic paranoid schizophrenia. Often, there is overlap with symptoms related to comorbid diagnoses such as obsessive-compulsive disorder. Psychotic symptoms will usually respond in whole or in part when treated with antipsychotic medication alone. Panic symptoms, however, will usually continue with absent or diminished psychotic features. Negative symptoms of social and emotional withdrawal typically persist. In at least some patients, the withdrawal may have an agoraphobic component. For example, if a patient is paranoid about leaving the house, an antipsychotic might render him or her nonpsychotic but still reclusive.

**DIAGNOSIS OF PANIC DISORDER IN SCHIZOPHRENIA**

To make the diagnosis of panic disorder, the clinician must possess specific interviewing skills and be motivated to investigate potential panic symptoms. Among actively psychotic patients, the exploration may begin with questions about psychotic phenomena potentially related to panic symptoms. For example, consider the patient who has intermittently active auditory hallucinations. The patient is then asked to focus on that paroxysmal moment. Does the patient also notice the sudden onset of voices? The clinician should acknowledge that such symptoms may well be related to the onset of voices. If such a pattern is present, the paroxysmal onset of voices should be considered a possible marker for a panic attack, with voices as an added symptom. Other patients may experience a paroxysmal increase in paranoid fear, which may then be examined similarly. For example, one patient with schizophrenia, while in public, would become abruptly more afraid that other people were reading her mind and plotting against her.

During nonpsychotic periods, including periods when antipsychotic medication is effective, panic attacks may continue without psychotic features. The history of these episodes may be gathered through more conventional questions about abrupt onset of panic, chest pain, tachycardia, or shortness of breath. Commonly, nonpsychotic patients with schizophrenia also have symptoms of panic disorder that are mistakenly labeled as medical diagnoses or mere physical complaints (eg, noncardiac chest pain, dizziness, asthma, and seizures). Because nonpsychotic panic attacks may seem mild to the patient, careful inquiry is required for diagnosis.

Finally, if a patient does have diagnoses of panic disorder and schizophrenia, it is useful to understand the chronology of symptoms. Patients often recall nonpsychotic panic attacks.
that preceded the onset of paroxysmal psychotic symptoms by months or years.5

**PHARMACOLOGIC TREATMENT**

Adjunctive alprazolam has been used in the treatment of unselected schizophrenia.23,24 In these studies, some patients experienced significant reductions in positive and negative symptoms, whereas other patients were unaffected. These disparate responses were at first unexplained. However, adjunctive alprazolam produces a uniformly beneficial effect for patients with both panic disorder and schizophrenia,11,12 suggesting that panic is not only a significant marker for the response to alprazolam (and clonazepam) in schizophrenia, but also a pathogenetic contributor.

Effective pharmacotherapy begins with both antipsychotic and antipanic medications. No specific antipsychotic appears to be more useful for patients who have comorbid panic and schizophrenia. However, the newer atypical antipsychotics are at least as effective as the older antipsychotics, but have fewer side effects. Anecdotal evidence suggests that antipsychotics worsen panic in some patients.25 Of the numerous antipanic medications currently available, clonazepam and alprazolam are clearly superior. Clonazepam is preferred because of its longer half-life and lower potential for abuse.26,27 Some generic preparations of clonazepam may have variable or reduced potency.

Other antipanic medications include tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), which may be effective for the panic attacks of patients who have both panic disorder and schizophrenia.28-30 However, TCAs and SSRIs appear to be far less effective for the concomitant reduction of positive and negative symptoms of schizophrenia. A considerable body of research supports the adjunctive use of benzodiazepines in the treatment of schizophrenia.25,31,32 However, only alprazolam and clonazepam appear to have substantial antipanic effects, as well as substantial effects on both positive and negative schizophrenic symptoms.

Clonazepam and antipsychotics may be started concurrently when indicated. During inpa-

The addition of clonazepam has several benefits. Patients typically report a prompt reduction of anxiety. The cessation of panic attacks is typically associated with a further reduction in anxiety, a reduction in phobia, increased social interaction, and increased affective relatedness. These benefits are accompanied by, and may correspond to, a reduction in negative symptoms.33 At the same time, positive symptoms such as auditory hallucinations and paranoid delusions may improve rapidly. In those patients with a robust response to an antipanic medication, the requirements for antipsychotics may decrease as well.

The patients who appear to have the best response to the addition of antipanic pharma-

**TREATMENT PRECAUTIONS**

Although clonazepam has benefits, it also has drawbacks. Clonazepam may cause drowsiness at the beginning of treatment, or with increases in dosage. Although this sedation will diminish over time, patients often complain of tiredness. This is an important concern for those patients who drive or use machinery, or who take other sedating medications. Clonazepam may cause or contribute to gait disturbances and falls, especially in patients with central nervous system damage. Clonazepam, like all benzodiazepines, may cause physical dependence and consequent
risk of withdrawal symptoms. However, because it does not produce a "high," it has a lower potential for abuse, even among patients who abuse drugs or alcohol. Nevertheless, caution is warranted when prescribing clonazepam to patients who are substance abusers. The use of clonazepam for the treatment of panic disorder does not lead to escalating dose requirements. Alprazolam has been reported to cause manic excitation and dyscontrol in some patients, which is yet another reason for caution.34-36

Their response to medication may cause patients with panic disorder and schizophrenia to become noncompliant. The reduction of symptoms may be distressing, especially among patients with long-standing panic disorder and schizophrenia. Initially, patients are often delighted that their symptoms are improving. However, after several weeks, their complaints of side effects and drowsiness increase, although the sedative effect of clonazepam is likely to have diminished by then. The clinician should acknowledge the side effects, recognize the changes in the patient’s life, and explore ways to help the patient adapt. Because outpatients are more difficult to monitor than inpatients and receive less psychotherapeutic support, they should be given lower doses of clonazepam initially and these doses should be increased more gradually.

As patients’ conditions improve, other comorbid diagnoses must be reassessed, including obsessive-compulsive disorder, social phobia, and atypical depression.

PSYCHOTHERAPY

The symptoms of panic disorder and schizophrenia are usually overwhelming to patients and have profound effects on their cognition, personal relationships, and daily functioning. The longer the symptoms last, the more familiar and extreme they become. Effective pharmacotherapy can be a double-edged sword. Although it may relieve long-standing symptoms, often the patient’s world becomes an unfamiliar place. Life becomes both more pleasant and more frightening. To be effective, psychotherapy must address the reduction and/or disappearance of severe and long-term symptoms, the growth of new opportunities, and the presence of emotional conflicts that inevitably cloud these issues. Failure to provide proper support and psychotherapy will increase the likelihood of noncompliance and treatment failure.37

CONCLUSION AND FURTHER RESEARCH

Panic disorder and schizophrenia often occur comorbidly, and panic disorder has important treatment implications. Adjunctive clonazepam will often result in substantial improvement of panic symptoms and both positive and negative symptoms of schizophrenia. A major impediment to ongoing benefit is the psychological response to symptom reduction, which needs to be addressed in psychotherapy.

The comorbidity of panic disorder, its premorbid occurrence, the concurrence of panic attacks with psychotic exacerbation, and the global response to antipanic treatment all suggest that panic disorder may have a pathogenetic relationship to schizophrenia. For example, one patient with schizophrenia but without apparent panic disorder underwent a 35% carbon dioxide challenge to assess for panic (J. P. Kahn, MD, unpublished data, 1988).38 The patient responded with panic and auditory hallucinations. As a result of this experience, she was able to describe similar panic symptoms concurrent with previous hallucinations, and also preceding the initial onset of her psychosis. Adjunctive alprazolam then produced marked clinical improvement.

This is but one kind of research that could help us to understand the relationship between panic disorder and schizophrenia. Other avenues might include the clinical analogy to amphetamine psychosis and the commonality of dopaminergic and GABAergic mechanisms in both panic disorder and schizophrenia. Well-designed studies are needed to explore, confirm, and expand these observations about panic disorder and schizophrenia. In particular, phenomenology, natural history, diagnosis, treatment, and underlying pathophysiology need further examination. It may well be that some cases that are currently considered schizophrenia are actually panic psychosis.
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