First-episode psychosis: An update

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Interest in the subject of first-episode psychosis has increased considerably in the last two decades. At present, a number of centres around the world focus on early identification and intervention in people with psychotic disorders. Researchers have focused particularly on people who are possibly experiencing the prodromal phase of the illness in the hope that, by instituting appropriate early intervention, the outcome of schizophrenia will be improved. Patients with first-episode psychosis present with different symptom domains that should be taken into account when planning treatment. Most patients initially respond to treatment; however, there is a high rate of relapse within a few years. It is therefore important that we continue to seek improved relapse prevention strategies. There has also been a resurgence of interest in psychosocial risk factors for the development of schizophrenia in the recent literature. We review the literature on first-episode psychosis and highlight the significant findings.

Schizophrenia is a devastating illness for the majority of its sufferers. Despite many years of research, it remains one of the most burdensome and costly illnesses worldwide.[1] In addition to direct treatment costs, patients' families have to deal with many further burdens. During the last two decades, interest in first-episode psychosis has increased dramatically. Studying this population has not only allowed researchers to study the illness relatively free of confounders,[2] but has also renewed hope that the outcome of the illness can be positively influenced by early intervention.[3]

The clinical picture of schizophrenia is complex; factor analysis has shown it to comprise various symptom complexes or domains, each of which is clinically relevant and may require different treatment strategies. These domains include positive symptoms, negative symptoms, mood symptoms and cognitive symptoms, and it is postulated that there are specific pathophysiological processes underlying each domain.[4] These processes may be present to a greater or lesser degree from the first episode.

The prodromal phase

Most patients with schizophrenia experience a period of disturbance before the onset of florid psychotic symptoms, which has come to be called the prodromal phase. Typically, the prodrome is characterised by nonspecific mood and anxiety symptoms, negative symptoms (such as poor drive, low energy and poor interpersonal skills) and attenuated positive symptoms (e.g. hallucinations and odd thinking).[5] More often than not, there is marked deterioration in social and occupational functioning.[6] Owing to its insidious nature, however, the prodrome is commonly only identified retrospectively at the onset of psychosis. Recently, a number of researchers have tried to identify the prodrome premorbidly in young people seeking medical assistance.[7-11] Accurate identification of patients during the prodromal phase may allow opportunities for intervention before the onset of psychosis. This is important in the context of the 'critical period hypothesis', which emphasises the importance of early intervention as a means of minimising further deterioration in function, and optimising outcome.[12]

However, identification of the prodrome is not straightforward as symptoms are nonspecific, and many young people seem to experience quasi-psychotic symptoms without going on to develop schizophrenia.[5] This raises important ethical concerns regarding prodromal phase interventions. As the prodromal period at this point can only truly be identified in retrospect, we need to be cautious in identifying candidates for early intervention. The concerns raised include stigma, confidentiality and issues of autonomy. There is also a risk of committing falsely positive individuals to long-term treatment.[13] These ethical concerns have been addressed at specialised early psychosis centres.[14] However, individual clinicians must take cognisance of the ethical issues involved when dealing with people at risk for psychosis, especially since the absolute benefits of early intervention have yet to be proven in a rigorous and convincing manner. One approach to resolving this clinical dilemma is the development of diagnostic criteria for the prodromal phase. For example, the Ultra High Risk Criteria developed by McGorry's group, attempt to predict the experiencing of a true prodrome and thus the likelihood of developing a first episode of psychosis in the near future. Patients must have either (*a*) the presence of attenuated (subthreshold) psychotic symptoms, or (*b*) a history of brief self-limited psychotic symptoms, or (*c*) a family history

of psychosis and deteriorating social function.[15] When these criteria are applied to young people seeking help, they are effective in identifying the majority of patients likely to develop a first episode of psychosis within a year.[16] Unfortunately, there are many people who develop schizophrenia without meeting these criteria.

Accompanying the development of early diagnostic criteria is a renewed focus on therapeutic interventions in first-episode psychosis. These interventions are aimed at treating the presenting symptoms as well as delaying or even preventing the onset of psychosis. There are now a number of specialised early psychosis centres around the world that use a multi-disciplinary, holistic approach to prodromal interventions.[7-11] Individual elements of these interventions have been studied. For example, several studies demonstrate that treatment with low doses of the second-generation antipsychotics olanzapine and risperidone improves psychotic-like symptoms during the prodrome.[17,18] Olanzapine has also been shown to reduce the rate of conversion to psychosis and also delay onset.[18] Combining low-dose risperidone with cognitive behavioural therapy (CBT) has been shown to decrease the rate of transition to psychosis, with a low incidence of adverse effects.[7] Psychological interventions alone (such as CBT) have also been shown to improve symptoms, prevent social decline, and prevent or delay progression to psychosis. In general, patients find psychological interventions more acceptable, tolerable and less stigmatising than taking medication.[19] Currently, we do not have clarity on whether any one of these treatment modalities is more effective than the others.

The acute phase

The acute phase begins in earnest with the onset of florid psychotic symptoms. Acute-phase symptoms include all the symptom domains of schizophrenia, although most attention is focused on positive symptoms. The majority of patients with first-episode psychosis seek help from services during the acute phase, although their illness started in the prodromal phase a few months or even years previously.

Positive symptoms

Delusions, hallucinations and disorganised speech have long been considered the hallmark of schizophrenia. Positive symptoms, however, are not sufficient to warrant the diagnosis of schizophrenia, and may in fact occur in a number of disorders, including mania, substance-induced psychosis

and brief psychotic episodes. The *DSM-IV-TR* criteria for schizophrenia[20] are presented in Table I.

Mood symptoms

Symptoms of depression are common in schizophrenia, and are nearly always a feature of first-episode psychosis.[21] Depressive symptoms are more common during the acute phase, but may occur after the acute phase and are then termed 'post-psychotic depression'.[22] We now know that depressive symptoms differ in their significance, depending on the phase of illness in which they occur. The majority of depressive symptoms in the acute phase resolve after antipsychotic treatment.[22] Their presence in this phase is actually regarded as a positive prognostic factor, as patients with prominent depressive symptoms have fewer negative symptoms and are therefore more likely to have a better outcome.[23]

Symptoms of depression that persist beyond the acute phase or that emerge after the acute phase (post-psychotic depression) are, however, associated with a poorer outcome. These symptoms are not responsive to antipsychotic treatment and therefore require additional interventions.[24] Post-psychotic depression may occur in patients who attribute their illness to loss, humiliation or entrapment. The manner in which patients view the meaning of their psychosis predicts the development of depression.[25] Psychological intervention is thus indicated in these patients, in addition to pharmacological treatment. It is important to note that patients who suffer from both first-

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Table I. *DSM-IV-TR* diagnostic criteria for schizophrenia

A. Two or more of the following symptoms present for 1 month:

    (a) delusions

    (b) hallucinations

    (c) disorganised speech

    (d) disorganised or catatonic behaviour

    (e) negative symptoms, e.g. emotional blunting, poor drive, or alogia

B. Deterioration in the level of functioning at work, in social relationships, or with regard to self-care

C. Signs of the disturbance must be present for at least 6 months

D. Mood disorders have been ruled out

E. The disturbance is not due to a general medical condition or the effects of a substance

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episode schizophrenia and major depression have a poorer subjective quality of life. These patients are often younger and have greater insight into their illness.[26] The most serious complication of depression is suicide – the risk for suicide in schizophrenia is highest during the early stages of the illness.[27] Clinicians therefore need to be particularly vigilant in evaluating and monitoring for symptoms of depression during the acute phase and post-acute phase of schizophrenia. Although many different rating scales have been developed for the assessment of depression, the most suitable tool for accurately assessing depression in schizophrenia is the Calgary Depression Scale for Schizophrenia.[28]

Negative symptoms

Negative symptoms such as poor drive, low energy, poor self-care and emotional withdrawal are important and inherent to schizophrenia, and may be present from the early phases of the illness. First-episode psychosis patients have negative symptoms similar to, but not as severe as, chronic schizophrenia. Negative symptoms have been associated with delay in seeking treatment.[29] It is still difficult to differentiate true negative (primary negative) symptoms from secondary negative symptoms, i.e. those that are secondary to positive and mood symptoms or the effects of medication.[30] In first-episode psychosis, depression and parkinsonism (as a side-effect of medication) are the main causes of secondary negative symptoms.[29]

Cognitive symptoms

Cognitive impairment is a core feature in schizophrenia. It has been demonstrated in high-risk individuals, prior to onset of first-episode psychosis.[31] The pattern and severity of cognitive deficits found in first-episode patients is similar to that found in chronic schizophrenia. Cognitive dysfunction is present across a variety of cognitive domains, including attention, working memory and executive functioning.[32] A standardised cognitive battery for schizophrenia is being developed, as it has been difficult to compare results from different studies using different tests.[33] Cognitive dysfunction is associated with poor social and occupational function, and seems to be a more important determinant of social re-integration than any of the other symptom domains. Therefore, treating cognitive deficits can potentially improve functional outcome.[34]

Risk factors

Risk factors for the development of psychosis are complex and multi-factorial. They include genetic factors, cannabis use, immigration, urbanisation, obstetric complications and winter births.[35,36] Genetic epidemiological studies have strongly implicated genetic factors in the aetiology of schizophrenia; however, studies to date have failed to produce definitive answers on which loci or genes are involved. It now seems unlikely that schizophrenia is caused by one or two genes, but is more likely the result of a number of interacting genes with small effects. The susceptibility genes with the strongest evidence are dystrobrevin binding protein 1 or dysbindin (DTNB1) and neuregulin 1 (NRG1). DTNB1 is part of the protein complex in postsynaptic densities in the brain. NRG1 plays an important role in neuronal migration.[37] The identification of candidate genes may have important implications for our understanding of the pathophysiology of schizophrenia. However, 'genetic cases' probably represent only a subset of patients with this disease.

The controversy surrounding cannabis and psychosis seems to have been resolved. Population-based studies have clearly shown that cannabis use is associated with a risk of onset of schizophrenia.[38] Cannabis is now regarded as a moderate risk factor for the development of psychosis. The risk of developing psychosis increases with longer duration of exposure to cannabis,[39] with adolescents at particular risk. It is postulated that the adolescent's brain is most vulnerable as it is still undergoing development. People who develop psychosis following cannabis use are clearly part of a vulnerable, susceptible group.[40] Recently, it has been shown that genetic vulnerability (functional polymorphism in the COMT gene) interacts with cannabis use in the adolescent, leading to adult psychosis.[41] This is a good example of gene-environment interactions. It has been postulated that if we can minimise environmental risk factors, we may be able to neutralise the genetic risk in some individuals, thus positively influencing the incidence of schizophrenia.[42] This tactic provides a good rationale for public health measures aimed at reducing adolescent cannabis use.

Other environmental risk factors for schizophrenia have also been revisited. The association between schizophrenia and migration has drawn considerable recent interest. It is now apparent that a personal or family history of recent migration increases the risk of developing schizophrenia.[35] Second-generation immigrants are also at an increased risk of developing schizophrenia.[36] The social defeat theory has been put forward as a possible explanation of this increased risk. Immigrants constantly feel that they are outsiders and are forced into a subordinate role, compared with the dominant population.[35] This perception leads to specific,

potentially paranoid thought patterns that may become part of the psychotic illness. Urban upbringing or environment has also been associated with an increased incidence of schizophrenia.[42] Interestingly, it has been shown that urbanisation and genetic factors can act together to increase the risk of schizophrenia,[43] again pointing to the inextricable interaction of genetic vulnerability with environmental factors.

Treatment

Experience of treating schizophrenia has left many clinicians pessimistic about the outcome of the illness. Its long-term outcome has been described as poor; many patients have recurrent relapses, require frequent hospitalisation, and have impairment as the result of negative symptoms, cognitive deterioration and side-effects.[2] Studies of first-episode psychosis patients, however, provide a more optimistic picture. Most first-episode psychosis patients respond to treatment, and more than 80% will remit within 1 year.[44] This good response further supports the critical period for intervention theory,[12] which states that treatment in the first 5 years of illness may limit and even prevent deterioration in social and occupational functioning. It is now evident that the earlier antipsychotics are started, following onset of the illness, the better the response to treatment.[3]

Conventional wisdom holds that there is a delay in onset of action of a few weeks in treatment with antipsychotic medication. More recent findings, however, suggest that in fact the majority of the antipsychotic effect takes place within the first week of treatment.[45] Onset of action of antipsychotics has even been shown to occur as early as 24 hours after commencing treatment, with changes apparent on rating scales.[46] First-episode psychosis patients, however, have been shown to have a much more varied response rate.[47] In a study by Emsley *et al.* many patients responded after only 4 weeks of treatment. Whenever possible, antipsychotic trials should therefore be extended for longer than 1 month in first-episode patients.[47]

In recent years, there has been a great increase in the use of second-generation antipsychotics for the treatment of schizophrenia. Second-generation antipsychotics have been considered superior to typical antipsychotics, as they are less likely to cause extrapyramidal symptoms,[48] and are more effective in treating negative symptoms, mood symptoms and cognitive symptoms of schizophrenia.[49] Two important studies published in the last 2 years have, however, cast some doubts over the superiority of these medications when compared with conventional antipsychotics. Both studies were designed in such a manner as to closely mirror everyday clinical situations[50] and neither was funded by pharmaceutical companies. The CATIE Trial examined the effectiveness of a number of antipsychotics, comparing four second-generation antipsychotics (olanzapine, risperidone, quetiapine and ziprasidone) with perphenazine, a first-generation antipsychotic.[51] The most significant and unintended finding of this study (and a finding that has subsequently received a great deal of attention) was that 74% of subjects discontinued their treatment before the end of the study. This finding has once again highlighted the fact that medication discontinuation remains a major obstacle in the treatment of schizophrenia. Furthermore, the introduction of second-generation antipsychotics has not significantly improved medication compliance.[50] The second study (of quality of life in patients with schizophrenia) compared a group on first-generation antipsychotics with a group on second-generation antipsychotics.[52] This study found no differences between the two treatment groups and even reported a trend favouring the first-generation antipsychotics.

A further issue relates to the acquisition cost of second-generation antipsychotics, which has resulted in only limited availability of these agents in lower-income countries.[53] Typical antipsychotics therefore still form the mainstay of treatment for the majority of patients worldwide. The two recent studies cited above seem to suggest that patients can have a similar quality of life on typical antipsychotics if we carefully determine an effective dose with minimum side-effects. The studies also support previous studies which indicated that low doses of first-generation antipsychotics such as haloperidol are effective and well tolerated in patients with first-episode schizophrenia.[54-56]

Although first-episode psychosis patients respond well to treatment, they have a high relapse rate within the first few years of the illness.[57] It now seems likely that, with each relapse, patients are less likely to return to their previous level of functioning.[58] Prevention of relapse therefore becomes a major challenge in the management of first-episode psychosis patients. Since medication discontinuation has been found to be the strongest predictor of relapse,[57] assured delivery of an antipsychotic by means of a long-acting injection may be one strategy to improve outcome. Until recently, only first-generation antipsychotics were available as long-acting injections. Sensitivity to extrapyramidal effects has limited their use in first-episode psychosis.[59] Long-acting risperidone

is the first second-generation antipsychotic to be available as an intramuscular formulation. It has been shown to be safe, well tolerated and effective in first-episode psychosis[60] and may be a treatment of choice in this group of patients where sustained intervention is so important.

Studies with patients experiencing a first episode of psychosis have clearly shown that there is a large role for psychosocial interventions in schizophrenia. In many countries around the world, these patients are treated in special early psychosis programmes that integrate pharmacological treatment with psychosocial interventions. The majority of programmes include features such as early detection; individual, group or family therapy; and case management.[61] There is some evidence that comprehensive programmes are more likely to produce superior outcomes compared with generic mental health services.[62] Therefore, early referral to specialised early psychosis programmes where available, is advisable. Researchers have also looked at the effectiveness of individual components of psychosocial interventions in first-episode psychosis. Individual CBT has been shown to be of benefit in reducing symptoms and improving adaptation to the illness and the subjective quality of life, but it has not been effective in reducing relapse rates or re-hospitalisation.[62] Family therapy has, however, been shown to reduce rates of relapse in schizophrenia.[63] Moreover, family work during the first episode has been found to be highly acceptable to family members, as opposed to families of patients who have had multiple relapses.[63] For clinicians working in areas without early psychosis programmes, it is encouraging to note that individual CBT or family therapy is effective and can therefore be used even when specialised units are not available.

Predictors of outcome

Predictors of treatment outcome are relatively well studied, and a large number of factors that can determine outcome in first-episode psychosis have been identified. Male gender, poor obstetric history, severe positive symptoms, poor attention at baseline and the development of parkinsonism during antipsychotic treatment are all predictors of poor outcome.[59] A recent meta-analysis has shown that longer duration of untreated psychosis (DUP) is associated with inferior recovery from first-episode psychosis.[64] Increased DUP has also been found to be associated with a poorer response of negative symptoms.[65] These findings are of particular importance as DUP is one of a few factors that are potentially modifiable, which again emphasises the need for early detection and effective treatment. Recently, researchers have tried to combine baseline clinical features with early treatment response in order to predict accurately which patients will reach remission.[66] They found that by combining neurological soft signs, DUP, marital status, positive and negative syndrome scale (PANSS) excited factor baseline score and early treatment response, they were able to identify accurately which patients will reach remission. This model attempts to make the predictors of outcome variables more clinically useful.

Conclusion

Studies of first-episode psychosis conducted over the last two decades have increased our knowledge of the pathophysiology of schizophrenia. It is now clear that early intervention in schizophrenia increases the likelihood of a more positive outcome in this disorder. The role of the clinician has been extended, and clinicians can now offer holistic interventions with renewed hope for a better outcome for their patients.

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