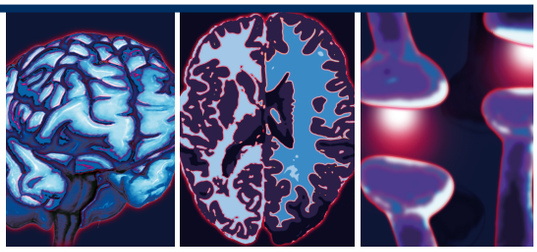

Does early diagnosis and treatment of schizophrenia lead to improved long-term outcomes?

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Practice points

- The aim of early intervention in psychotic illness is to intervine as early as possible and to offer a treatment package that is appropriate to the stage of the illness.
- Treatment of the 'prodromal phase' continues to be experimental, and it is not yet recommended that services for the treatment of the prodrome or 'ultra-high-risk mental state' be established outside of experimental conditions.
- The treatment of first-episode psychosis requires a dedicated team with a psychiatrist, nurses, social workers, occupational therapists and psychologists to work together to achieve optimum care for the patient.
- The aim of treating a first psychotic episode is to return the patient to work or education as effectively and expediciously as possible.
- Medication in first-episode psychosis should be at optimal effective dosages and should be delivered in such a way as to ensure future concordance with treatment.
- All of the social needs of first-episode patients need to be assessed, including housing, food and benefits, and steps need to be taken in the care plan to address them.
- A care coordinator should be appointed for every first-episode patient, and a written care plan should be produced that is agreed to by all parties involved, including the patient's family, and then implemented.
- A long duration of untreated psychosis leads to poor prognosis, so steps should be taken to reduce the duration of untreated psychosis, such as education in schools and for the general population.

SUMMARY Early intervention for psychosis services is a very important area of development in community mental health since it has the potential to improve long-term outcomes. Two types of early intervention services are described: those that work with patients who are in their first episode of psychosis and follow patients through the 3-year critical period, and those that are still experimental, which attempt to work within the

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prodrome in order to prevent psychosis developing. Here, we attempt to describe the general principles on which early intervention services are based, the interventions that such services carry out and the expected outcomes according to the latest literature. Finally, we speculate on how outcomes could be further improved by improving techniques of early intervention.

Early intervention (EI) for psychosis services has been a very important area of development in community mental health in recent years. Standards outlined by 'The WHO Declaration for Mental Health In Europe' [1] and developed in 'Guidelines for Community Mental Health in Europe' [2] recommend that there should be targeted care for people who develop mental illness for the first time, specifically in the young.

According to McGorry, a pioneer of EI, the application of EI to psychosis "amounts to deciding if a psychotic disorder has commenced and then offering effective treatment at the earliest possible point and secondly ensuring that intervention constitutes best practice for this phase of the illness, and is not just the translation of standard treatments developed for later stages and more persistently ill subgroups of the disorder" [3].

In the UK, when a psychotic episode has clearly occurred, there are EI services set up in each county that are targeted at persons between the ages of 15 and 35 years. These treat all forms of psychotic illness for 3 years, reflecting the fact that there is marked diagnostic instability in the first few months of psychotic illness.

Intervening in the prodromal phase of the illness, with the aim of preventing or delaying the first psychotic episode, is still somewhat experimental. However, due to the growing evidence base, a number of clinics dedicated to this approach have been set up. The two main challenges facing intervention at the prodromal phase are correct diagnosis and interventions that offer benefit with minimal risk of unwanted effects on the developing brain.

General principles on which EI are based

■ The staging model of psychotic illness

This is a model of how psychosis develops, which was first put forward by McGorry *et al*. It suggests that the development of psychotic illness can be staged [4]. The prodromal stage of the illness would be the first stage, and the first episode of the illness would be the second stage, while further, more chronic forms of the illness would be the third and later stages. It is possible to correlate MRI findings with these different stages of the illness. Thus, there is a gradual increase in the loss of gray matter from stage 1 (the prodrome) to stage 3 (the chronic illness) [5–8], while the pituitary volume increases in stage 1 and is reduced by stage 3 [9,10]. The aims of treatment, the appropriate treatment and the expected outcomes of treatment will be different in each phase of the disease.

Here, we are concerned with the first two stages of this disease process, and we will state the intended aims of treatment and outcomes of the illness as we describe each stage.

■ The critical period & the duration of untreated psychosis

The critical period hypothesis is derived from an analysis by Birchwood *et al*. [11] of data from the Northwick Park longitudinal study of the development of psychosis [12]. They observed that there is a major change in the psychosocial functioning of patients with schizophreniform illnesses within the first 3 years of its onset, but that thereafter, the deterioration tends to plateau [11]. He therefore proposed that the first 3 years of the illness constituted a 'critical period', and therefore, intensive input in the first 3 years of the illness could improve their prognosis.

The delay between the onset of the first psychotic symptom and the commencement of treatment with antipsychotic medication is called the 'duration of untreated psychosis' (DUP). DUP has been shown to be associated with an unfavorable course of schizophrenia [11,13–15]. The DUP reduces the available time for treatment during the critical period and we know that long DUP is associated with more frequent hospital admissions, seclusion, necessity of a higher dose of medication to stabilize the patient and possible police involvement [3]. Sometimes, a long DUP can be correlated with difficulty in diagnosis.

The two major meta-analyses of outcome related to DUP have both shown that the very large majority of studies demonstrate a moderate improvement in outcome of psychotic illness with a reduction in DUP, even though a few studies did not show this effect [14,15]. The first of these meta-analyses has pointed out that the

decline in functioning linked with prolonged DUP actually begins in the prodromal phase of the illness [14].

The UK Government Policy Implementation Guide recognizes the importance of the DUP, and so the aim of UK EI services is that patients with a clear first psychotic episode will receive appropriate psychosocial and medical interventions from EI teams for a period of 3 years from first presentation [16]. The problem with this is the difficulty of engaging with patients who are psychotic for the first time. There are many causes of long DUP, including difficulties that the patients and families have in identifying that something is wrong, denial, not knowing where to go for help, stigma, positive experience of symptoms, symptoms (especially paranoia) that may prevent disclosure of illness, the tendency of patients to feel that they are not really ill and failure by health professionals to diagnose and treat psychosis appropriately.

In order to achieve a reduction in the DUP by decreasing time to diagnosis, some services have committed themselves to an important effort in outreach, including public advertisement and education [11,13,17,18]. Thus, improving the 'pathway to care' for patients with psychosis is a key factor in improving the prognosis of patients with psychosis.

The stress–vulnerability model

The stress–vulnerability model of psychosis was first proposed by Zubin and Spring. It suggests that although a specific vulnerability to psychosis may exist, it is a combination of stressors that precipitates the illness [19].

Thus, genetic factors, intrauterine factors and head injuries cause certain individuals to have an increased vulnerability to psychosis. The actual onset of psychosis occurs when these vulnerable people are exposed to various stressors.

The stress–vulnerability model has become a cornerstone of the design of the interventions used in all EI services, especially the psychoeducation programs. They lead to the development of strategies for identifying early signs of relapse, and thus treating such relapses early and preventing their development. If the early signs of relapse are observed, the patient is encouraged by his care coordinator to reduce stress, and the dose of antipsychotic is temporarily increased until the danger is passed. This is how it is possible to prevent relapse early throughout the 3 years of the critical period.

Concept of the prodrome

The prodrome can be considered either the earliest form of a psychotic disorder, or a syndrome conferring increased vulnerability to psychosis (i.e., an 'at-risk mental state' or 'precursor state'). It has been recently pointed out that there is a lot of very diverse terminology applied to this state [20]. Hence, it is important that we define here what we mean by the prodrome of a psychotic illness. For us and the purposes of this article, the prodrome is the first stage in a series of stages in the development of a psychotic illness (according to the staging model of psychotic illness, first described by McGorry *et al.* [4]), in which symptoms are indeed variable and nonspecific, but in which on MRI scans, progressive loss of gray matter can be seen in the brain, as first demonstrated by Pantelis *et al.* [21] and later replicated by Koutsouleris *et al.* [22].

It is in the nature of this phase of the development of the illness that the clinical features of the prodrome (if present) are variable and nonspecific, and indeed that some persons demonstrating these symptoms may never move forward to developing the next stage of the illness, or indeed may never have been ill at all.

The difficulty in identifying patients in the prodrome of psychotic illness is illustrated by the following list of prodromal symptoms that are most commonly described in first-episode studies, in descending order of frequency [23]:

- Reduced concentration and attention
- Reduced drive and motivation and anergia
- Depressed mood
- Sleep disturbance
- Anxiety
- Social withdrawal
- Suspiciousness
- Deterioration in role functioning
- Irritability

These are not discrete diagnostic indicators for this phase as these symptoms are not specific to psychosis, and estimates of the duration of the prodrome vary from a mean of 2 years [23] up to 5 years [24,25].

The first stage

EI in the prodrome

The aim of EI at this stage of the illness should be to prevent the patient from developing the first psychotic episode at all [26–28], while at the same time avoiding the potential harm caused

by treatment to the developing brain. It is a combination of the difficulty of identifying patients who are in need of treatment with the difficulty in finding 'safe' treatments for this stage of the illness that continues to make treatment in the prodromal phase of psychotic illness both experimental and controversial. EI services (as set up by the UK Government) are not mandated to work with patients in this phase of the illness because of the still quasiexperimental nature of the work. However, some centers do carry out research programs in this first or prodromal phase of psychotic illness.

Given that it is necessary to identify clinically which patients are appropriate to treat, and that it is not present practice to attempt to use MRI to identify loss of gray matter (presumably caused by abnormal apoptosis) or abnormal changes in plasticity in the brain in the prodromal stage, then it becomes necessary to develop a clinical prospective framework by observing the onset of a psychotic illness and observing how the symptom pattern of psychosis changes with time. Hence the frequently quoted statement that "The prodromal phase can only be identified [clinically] retrospectively," and the need to develop the term at 'ultra-high-risk mental state', as used by McGorry *et al.* to describe patients within the prodromal stage of the illness who are very likely to develop full psychosis soon and therefore who may benefit from treatment [29]. They referred to this identifying of such patients in need of treatment as the 'close-in' strategy.

By clearly placing the development of the concept of 'ultra-high-risk mental state' and the 'close-in' strategy within the model of the prodromal stage of psychotic illness, we have attempted to resolve the "near Babylonian speech confusion" in the field referred to by Schultze-Lutter *et al.* [20].

Therefore, various symptom inventories have been created in an effort to identify the progression of prodromal symptoms and stratify patients who are at risk. These inventories examine symptom development.

In recent years, rating scales, such as the Comprehensive Assessment of At-Risk Mental States (CAARMS; developed by McGorry and Yung's team in Melbourne, Australia) [30], Structured Interview for Prodromal Syndromes (SIPS) and Scale of Prodromal Symptoms (SOPS; developed by McGlashan's team in Yale, CT, USA), have been developed for patients at ultra-high risk and hence aid the investigation into the point of conversion to full-blown psychosis [29,31]. McGorry *et al.* also introduced the term 'at ultra-high risk of developing psychosis' as a way of prospectively designating patients who appeared to be in the prodromal stage of psychosis [29]. Yung was able, by using the criteria developed for use with her CAARMS scale – including a strong family history of psychosis, attenuated signs of psychotic symptoms and brief limited intermittent psychotic symptoms (or blips) – to identify a group of patients of whom 40% were likely to become fully psychotic within 12 months [29].

German colleagues tend to divide the prodrome into phases. According to Wolbrock, the late initial prodromal state is characterized by more overt psychotic symptoms, such as ideas of reference and paranoid ideation [32]. This is in contrast to the early initial prodromal state, which involves more vague symptoms such as thought disturbances, along with a known family history of schizophrenia or peri-/pre-natal complications.

It is clear that the point at which conversion to full psychosis occurs is an artificial dividing line. In MRI studies, both Pantelis *et al.* [21] and Koutsouleris *et al.* [22] have shown that gray matter loss, and hence cell damage, occurs during the prodromal phase, and that it is possible to demonstrate the increase in loss of gray matter over the prodromal phase, from the early to the late prodrome.

Methods of managing the prodrome

Various studies have been carried out to identify interventions that might delay the onset of full-blown psychosis in patients in the late phase of the prodrome.

Our group recently carried out a meta-analysis of all the trials of treatment in the prodrome of schizophrenia [33,34]. The treatments studied are summarized in the **Table 1**. As is shown, the interventions considered are wide ranging – from pharmacological treatments such as antipsychotics or antidepressants to nonpharmacological methods such as cognitive–behavioral therapy (CBT). Of the studies listed above, two were excluded from the meta-analysis – Woods *et al.* [35] and Morrison *et al.* [36] – on the basis of there being a lack of an adequate control. With the exception of the studies using olanzapine [37,38], all the remaining studies reached statistical significance (i.e., $p < 0.05$) with respect to slowing down the conversion to acute psychosis. Even the olanzapine study "tended towards significance,"

Table 1. Interventions for the prodromal phase of schizophrenia.

Author (year)	Intervention	Control	Ref.
Ruhrmann *et al.* (2007)	Amisulpride	Needs-focused intervention	[69]
McGlashan *et al.* (2003, 2006)	Olanzapine	Placebo	[37,38]
Cornblatt *et al.* (2003, 2007, 2009)	Antidepressants	Second-generation antipsychotics	[70–72]
McGorry *et al.* (2002)	Risperidone + CBT	Needs-based Tx (antidepressants + psychotherapy, not antipsychotics)	[40]
Morrison *et al.* (2004)	CBT	Monitoring	[73]
Bechdolf *et al.* (2007)	CBT	Supportive counseling	[74]
Nordentoft *et al.* (2006)	Integrated care	Standard Copenhagen Care	[75]
Berger *et al.* (2007)	Omega-3 fatty acids	Placebo	[39]
Amminger *et al.* (2010)	Omega-3 fatty acids	Placebo	[41]
Woods *et al.* (2007)	Aripiprazole	No control	[35]
Morrison *et al.* (2002)	CBT	Nonpatient population	[36]

CBT: Cognitive–behavioral therapy; Tx: Treatment.

indicating that this drug may also have a role in the treatment of patients during the prodrome.

Outcomes for treating the prodrome

Clearly, the idea that intervention in the prodrome may improve the overall prognosis of patients with schizophrenia is exciting. However, there is still a lot of work to be done before the treatment of patients so early in their illness is likely to become accepted as routine practice. As discussed earlier, even the definition of the prodrome is not clear-cut. This makes it challenging not only to identify patients for treatment, but also to know at exactly what point interventions would be most beneficial. In addition, the modes of potential treatments are extremely varied, so more research is required to better define which type of intervention is best.

In considering possible treatments, it is important to weigh up the benefits of delaying psychosis against any harmful effects of the intervention. When it comes to pharmacological treatments, the ethics of giving drugs with considerable side effects to patients that may not necessarily go on to develop psychosis has already been questioned [39]. As part of our meta-analysis, we considered the side effects of the drugs used in the various studies [33,34]. We found that while low-dose risperidone (1–2 mg) showed few extrapyramidal side effects, full-dose olanzapine showed the considerable side effect of weight gain. Amisulpride was associated with hyperprolactinemia and aripiprazole with early akathisia.

Thus, even if pharmacological treatments are promising in terms of their effects of delaying psychosis, there are still issues surrounding their overall safety. It is interesting that McGorry *et al.* achieved significant results even using a lower dose of risperidone than is usually used to treat psychosis [40]. It is the opinion of the present authors that if pharmacological measures are to be used in the treatment of the prodrome, further research is required to work out the optimum dose of drug that is still effective, but has minimal side effects. The aim in developing alternative treatments for the prodrome (or for treating the 'ultra-high-risk mental state') is to identify new compounds that are neuroprotective and that can be used to influence the processes of apoptosis that occurs in the development of the adult brain [39]. Antidepressants and omega-3 fatty acids are only two of a number of such compounds presently under consideration. In particular, the recent study by Amminger *et al.* shows promise because omega-3 fatty acids appear both neuroprotective and safe; however, this study was only over 3 months, so a longer study would be appropriate [41]. In addition, further investigation into treatments such as CBT would be useful; indeed, one such study on CBT is at present ongoing. If, as current studies suggest, these interventions are of similar effectiveness to drug therapies, they may provide a safer alternative to pharmacological methods.

■ The second stage

The first psychotic episode

At this stage, the patient has developed full psychosis for the first time. The aim of treatment at this stage is to bring the psychotic episode to an end as soon as possible, and to return the patient to work or education, as well as to prevent relapse.

This is the aim of EI services as set up by the UK Government. The most controversial issue at present here is the evaluation of the long-term outcomes of such services.

Methods of managing first-episode psychosis

Service development

As a consequence of the basic concepts mentioned above, there is now a worldwide attempt to develop new services to deliver effective care to younger psychotic patients. EI in the UK was historically developed as an improvement in service provision, with the development of service guidelines first enunciated in the 'Initiative to Reduce the Impact of Schizophrenia (IRIS) Guidelines' [3], and then developed into the Early Psychosis Declaration published by Rethink [101], and then subsequently adopted by WHO [102]. This led to the development of the EI teams that implement this care, which are fully integrated teams including psychiatrists, nurses, social workers, psychologists and occupational therapists. All these professionals have skills that will be utilized in providing tailored treatment for each patient. A full assessment of needs, the development of comprehensive care plans for individual patients, including all necessary social interventions, the provision of services along the model of assertive case management and working in a youth-centered way is seen as key to good outcomes [42–44]. This also includes support for carers.

The aim of such teams is to treat all patients with a first episode of psychosis of any diagnostic category who present between the ages of 15 and 35 years, and to follow them for 3 years. Even though the provision of such services may be seen as justified by the data on DUP, it remains controversial, with some services now at risk of closure in this time of financial stringency, because of a controversy that will be referred to later in this article regarding long-term outcomes. Hence the need to enunciate clearly what the service consists of.

Although most of the evidence for EI is regarding schizophrenia, in first psychotic episodes, there is often diagnostic instability. Much recent work has suggested a number of different factors that explain such instability. These include "fluctuation of disease manifestation over time or presence of comorbid psychiatric illness in combination with rigid diagnostic criteria that are unable to capture the multiple psychopathologies of the functional psychoses that results in differential diagnoses and therefore diagnostic instability" [45]. Such instability has been described as "an indictment of our current psychiatric diagnostic practice" [46]. The present authors would argue that the changes in the disease picture described by diagnostic instability argue for the need for the taking of a full longitudinal history of a psychotic illness, and for a disease classification based more on the concept of a spectrum of illness, with a particular illness developing over time as different genetic and epigenetic factors come into play. There is evidence that other forms of psychosis may have as long a DUP as schizophrenia (e.g., manic depressive psychosis [bipolar disorder]) [47,48]. Therefore, in EI services, the whole of the 'schizophrenia spectrum', including patients with affective symptoms, are treated, following the lead of the Early Psychosis Prevention and Intervention Centre (EPPIC) and the International Early Psychosis Association.

Pharmacotherapy & psychological treatment

In order to maximize benefits, improve compliance and reduce side effects, the use of low-dose medications (in the UK, we are now clear that this means the lowest effective dose of atypical antipsychotics) is advocated, in conjunction with psychological therapies.

Previously, it was considered good policy to use very low dosages of typical antipsychotic medications, such as haloperidol, in order to attempt to avoid extrapyramidal side effects. Today, however, it has been demonstrated that the therapeutic window for typical medications is too narrow for such a medication strategy to be routinely effective, so this policy has been superseded by the use of atypical antipsychotic medications [49–51]. The difficulty posed by the narrow therapeutic window of typical antipsychotics in first-episode psychosis needs to be borne in mind when interpreting the present National Institute for Health and Clinical Excellence (NICE) guidelines [52], which, unlike the previous edition, state that the physician can choose between the use of typical and atypical medications in first-episode psychosis.

The plan in UK services is to ensure that patients who have had a psychotic episode should usually continue on preventive antipsychotic medication for a period of 3 years, which is the period of time that the patients remain within the EI service. Further treatment will be decided according to the circumstances of the individual case, and on occasion, if a patient appears to be fully recovered, doctors and patients can jointly decide to stop medication before the 3 years are

over, provided that the patient remains under the observation of the service. We have reported on some patients who terminated medication early in this way in our service [53]. After a study of the literature, our own service has recommended that possible first-line medications should be risperidone 4–6 mg, quetiapine 600 mg or olanzapine 10–15 mg. We recommend, in line with the Maudsley guidelines [54], that first one then a second atypical antipsychotic should be administered, each trial being for 6 weeks. If neither of these two drugs are effective, then resistant positive symptoms should be treated by clozapine, at an appropriate dose. In resistant cases, it is also important to establish that cannabis is not being used by the patient concurrently. Aripiprazole is a new medication, and is now in clinical use, starting at a dose of 5 mg to avoid akathisia, which is common in the first few days, and then gradually increasing to 10 mg, up to a maximum of 30 mg.

Amisulpride is used in young patients aged 14 or 15 years, because the product licence of this drug permits its use at an age that is lower than that licensed for the other antipsychotics [49–51].

Regarding patients with a mood component to their illness, patients with mania are treated with olanzapine or quetiapine, as well as a mood stabilizer, often semi-sodium valproate; however, valproate should not be prescribed to pregnant women because of the risk of teratogenesis. Indeed, valproate should not be used in women of childbearing age unless there is concurrent use of very effective contraception. On balance, atypical antipsychotics are considered the best mood stabilizers in this category of patient. Furthermore, since patients treated in EI services often have a mood component, and hence may also suffer from depression, antidepressants may well need to be used – preferably selective serotonin-reupake inhibitors – but always keeping in mind the cautions related to the use of antidepressants in patients suffering from bipolar disorder. New indications for the use of atypical antipsychotics in treating depression and bipolar disorder provide useful additions to our armamentarium.

Psychological interventions, including CBT and family interventions, are treatments that can be used to reduce stress, in combination with appropriate medication, in order to adequately intervene in both elements of the stress–vulnerability model.

There is good evidence that CBT can reduce the distress caused by psychotic symptoms such as hallucinations and delusions, but this is mostly from trials of the intervention with chronic patients. More evidence is now being produced regarding the use of CBT in first psychotic episodes [55,56]. Much CBT work in EI is in fact treating depression and anxiety symptoms that occur as the patient recovers from psychosis. Approximately 30% of patients with psychosis suffer postpsychotic depression in the recovery stage of the illness. Some may become so distressed that they may commit suicide. The patients who are most at risk are the 'integrators', who are most likely to be severely affected by low self-esteem and a deep sense of personal loss as a result of their illness. Patients who 'seal over' their psychotic experience are unlikely to suffer from depression.

Another form of CBT is 'compliance therapy', which is a motivational interviewing technique used to enable patients to adhere to their medication [57].

Family interventions are now well established as a means of reducing high expressed emotion, which is a known cause of psychotic relapse. However, in first-episode psychosis, it is often the case that high expressed emotion has not had time to become established, but the family is severely distressed. The intervention therefore needs to be modified in order to be appropriate for the needs of the families who are being helped [58]. Group interventions for families, patients and psychoeducation groups are also known to be effective in assisting patients and their families [59].

All patients and their families are educated to identify early signs of relapse, and these patients will then work out a relapse prevention plan with their care coordinator.

Outcomes of EI in first-onset psychosis

It is becoming clear from reported results that there are marked advantages in developing dedicated teams to deal with early psychosis, and that this treatment is better than treatment as usual in ordinary community mental health teams **(Table 2)**.

Our own group reported on 62 patients who had been treated for 3 years in an *ad hoc*, assertive treatment team for patients who had suffered a first psychotic episode, and compared their outcomes with 62 patients who had been followed up after a first psychotic episode in a standard community mental health team [53]. All patients had suffered a first or early psychotic

Table 2. Summary of some studies comparing outcomes for early intervention teams with community mental health teams in first-episode psychosis.

Project	Study (year)	Outcomes for EI services	Ref.
Swedish Parachute project	Cullberg *et al.* (2002)	Fewer inpatient hospital days Less neuroleptic medication when combined with intensive psychosocial treatment and support High patient satisfaction	[76]
LEO study	Craig *et al.* (2004) Garety *et al.* (2006)	Fewer readmissions Less likely to drop out of the study than those receiving CMHT care Less likely to relapse; however, when adjustment was made for sex, previous psychotic episode and ethnicity, this difference ceased to be significant Better social and vocational functioning High patient satisfaction Higher quality of life Better medication adherence	[77,78]
OPUS study	Nordentoft *et al.* (2002, 2006) Petersen *et al.* (2005) Jeppesen *et al.* (2005) Thorup *et al.* (2005, 2010) Bertelsen *et al.* (2008, 2009)	Fewer psychotic and negative symptoms Less comorbid substance abuse Better adherence to treatment More satisfaction with treatment Reduced family burden of illness	[60–62,79–84]
Danish National Schizophrenia Study	Rosenbaum *et al.* (2005, 2006)	Nonsignificant tendency towards a greater improvement in social functioning. If allowance was made for the confounding effects of drug and alcohol abuse, then significance was reached in some measures	[85,86]

CMHT: Community mental health team; EI: Early intervention.

episode. The main differences between the two teams was that the *ad hoc* team was assertive in its approach, offered more structured psychoeducation, relapse prevention and psychosocial interventions and had a policy of using atypical antipsychotics at the lowest effective dose.

There were many differences in outcome measures at the end of 3 years between the two groups. The EI patients were more likely to be:

- Taking medications at the end of 3 years
- Compliant with medication
- Prescribed atypical medication
- Returned to work or education
- Living with families

The EI patients were less likely to:

- Suffer depression requiring antidepressants
- Make suicide attempts
- Suffer relapse and rehospitalization
- Have involuntary admission to hospital
- Be using illicit drugs

The EI patients had systematic relapse prevention plans based on the identification of early warning signs of relapse, and they and their families received more psychoeducation. These facts suggest that the EI patients are, at the end of 3 years, better able to manage their illness/vulnerability on their own than the community mental health team patients. Hence, it appears that in our service, the better outcomes after 3 years were in great part due to the assertive treatment offered by the care coordinators, even despite the long DUP of many patients in our study.

All the above changes were statistically significant except for the total improvement in employment status and education status, which approached significance, however. These results suggest that an *ad hoc* EI team is more effective than standard community mental health teams in treating psychotic illness.

Recently, there have been further reports from the OPUS study. This involved a 2-year assertive intervention from an *ad hoc* team, and now the team has reported on the 5-year follow-up once the assertive interventions had ceased at the end of the second year. The intensive EI program improved clinical outcomes after 2 years, but the effects, as measured by a reduction in positive and negative symptoms, did not appear to be sustained at 5-year follow-up [60].

However, the number of patients living in supported housing and number of days in hospital at 5-year follow-up appeared to favor the assertive EI program [61]. It has also been reported that the rates of recovery (defined as no psychotic or negative symptoms, living independently, Global Assessment of Functioning >59, working or studying) and institutionalization at 2 years and 5 years during this study were the same, being 18% recovery after 5 years, and 13% were institutionalized either at hospital or supported housing after 5 years. Thus, it appears that in this group, the illness did not deteriorate progressively, since no changes in the rates were seen from 2 to 5 years [60]. The OPUS study has also reported that patients who were offered inpatient rehabilitation and supportive psychotherapy used more hospital bed-days and spent more time in sheltered accommodation than those who were given assertive treatment in the community. Although this was a small sample, it did suggest that patients who received assertive treatment for 2 years had a better quality of life over 5 years [62].

Subsequently, the LEO study from London, UK, reported on the 5-year outcomes of their study. They showed a loss of any improvement in admission rates at the end of 5 years, since both the group who had EI and the group that did not appeared to have the same admission rates and the same number of bed-days by 5 years. It should be noted, however, that at least in this study there had clearly been a fall in the number of admissions in both groups over the years [63].

Our own team have similarly analyzed our data for admission rates and bed-days over 6 years of treatment. We found similar results to the LEO service, but were able to show that a group of patients who had experienced repeated relapses in the first 3 years, and therefore had received particularly intense assertive treatment had reduced relapses in the subsequent 3 years, thus illustrating the critical period hypothesis [64].

These results have led to reappraisal of the design of services for schizophrenia [65]. It appears clear that the improvement of outcomes provided by EI teams only continues so long as the assertive engagement with the patients continues.

This was demonstrated by Zaytseva *et al.* [66,67]. They reported on the 5-year outcomes of treatment on EI principles in Moscow. They found that the integrated program achieved a significant decrease in the number of hospital admissions and duration of hospital stays, while it maintained a higher level of social functioning in patients, as demonstrated by maintenance of education or employment, reduction of family burden and better social support networks. In the Zaytseva study, the assertive approach continued to be followed for the whole of the 5-year period.

In general, it appears that assertive EI during the critical period offers better results than treatment as usual, so long as the assertive intervention is maintained [68].

Conclusion & future perspective

Planning future research on how to optimize treatment and hence outcomes in treating psychotic illnesses/schizophrenia benefits from the conceptual model of staging in schizophrenia. This model, first proposed by McGorry, has been discussed by our group [4]. This model is underlain by the neuroimaging evidence of Pantelis and others [5–7]. Furthermore, different stages of the illness appear to be mirrored in different patterns of changes in structures including the hippocampus and the amygdala [8], as well as changes in pituitary volume [9,10].

The consequence of this model is that both treatments and targets for patient outcomes will be different in different stages of the illness. For psychosis, there are three stages: the prodrome; the first episode and the critical period; and the phase of recovery.

Regarding the prodrome or at-risk-of-psychosis phase, the effectiveness of attempts to prevent the development of psychotic illness by intervening in the prodrome remains a goal to be achieved rather than a proven treatment policy. The aim of further research will be to identify agents that are neuroprotective and that modulate in a protective manner the process of apoptosis and the changes in plasticity while developing the adult brain. Various compounds are presently under consideration [39]. Regarding the use of antipsychotics in this phase, current trials are relatively small, and we await the development of techniques for delivering safer and more effective treatments. Presently, CBT, the use of antidepressants and omega-3 fatty acids appear promising.

Regarding the first-episode phase, it appears that treating first psychotic episodes over the first 3 years of the illness in the community with assertive delivery of treatment, including pharmaceutical, psychological and social interventions, does improve the outcome of treatment

for many patients at present. It appears, however, that the improved outcomes can only be sustained for all patients while assertive treatment is continued. Further improvements will occur if further developments in antipsychotic therapy improve cognition, thus countering the cognitive deficits that develop early in psychotic illness. There are new antipsychotic agents that show some promise in improving cognition, and trials of the use of cognitive enhancers as an adjuvant to antipsychotic treatment are ongoing. There is the possibility of the development of new antipsychotics that will work on the glutamate/GABA pathways of the brain rather than dopamine pathways. However, such approaches require further development.

Regarding the final or recovery phase of schizophrenia, it is clear that both optimal antipsychotic therapy and continued psychosocial intervention delivered assertively are essential to maintain the recovery that has been achieved and to achieve optimal social inclusion.

A further point needs to be made from the point of view of general practice. It is clear that the point at which conversion to full psychosis occurs is an artificial dividing line, and both Pantelis *et al.* [21] and Koutsouleris *et al.* [22] have shown that gray matter loss, and hence cell damage, occurs during the prodromal phase. Hence, if a general practitioner is presented with a patient who may be psychotic, but the symptoms are such that the general practitioner is not completely convinced that the patient is fully psychotic, they should still refer the patient urgently for evaluation, as loss of time while symptoms become 'classical' will only lead to an increased DUP and further detriment to the patient. It will then be for the specialists to decide how each individual patient is best treated.

The possibility of future developments in EI in psychosis continues to be exciting, because of the possibility of vanquishing a very debilitating disease; however, different approaches and much independent but parallel work has led to the conceptual confusion mentioned by Schultze-Lutter *et al.* [20]. In the present authors' attempt to disentangle this semantic confusion, we have, perhaps for the first time explicitly, come up with a definition of the prodrome as a stage that is defined by MRI findings and 'ultra-high risk' as a clinical syndrome within that stage. This may in future lead to an approach wherein patients might be clinically identified as 'ultra-high risk', and then MRI studies might be carried out in order to help decide which patients to treat with whatever best treatment option is available.

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