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Editorial

Schizophrenia – an anxiety disorder?

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Summary
Anxiety and affective symptoms are prominent features of schizophrenia which are often present in the prodromal phase of the illness and preceding psychotic relapses. A number of studies suggest that genetic risk for the disorder may be associated with increased anxiety long before the onset of psychotic symptoms. Targeting anxiety symptoms may represent an important strategy for primary and secondary prevention in schizophrenia.

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The importance of anxiety in schizophrenia has long been recognised.[1,2] Indeed, Sigmund Freud considered psychotic symptoms to arise as a defence against underlying states of heightened anxiety, and Bleuler highlighted affective disturbance among his fundamental symptoms of schizophrenia. An increasing number of studies now provide experimental evidence suggesting that heightened anxiety may be important in both the development of psychosis and psychotic relapses. This work highlights the fundamental importance of anxiety and affective symptoms in the disorder and the potential to target anxiety symptoms in primary and secondary prevention.

Anxiety in schizophrenia and the schizophrenia prodrome

There is strong evidence of significant comorbidity between schizophrenia and anxiety disorders. This is apparent despite the tendency for diagnostic overshadowing in which anxiety disorders may not be recorded once a diagnosis of schizophrenia is established, a factor contributed to by the hierarchical nature of psychiatric classification schemes. Meta-analyses and systematic reviews have nevertheless confirmed high rates of social phobia, obsessive–compulsive disorder, post-traumatic stress disorder, panic disorder and generalised anxiety disorder in patients with schizophrenia.[1,2] These categorical anxiety disorders are likely to represent just a component of a broader continuum of anxiety symptoms in these patients, which may fluctuate across the course of the disorder.

There is also substantial evidence that anxiety and affective symptoms are a common feature of the schizophrenia prodrome.[3] This work is important in identifying increased anxiety as a precursor to psychosis, suggesting the possibility that anxiety may not simply co-exist with schizophrenia but may be part of the pathway leading to the development of the condition. However, as most studies of the schizophrenia prodrome focus on individuals in the 'at risk mental state' who have already developed attenuated psychotic symptoms, it is hard to determine whether anxiety and affective symptoms are a true precursor to the onset of psychosis or arise as a result of the development of early psychotic symptoms. The possibility that anxiety symptoms are a precursor of schizophrenia is strengthened by results in prospective birth cohort studies, which have shown heightened anxiety levels in children who later go on to develop schizophrenia decades later,[4] although these studies do not directly investigate the relationship between specific risk factors for schizophrenia and increased anxiety.

Genetic risk factors for schizophrenia and anxiety

Genetic factors are known to play a significant role in mediating risk for schizophrenia and a number of studies have investigated the influence of genetic risk for schizophrenia on anxiety. Until recently genetic risk could only be studied with family designs looking at the at-risk genetic relatives of individuals with schizophrenia. In one of the largest such studies, the Edinburgh High Risk Study of schizophrenia, heightened anxiety, tension and mood symptoms were found to precede the onset of psychotic symptoms in those who went on to develop the disorder.[5] These findings are important as the detailed prospective clinical examination of these individuals in the advance of the development of any illness showed that anxiety symptoms in many cases preceded the development of even attenuated or prodromal psychotic symptoms.

Recent advances in the understanding of the genetic architecture of schizophrenia have now made it possible to directly investigate the influence of genetic risk factors for the condition on anxiety states. In a large study of healthy adolescent individuals from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, Jones and colleagues investigated the effect of burden of polygenic genetic risk for schizophrenia on anxiety levels and psychotic and negative symptoms.[6] Strikingly, genetic risk for schizophrenia, indexed using a polygenic risk score, was strongly associated with increased anxiety levels as well as negative symptoms, but was not associated with prodromal psychotic symptoms.[6] Other genetic studies have also found evidence of an overlap between polygenic risk for neuroticism and genetic risk for schizophrenia, further supporting a key role for neurotic symptoms in the pathogenesis of schizophrenia.[7]

Early increases in anxiety symptoms have also been reported for rarer but more penetrant genetic risk factors for schizophrenia. The most studied of these is the 22q11.2 chromosomal deletion syndrome (22q11DS), which is known to confer a more than 50-fold increase in risk for schizophrenia. Large collaborative studies of >1000 individuals with 22q11DS have identified anxiety as a prominent symptom that is present much earlier than the age

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at which psychotic symptoms emerge.[8] These findings are supported by prospective longitudinal studies of children with 22Q11DS, which also show prominent anxiety symptoms emerging in the first decade of life. As yet however, these studies have not generally followed up children with 22Q11DS for a sufficient period to determine whether heightened anxiety is associated with the later development of a psychotic illness.

Taken together, results from the study of genetic risk for schizophrenia suggest that anxiety symptoms are a prominent early feature of risk for the disorder and do not simply arise as a consequence of the development of psychotic symptoms. Notably a number of non-genetic risk factors for psychosis – such as stress, abuse, migration and cannabis misuse – can also increase anxiety levels, suggesting that elevated anxiety may represent a common consequence of both genetic and environmental risk factors for schizophrenia. Overall heightened anxiety, which can bias both perception and cognition, may contribute to the development of psychotic symptoms in individuals with a range of genetic and environmental risk factors.

Anxiety in psychotic relapse

If anxiety is such a prominent feature of risk for developing schizophrenia, is heightened anxiety also a marker of impending psychotic relapse? It is increasingly recognised that psychotic relapses are also preceded by a prodromal period.[9] A number of studies have investigated the symptoms associated with relapse into psychosis in those with schizophreniform conditions. Evidence suggests that anxiety and dysphoric symptoms are also prominent during the relapse prodrome, although more studies are warranted to address this issue in further detail.[9] Elevated anxiety and affective symptoms may thus potentially represent a target for treatment (pharmacological or psychological) as a secondary prevention measure in preventing psychotic relapse.

Targeting anxiety and affective symptoms in the primary and secondary prevention of psychosis

Is there any evidence that the treatment of anxiety and affective symptoms can be effective in either the primary or secondary prevention of psychosis? Studies of treatment in the schizophrenia prodrome, before the onset of illness, are notoriously difficult due to the problems associated with identifying prodromal cases, low conversion rates and problems in determining who is most likely to go on to develop a syndromal illness. Nevertheless, an intriguing non-randomised study of treatment in prodromal cases suggested a significant effect of antidepressant medication in reducing conversion to full-blown psychosis,[10] and preclinical studies have suggested that peripubertal treatment with benzodiazepines may decrease the later emergence of a hyperdopaminergic state.[11] In addition, cognitive–behavioural therapy approaches, which are known to be effective in targeting anxiety and depressive symptoms, have also shown some efficacy in decreasing symptoms and early conversion rates in prodromal groups.

Studies of secondary prevention of relapses in psychosis using anti-anxiety/depression treatments are not common. However, a recent meta-analysis of trials of the addition of antidepressant treatment to antipsychotics in schizophrenia showed benefits not only in terms of affective symptoms but also primary psychotic symptoms.[12] In addition, a substantive, but as yet unreplicated, trial showed that the addition of benzodiazepine treatment to decrease anxiety in schizophrenia reduced relapse rates.[13] Given the availability of a variety of safe pharmacological and psychological treatments for anxiety, further studies examining the benefits of targeting affective and anxiety symptoms for relapse prevention in psychosis are warranted.[2] Such intervention studies also importantly have the potential to explore the causal relationship between anxiety and psychosis.

Summary and conclusions

Anxiety symptoms are prominent in schizophrenia and are seen during the prodromal phases of the illness and preceding psychotic relapses. Their importance is suggested by studies showing that genetic risk factors for schizophrenia are directly associated with increased anxiety states. Relatively few studies have examined the potential for targeting anxiety and affective symptoms as a means to primary and secondary prevention in schizophrenia, but those studies that have taken this approach are encouraging and suggest that more systematic investigation of anti-anxiety treatments in the management of schizophrenia are warranted.

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