

# Early intervention in schizophrenia patients—rationale for its implementation and practice

EYH Chen

**This review examines the clinical and theoretical evidence justifying early intervention in individuals with schizophrenia. Potential reasons for the previous lack of emphasis on early intervention are discussed. Interventions that target psychosis are distinguished from those that work on prodromal symptoms. It is suggested that early intervention programmes should try to reduce the duration of untreated psychosis. The relationship between this and outcome is discussed. Improving service accessibility alone may not be sufficient, and education and destigmatisation input may be required. Once a patient is identified, vigorous pharmacological and psychosocial interventions are important to improve the long-term clinical outcome. An effective early intervention programme for psychosis provides a basis for the future development of a prodrome intervention programme.**

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## Introduction

Schizophrenia affects young adults of both sexes with an incidence of approximately 5 in 1000 people in the general population.<sup>1</sup> The illness produces devastating effects on the subjective experiences of patients in the form of hallucinations and delusions (psychotic episodes). In addition, schizophrenia also leads to lasting behavioural deterioration similar to the changes seen in patients with gross prefrontal lesions; changes include disinhibition of behaviour, loss of drive, social withdrawal, and a loss of emotional expression (the latter three are termed 'negative symptoms'). These effects lead to devastating long-term functional consequences for patients. Furthermore, schizophrenic patients suffer from severe cognitive deficits such as attention, memory, and executive function impairments.<sup>2</sup> These deficits are persistent and may critically affect the occupational capacity of patients.

Schizophrenia also tends to have a relapsing course.<sup>3</sup> There is evidence that after each relapse, some patients have difficulty in returning to their previous level of functioning.<sup>4</sup> Maintaining antipsychotic medication is known to be effective against relapses. Unfortunately, a proportion of patients pro-

gress during the course of their illness to become resistant to antipsychotic treatment.<sup>5</sup>

## The principle of early intervention

Awareness of the need for early intervention is well-developed for progressive diseases (eg tumour) in which a delay in treatment carries conspicuous penalties in terms of mortality and morbidity. But until recently, awareness has been surprisingly underemphasised in the management of schizophrenia. This shortcoming may be related to a prevailing view of schizophrenia as a developmental disorder exhibiting a static course.<sup>6</sup> This view has been challenged with the observation that, at least for some patients, the illness runs a progressive course, and that medication might protect against such progression.<sup>7-10</sup> Another reason for a lack of intervention may be the belief that negative symptoms (and hence functional outcome) are not responsive to antipsychotic treatment.<sup>11</sup> Recent studies suggest, however, that some negative symptoms may improve with antipsychotic treatment.<sup>12</sup> In addition, effective psychological and social management methods (eg family therapy) are now recognised. Last but not least, the period of psychosis is associated with a multitude of risks and suffering for the individual, the family, and the community. Consequences can include the lost opportunity for normal life experience and personal development, as well as the adverse social consequences from any psychotic behaviour (including self-harm and violence) over the period of the psychosis, which may

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Department of Psychiatry, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong  
EYH Chen, FRCPsych, FHKAM (Psychiatry)

Correspondence to: Dr EYH Chen

span years. The importance of early intervention has been emphasised in many recent reports.<sup>13-15</sup>

### **The relationship between duration of untreated psychosis and long-term outcome**

The onset of the first psychotic episode tends to be preceded by functional and personality changes, as well as a range of non-specific psychological experiences.<sup>16,17</sup> This prodromal phase may last for several years, but once psychotic symptoms become established, they gradually lead to increasing disturbance of the individual's behaviour and eventually lead to contact with the health service. The time lag between psychosis onset and treatment (duration of untreated psychosis [DUP]) can be lengthy. It is suggested that early intervention primarily targets a reduction of this lag time and raises the issue of how the DUP could be effectively reduced.

Methodological refinement of the onset assessment<sup>18,19</sup> have enabled studies to address the relationship between DUP with better outcome in first-episode schizophrenic patients.<sup>13,20-26</sup> Most of these studies have shown a correlation between a shorter DUP with better outcome, in spite of variations in methodology and clinical settings.<sup>20</sup> In addition, a meta-analysis that compared patients who have been treated with medication at particular stages in their illness with relatively similar patients who have not been treated at those stages indicated that the treated group achieved better long-term outcome.<sup>4</sup>

Strictly speaking, correlational evidence does not prove that better outcome is caused by early treatment. It is theoretically possible that both outcome and early treatment are mediated by a third variable.<sup>27</sup> To clarify this possibility, it will be necessary to conduct controlled studies in which patients are randomised into an early intervention group and their outcome compared with a group without early intervention. Such studies are difficult to arrange because of the ethical issues that may arise. In particular, having identified patients suffering from psychosis, it would be ethically difficult to randomise such patients into a control group and withhold treatment for a defined period of time during which suffering and risks would continue to be incurred.

### **Reasons behind a lengthy duration of untreated psychosis**

The DUP is commonly lengthy (12-24 months), even in communities where psychiatric services are well

developed.<sup>13,20,22,28</sup> This means that merely improving service accessibility is probably not going to be sufficient on its own. It is important to understand additional obstacles that hinder timely contact between patients and the health service. Although there is a lack of systematic data on this issue, it is worthwhile highlighting some potentially important barriers.

When an individual experiences psychotic symptoms, the link to mental illness is seldom related to mental illness. Often the individual is so convinced by the sense of reality of the psychotic experience that they do not realise that there is anything wrong with them. In some cases, the psychotic experience causes sufficient social disruption for the individual to be brought to the attention of the health care system. In other cases, such a crisis may not occur until a considerable amount of time has elapsed. A study investigating the general public perception of psychotic symptoms in Hong Kong showed that psychotic symptoms are often regarded as merely psychological reactions to stress rather than signs of an illness that may require treatment.<sup>29</sup> Such a low-key view may lead relatives and carers to 'wait and see' rather than seek help early.

Much of the delay, however, can also be attributed to an inherent reluctance by both the patient and the family to acknowledge the possibility of a mental disorder being the cause. This hesitation is understandable, as even in more liberal and progressive societies, schizophrenia still carries considerable stigma.<sup>30</sup>

### **Strategies for reducing the period of untreated psychosis**

Most early intervention programmes emphasise the need to address some of the obstacles that keep patients and their families from seeking help. Existing strategies include the need to make mental health care easily available; the need to not make patients pessimistic about their outcome; and the need for good patient, professional, and public education about the disease.

#### *Accessibility of service*

Most programmes emphasise a need to minimise the effort that has to be made by the already troubled patients and their families to come into contact with the service. This includes convenient referral routes, very short waiting lists, assessments at patients' homes, and geographically convenient locations for assessment centres. These objectives and practices can mostly be achieved by establishing a well-developed community-oriented service.

### ***Destigmatisation***

Destigmatisation could be approached by minimising stereotyping and labelling to patients. Some programmes suggest that separate in-patient facilities should exist for first-episode patients and chronic patients. This measure serves to reduce contact between first episode patients and chronic hospitalised patients (a biased sample of patients with a less favourable outcome) to avoid giving first-episode patients the impression that their illness will inevitably progress to an unfavourable outcome.<sup>15</sup>

### ***Education***

Education involves the effective provision of information in several different settings with different objectives—for example, material written for the general public, at-risk populations, relevant professional workers, patients, and their families.

As stigmatisation is aggravated by ignorance,<sup>31,32</sup> enhancing general public knowledge of schizophrenia and its treatment should lead to a reduction in negative stereotyping. Less stigmatisation could also reduce the reluctance of psychotic patients and their families to seek professional help. Education of the at-risk population aims to increase individual awareness of the potential symptoms of schizophrenia—for example, those at risk because of genetic reasons (the siblings or the offspring of patients have a lifetime risk of approximately 10% of becoming schizophrenic). Another approach is to set up ‘prodrome clinics’ for individuals with prodromal symptoms where assessment, counselling, education, and follow-up services could be offered.

Systematic information concerning the symptoms of schizophrenia can be provided to professional workers likely to be in contact with individuals suffering from an initial psychosis. These professionals include teachers, counsellors, social workers, police officers, ministers of religion, and general practitioners.<sup>33</sup> Such information could help with the early identification of patients so that expedient referral to a specialised service could be made.

Finally, comprehensive education can be offered to patients and their family members.<sup>34</sup> This practice is important for the establishment of a long-term partnership in the clinical management of the patient and is already present in many well-established clinical services.

### **Should one implement a specialised or generic service?**

One consideration is whether early intervention should occur by a specialised programme with a dedicated

team or whether it could be integrated with routine psychiatric services. Some aspects of intervention could be provided by existing general psychiatric service, especially in regions where a community-oriented psychiatric service is in operation. Such service settings often offer optimal accessibility for patients. However, the fact that a long DUP is common, even in areas where such a service exists, argues for a more intensive and focused approach to achieve a lower DUP to be used. With a dedicated service, issues such as minimising stigmatisation and focusing on early intensive treatment can be more thoroughly addressed.

### **Monitoring of prodromal symptoms**

‘Prodrome clinics’ have been set up to facilitate the early detection of those with psychotic illnesses.<sup>35</sup> During late adolescence and early adulthood, individuals go through stressful developmental stages involving major changes in roles. Some may have difficulty in coping with these changes and develop psychological symptoms, which may be similar to the prodromal symptoms of schizophrenia. The specificity of prodromal symptoms is generally relatively low<sup>36</sup>—of all individuals experiencing such symptoms, only a minority will eventually develop psychosis. Yet, for those who eventually have a psychotic illness, very early detection can be achieved. Prodrome clinics could also serve a more general purpose in providing a counselling service for individuals having difficulties adjusting to their diagnosis.

### **Should one advance early treatment into the prodrome phase?**

Several authors have discussed the possibility of implementing early intervention, in particular medication treatment, at the prodrome phase to prevent the development of psychosis altogether.<sup>13,33,37</sup> Suggested programmes are essentially similar to those outlined above except that screening and intervention are extended to prodromal symptoms. For instance, attempts have been made to offer low-dose antipsychotic medication to individuals experiencing prodromal symptoms. The cost of intervention at the prodrome phase is stigmatisation and side effects of medication, in the context of a programme with relatively low specificity (ie many false positive cases).

Although some investigators have suggested using an extensive list of risk factors (eg family history, neuropsychological performance, personality factors) to enhance specificity, it is still unclear whether those factors, when considered together, would add up to an

aggregate risk with more discriminatory power.<sup>35</sup> On the other hand, the potential gain from prodromal intervention could be a significant improvement in outcome, or even the prevention of a psychotic illness. Furthermore, the costs associated with medication side effects have been substantially lowered by the advent of the atypical antipsychotics.<sup>38</sup> These factors have strengthened the arguments for offering intervention at the prodrome stage. Currently, there is an urgent need to identify more discriminatory early markers so that a more accurate prediction of incipient psychotic illness can be made.<sup>13,27,37</sup>

## Principles of treatment for the first episode

### *Medication*

Proper treatment of the first psychotic episode is of the utmost importance. Inadequate management at this stage may foster the development of secondary consequences which can snowball and lead to a substantial deterioration in long-term outcome. For instance, lack of insight (ie unawareness of illness) is a frequently encountered problem in schizophrenia. If the degree of insight is low after the first episode, it can lead to reduced compliance to treatment, which in turn can increase the relapse rate and worsen the long-term outcome. Likewise, residual psychotic symptoms after the first episode may affect social and occupational functioning of patients and indirectly predispose them to stressful experiences (eg relationship or occupational problems). Difficulties like these lead to relapses and a poor long-term outcome. Hence, the thorough and vigorous treatment of the first episode is very important.

Previously, the medication given for first-episode schizophrenia have followed the treatment patterns used for patients experiencing a relapse. This treatment has resulted in a relatively high rate of extrapyramidal side effects. More recently, evidence has emerged that for first-episode patients, a lower antipsychotic dosage may be sufficient for the control of psychotic symptoms.<sup>39</sup> In a study of 231 consecutive patients, the mean maximum daily dose was 4 mg haloperidol (range, 0.5-15 mg/d); 80% responded to the medication and 64% were in remission by the end of three months of treatment.<sup>40</sup> It has to be mentioned, however, that the study was carried out in an area with a well-developed early intervention service, and consequently, the patients identified might have early and less intense symptoms than the average patient.

Awareness of medication side effects is also extremely important. Notable antipsychotic side effects

such as resting tremor, bradykinesia, and sedation are often reported by patients and may contribute to non-compliance. The adequate assessment of side effects, as well as dosage adjustments in order to minimise them, are key to the successful management of schizophrenia. Once patients develop views about medication, these can subsequently become fixed (possibly as a consequence of prefrontal-type cognitive abnormalities). The attribution of adverse consequences to taking the medication (whether justified or not) can be very difficult to shift at a later stage. The advent of a newer generation of antipsychotics that have fewer motor side effects now offer hope for better acceptance of medication treatment by patients.<sup>38,41,42</sup> For those patients with florid symptoms that are resistant to conventional antipsychotic medications, clozapine can be offered.<sup>43</sup>

### *Maintenance therapy*

One further issue is the length of maintenance therapy needed after a single episode of illness. Existing data suggests that a number of patients may not suffer a second episode even without maintenance treatment.<sup>44</sup> Unfortunately, it is not yet possible to identify those who will relapse and those who will not.<sup>28</sup> As yet, data from double-blind controlled studies that specifically address the optimal length of maintenance therapy are not available.<sup>28,45</sup> It appears, however, that continuing medication after the first episode seems to reduce the relapse rate in the subsequent 12 months from approximately 70% to approximately 40%.<sup>46</sup>

### *Management of depressive symptoms and suicide risk*

Depression is common in first-episode schizophrenic patients, with prospective studies reporting rates of identifiable depressive syndrome of around 50% of first episode patients.<sup>47</sup> The actual rate of depressive symptoms detected varied considerably between individual studies (from 20% to 80%), depending on the rating instruments used.<sup>48</sup> In most cases, depressive symptoms are worse at the time of the acute episode and tend to subside as the psychosis comes under control.<sup>49</sup> If depressive symptoms persist, antidepressant therapy should be commenced.<sup>49</sup>

The risk of suicide occurring is substantially increased in first-episode schizophrenia, especially among male patients. In a 2-year follow-up study, 5% of male patients but none of the female patients committed suicide.<sup>47,50</sup> Another large-scale study observed a suicide rate of 8.8 in 1000 male patients per year and 6.4 in 1000 female patients annually. This study also reported that the suicide rate increases with age.<sup>51</sup>

### **Psychosocial intervention**

Apart from medication, psychosocial rehabilitation efforts are particularly important for managing negative symptoms. Negative symptoms can be substantially present in the first episode.<sup>12,52,53</sup> Vigorous rehabilitation directed at these symptoms is particularly important in minimising secondary disabilities. Competence in social skills is also important in sustaining a social support network and is a crucial element in long-term management.<sup>54</sup> A further disability is the presence of substantial neurocognitive deficits.<sup>8,55,56</sup> By giving adequate medication treatment, some of these deficits may improve with time, but the improvement takes longer than does the improvement in symptoms.

The efficacy of cognitive remediation programmes in reducing neurocognitive deficits is still not established. In general, it is known that a high level of expressed emotion among carers of schizophrenics is predictive of more frequent relapses. Family behavioural therapy may be effective in modifying the amount of expressed emotion and the lower relapse rate in selected patients. For first-episode patients, however, data on the relationship between expressed emotion and relapse rate are conflicting and complicated by the potential confound of illness severity.<sup>57</sup>

### **Early treatment appears to be cost-effective**

This review does not include a full discussion of the cost-effectiveness analyses of early intervention programmes. There is evidence that the long-term treatment cost for patients with a longer DUP is more than the cost for patients with a shorter DUP.<sup>58</sup> Full cost-effectiveness analyses are difficult to perform because schizophrenia is a long-term illness with many subsequent disabilities and human costs. This makes the indirect costs difficult to quantify.<sup>59</sup> But cost-effectiveness analyses, despite their obvious limitations, are necessary to help focus on the potential long-term gains offered by initially costly early-intervention programmes.<sup>60</sup> The better management of a long-term illness such as schizophrenia provides a challenge for an accountable and humane system of health economics.<sup>59</sup>

### **Should early intervention for schizophrenia be implemented?**

Early intervention in cases of schizophrenia should specifically try to reduce the DUP, which is currently lengthy and appears to be resilient to generic community psychiatric approaches. There is a need for a more focused, dedicated programme to achieve a

reduction in DUP. There is strong evidence for a beneficial association between a short DUP and better outcome. While the limitations of correlational data are acknowledged, because of the need to reduce the torments and risks associated with prolonged psychosis, it seems worthwhile to support programmes of early intervention for schizophrenia. Actions taken at the prodrome phase are currently more contentious because of their low specificity; their implementation should probably await the results of further research. However, once an early intervention programme targeting DUP reduction is in place, it could provide an effective basis for the future development of a similar prodrome programme.

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