The promise of early intervention

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Abstract

The focus of this review is the research and clinical work in early psychosis and early intervention which over the past 10–15 years has had a tremendous impact on the field of schizophrenia. Unparalleled progress has been made in programme and service development with a wide range of reported research results, outcome studies, treatment approaches and new initiatives. Traditional areas are being explored in the first episode that can add to our knowledge of schizophrenia. New areas that have a specific relevance for early intervention such as the duration of untreated psychosis and pathways to care are being widely studied. Despite the criticism of the lack of randomized controlled trials, there is a wealth of positive outcome from both effectiveness studies and limited controlled trials. However, there are still many unanswered issues which are in developing stages or which require further investigation.

Key words: early intervention, first episode, outcome, psychosis, schizophrenia.

INTRODUCTION

Interest, which began almost 20 years ago, in the ‘first episode of psychosis’ and ‘early intervention’ has become a rapidly expanding field that is now part of the mainstream of psychiatry and mental health. A few landmarks marked the beginning of this movement that encompasses research, education, treatment and advocacy. Evidence of the impact of a long duration of untreated psychosis (DUP), the benefits of intervening early for subsequent recovery, the notion of a critical period and of course the advent of the second generation antipsychotics (SGAs) all contributed to, in the 1990s, increased optimism about the possibility of improved outcomes for individuals with schizophrenia and other psychoses.

The origins of the hypothesis that untreated psychosis is neurotoxic began with Wyatt’s classical paper on neuroleptics and the natural course of schizophrenia.1 This notion that untreated psychosis may be toxic to the brain was supported by studies from Hillside Hospital, Long Island, USA where it was observed that the longer the psychosis was untreated the poorer the outcome and that with the increasing number of relapses recovery for each subsequent relapse seemed to take longer and the recovery was less complete.2–4

Second, the early phase of psychosis was deemed to be a ‘critical period’5 because it had been observed that deterioration occurred in the pre-psychotic period and during early psychosis but that this often stabilized after two to 5 years.6 Birchwood suggested that intervention targeted in the early years after onset, particularly the first 3 years, may have a disproportionate impact relative to later interventions with major implications for secondary prevention of impairments and disabilities.5 The possible benefits of early intervention might include reduced morbidity, more rapid recovery, better prognosis, preservation of social skills, family and social supports and decreased need for hospitalization.

Third, the work of the Australian group at the University of Melbourne led by Patrick McGorry has had an unparalleled impact on the field.7 Their concerns with the quality of routine traditional clinical care for schizophrenia, the delay for those suffering to receive such treatment8,9 and that, although many treatments both pharmacological and psychosocial had been developed that could potentially impact schizophrenia, most people did not have access to
them,\textsuperscript{10} led to the development of The Early Psychosis Prevention and Intervention Clinic (EPPIC), one of the most comprehensive innovative programmes dedicated to the treatment of those experiencing a first episode of psychosis (FEP).

In reality, this was not a demand for ‘early intervention’ but in fact ‘on time intervention’ as these young people already could be diagnosed with schizophrenia or other psychotic disorders. The first stage of this ‘early intervention’ movement was to offer a wide range of treatments, as soon as possible, that were appropriate to the stage of the illness and the age of the sufferers and addressed psychosis in all its forms as early and as intensely as possible. Today, this ‘early intervention’ movement has spread worldwide. Programmes and services are being developed in every continent. It has its own international organization, The International Early Psychosis Association, with over 2500 members representing more than 60 countries, and most recently the launch of Early Intervention in Psychiatry, a journal representing an interest in early intervention in psychiatry beyond psychosis. Furthermore, work in early intervention and early psychosis has grown to include those who are at clinical high risk of developing a psychotic illness, that is, those who are presenting with attenuated psychotic symptoms who could potentially be prodromal for psychosis.

In response to debates about the rationale and feasibility of these new shifts\textsuperscript{11,12} the question whether early intervention has lived up to its promise is being asked. In an attempt to answer this question, this paper will review the current state of the field of FE psychosis. Searches for relevant literature were conducted using the following key words – first episode psychosis, early intervention and early psychosis. General selection criteria included studies or reviews published between 1990 and 2007 that involved patient populations presenting with an FE of non-affective psychosis, although several of the studies did include affective psychosis, and studies in which the subjects had received a diagnosis of a psychotic disorder according to DSM, International Classification of Disease or Research Diagnostic Criteria. Studies that focused on the ‘prodrome’, clinical high risk or ultra high risk were not included. This paper is not intended to be a systematic review but rather a comprehensive view of the current state of the area. Readers are directed to comprehensive and systematic reviews where they exist.

**WHAT IS EARLY INTERVENTION?**

In comparison with ‘standard care’, early intervention for an FEP aims to identify as soon as possible people who are already psychotic but who have not yet received adequate treatment and then to offer phase-specific treatments with the intention of promoting recovery from an FEP. Specialized treatment can occur in programmes already offering ‘standard care’, or may be obtained through specialized early intervention teams. Early intervention services typically offer a range of interventions enriched specifically to address issues relevant to this early phase of the illness and this population. Delivery of care can be flexible and is often based on a case management programme. These have been described as ‘multi-element’ programmes\textsuperscript{13} and offer a comprehensive array of specialized in- and outpatient services emphasizing both symptomatic and functional recovery. Many of the problems for young individuals experiencing psychosis, e.g. substance abuse, suicidality and engagement in the health system, are addressed through a range of targeted therapeutic approaches.

A large number of early psychosis clinical and research programmes have been established worldwide\textsuperscript{14,15} and an excellent guide to developing such services has been published.\textsuperscript{16} In the last decade, these newly established clinical and research programmes have developed into large scale networks of programmes with interest groups, diverse service initiatives and national and international conferences throughout, for example, Australia, Canada, the UK, Switzerland, the Netherlands, Scandinavia, Germany, Singapore and Hong Kong. There is an ever-increasing literature on programme development and resources are readily available for initiatives. Although there are no clear ‘standards of care’ yet developed,\textsuperscript{16} there are published clinical guidelines for FEP.\textsuperscript{17}

**STUDIES OF THE FIRST EPISODE OF PSYCHOSIS**

There is a wide range of studies examining FEP. Some are cross-sectional and essentially are descriptive of this population; others are longitudinal and report on changes over time. Some of these are real world effectiveness studies. Some studies evaluate multi-element interventions, which typically include community outreach, early detection efforts, in- and outpatient treatment, individual, group, and family treatment, case management plus pharmacological treatment or they evaluate specific single-element psychosocial interventions (e.g. cognitive-behaviour therapy (CBT)) or a medication approach. Treatment outcome studies tend to be uncontrolled, a few use a historical control group and randomized clinical trials are rare.
Improving our understanding of schizophrenia

There are many FE studies, by examining certain constructs at the beginning of the illness, which adds to our understanding of schizophrenia. It is beyond the scope of this paper to review all of them in any detail but typically include studies on cognition, functioning, symptoms, diagnosis, imaging, etc.

We have learned that at presentation for treatment FE patients often show compromised cognitive functioning, particularly in the domains of verbal learning and memory, psychomotor speed and attention, deficits that are often comparable to those with a more chronic course of illness. Longitudinal studies show high stability in cognition over the first and later years. Although small significant improvements have been observed, these tend not to be clinically significant and possibly due to practice effects. This supports accumulating evidence that a decline in cognitive functioning occurs well in advance of clinical symptoms.

Additionally, these young FE subjects have impaired social functioning and although there is an improvement over time, they continue to function more poorly than their age matched non-psychiatric peers. Functional recovery does not match symptomatic recovery. Both quality of life and functional outcome are addressed in more detail in a recent comprehensive review. Likewise premorbid functioning assessed at the FE is comparable to those with a more chronic course of illness and is associated with poor outcome up to 2 years, e.g. negative symptoms, overall clinical functioning and social functioning. Furthermore, specific patterns of premorbid functioning have been observed such that those having a deteriorating course over the developmental periods such as childhood, early and late adolescence had poorer outcome. A few recent studies have suggested a role for social cognition in the cognition-social functioning relationship. Deficits in social cognition are also observed longitudinally in this young group of patients.

A systematic review and meta-analysis of imaging studies suggests reduction in brain volume for FE patients but samples tend to be small, and there is a lack of replication with few robustly significant findings. Although the review confirms that grey matter deficits are present at the FE, it is still not known whether changes in grey matter volume at the FE are associated with disease progression itself or with the many correlates of disease such as antipsychotics, drugs abuse and alcoholism. In a second comprehensive review, Pantelis presents clear evidence that the onset of psychosis is a time of active brain changes with dynamic brain changes occurring in the early stages of a psychotic illness, possibly around the time of transition to full-blown psychosis. However, it remains to be determined whether schizophrenia is a neurodegenerative process that begins at about the time of symptom onset and manifests as progressive volumetric loss thereafter or whether it is better characterized as a neurodevelopmental process that results in abnormal brain volume beginning at an early age or whether there are several processes occurring at different stages of neurodevelopment and in the phases of early illness.

Duration of untreated psychosis

The period of duration of untreated psychosis (DUP) is an important variable; as unlike other prognostic factors, it has the potential to be reduced through changes in health service delivery. Several studies support an association between long DUP and a range of poor functional and symptomatic outcome whereas others do not. The inconsistency in findings may be related to variations in sample size and selection, type of treatment provided, inpatient versus outpatient samples, those who refuse to engage often have longer DUPs, differences in measurement of DUP and outcome, and length of follow-up. Most longitudinal studies have followed samples for 12 months or less and some for 2 years. At 4 years, long DUP remained associated with poorer functional and symptomatic outcome and even after 8 years, shorter DUP was significantly associated with less severe positive symptoms and improved social functioning and quality of life. However, associations are small to moderate often accounting for less than 15% of the variance in outcome factors. These results seem reasonably consistent in different parts of the world although there are some cultural variations.

The association of a long DUP with poor outcome occurs independently of other variables such as premorbid functioning, suggesting that DUP has an independent role in determining symptomatic outcome and is not a proxy for other factors. The absence of significant associations between DUP and several other correlates of outcome such as gender, substance use and cognitive functioning is relatively consistent. There is little support for associations between DUP and negative symptoms and a recent study even suggests that DUP may even be specifically associated with time to response to treatment for delusions. Recent imaging studies suggest an association...
between long DUP and reductions in temporal gray matter,⁶³ and with smaller hippocampal volumes.⁶⁴ Of course, this could be an abnormality observed in those who may have a more insidious course of illness with a later presentation and fit with other studies that do not support an association between brain changes and a long DUP.⁶⁵

Evidence of modest associations between DUP and a broad range of outcomes is further supported by two recent meta-analyses,⁶⁶,⁶⁷ and seems to be consistent when methodological shortcomings are taken into consideration.⁶⁸ Regardless, it must be underscored that this area of research is correlational in nature and that definitive evidence of a causal relationship between DUP and outcome can only come from a randomized controlled trial, a design that would certainly be challenging.⁶⁸ To date, the most noteworthy attempt at modification is the TIPS project.

The TIPS project (Early Identification and Treatment of Psychosis)

The TIPS project is a four-site prospective clinical trial in Norway and Denmark designed to investigate the effect of timing of treatment in FEP. The purpose was to determine whether it was possible to reduce the DUP for FE patients in a defined healthcare area through the introduction of an early detection programme compared with parallel healthcare areas without the early detection programme. This study has been described in detail elsewhere.⁶⁹,⁷⁰ This is a non-randomized quasi-experimental study of early detection and specialized treatment versus treatment from a specialized team alone for people presenting with an FEP. It most likely includes close to all patients with an FEP in its catchment areas. DUP was significantly shorter for those in the early detection area compared with those without (5 weeks vs. 16 weeks). At baseline, patients from the early detection area, compared with those who did not have early detection, had improved scores on positive and negative symptoms and the General Assessment of Functioning (GAF)⁷¹ but did not differ in either objective or subjective quality of life.⁷² This may be because deterioration in social functioning precedes overt symptom formation – a finding reported elsewhere.⁷³ One notable finding was that the rate of severe suicidality (plans or attempts) was significantly lower in subjects from the communities with the early detection programme relative to those from areas without.⁷⁴ At 1-year follow-up, the two groups did not differ in positive and general symptoms, functional outcome, time to remission and the course of psychosis over the first year, the only difference was that those in the early detection group had lower levels of negative symptoms.⁷⁵

This is the first study to investigate at least at a quasi-experimental level the impact of DUP. This study has demonstrated that through early detection, one can bring subjects in with lower levels of symptoms; however, there did not seem to be a later advantage for the early detection for positive symptoms and outcome. In other studies, average DUPs tend to be around 53 weeks with median or transformed DUPs of approximately 26 weeks. In this study, the mean DUP in the early detection group was 5 weeks, which is extremely short, and even the control group had an average DUP of 16 weeks that may have had an impact on later outcome. Furthermore, those who refused had a significantly higher DUP than those who consented (10 weeks vs. 32 weeks), which may have impacted outcome.⁷⁶ It is of course possible that interventions designed to reduce DUP improve outcome through increased detection of cases that have a more favourable outcome.

Pathways to care

An understanding of pathways to care, that is awareness of the number of attempts individuals make to obtain help and who is most likely to ensure appropriate treatment is obtained, is a prerequisite for early detection and the effective treatment of FEP.⁶⁹,⁷⁷,⁷⁸ A recent systematic review identifying 15 studies with six different ways to measure pathways to care revealed that there is no measure that has been devised on a well-developed theoretical or conceptual framework and had its psychometric properties established. Regardless, certain common themes emerged: pathways are highly varied and diverse; health professionals are usually first contact; irrespective of setting there is considerable delay in treatment; some delay occurs because of failure of carers and primary care in recognizing incipient psychosis; and there is a delay in initiating treatment for psychosis in those who are already engaged in mental health services.⁷⁹,⁸⁰ Change in premorbid functioning, suicidal ideation and positive psychotic symptoms all aid help-seeking.⁷⁷,⁷⁸

TREATMENT OUTCOME

Randomized controlled trials (RCTs)

The OPUS trial

OPUS is the first large (n = 547) randomized clinical trial of integrated treatment versus standard
treatment for people with an FEP. Treatment was for a minimum of 2 years with follow-ups at one, two and 5 years. The integrated treatment was 2 years of assertive community treatment that included family psychoeducation and social skills training. Those in the integrated group had better adherence to treatment. At 2 years, attrition from the integrated treatment was 25% compared with 40% of those in the control treatment. Dropouts had poorer prognosis. Integrated treatment at both 1- and 2-year follow-up reduced psychotic and negative symptoms more than standard treatment and although the effect was small, it was of clinical importance (at 2 years mean change for positive symptoms was –0.32 and for negative symptoms –0.45). More specifically, the integrated treatment patients demonstrated significantly fewer negative symptoms in all global scores of the Scale for Assessment of Negative Symptoms (SANS) and reduced positive symptoms was mainly accounted for by a reduction in hallucinations.

Outcome was determined by creating a measure of ‘any poor outcome’, e.g. symptoms, substance use or GAF rating, poor accommodation and not working or out of school. A global score was thus calculated, based on the assumption that poor outcome in any of these variables was considered disabling. At 1 year, the integrated treatment group had advantages in all areas of outcome. Only 11% in the whole sample attempted suicide in the first year with a significant improvement in hopelessness for the treatment group. Further advantages for the integrated treatment group were a perceived reduction in family burden. Limitations of the study included the absence of blind raters and differential attrition.

The Lambeth Early Onset (LEO) trial

The LEO trial was an RCT of 144 young people aged 16–40 years to determine the effectiveness of a service for early psychosis with evidence-based biopsychosocial intervention compared with standard care delivered by community mental health teams. Primary outcomes were relapse and remission. Compared with standard care, those in the specialized care group were less likely to relapse, were readmitted fewer times and were less likely to drop out of the study. When rates were adjusted for sex, previous psychotic episode and ethnicity, the difference in relapse was no longer significant and only readmissions (beta 0.39, 0.10−0.68) and dropout rates remained significant beta (0.28, 012–0.73). There were improvements over time for both groups but there was only an effect of the intervention for negative symptoms, treatment adherence, self-rated quality of life and service user satisfaction. Further analysis demonstrated that other benefits of this specialist service were in regaining or establishing social relationships, time spent in vocational activity and medication adherence based on case notes. The sample may have been underpowered. Furthermore, the study relied on hospital records for assessment of relapse.

Uncontrolled or historical controlled trials

Although many FE programmes are beginning to report outcome data, there are a few well-described and well-established FE programmes that have reported a wide range of outcomes. The Parachute Project in Sweden in comparison with a historical control group suggests that the FE patients in their programme have less hospital days, improved symptoms and functional outcome and reduced costs to health care. A quasi-experimental phase-specific approach in Australia has shown superior outcome for positive and negative symptoms and social functioning, reduction in self-harm and aggressive behaviour, and fewer hospitalizations.

Outcome results from these programmes suggest that after 1 year there is a significant improvement in positive and negative symptoms and in functional outcome. However, overall community functioning is influenced by a combination of other factors such as premorbid functioning, residual symptoms and cognition. Improved depression and insight was also reported.

In these outcome studies, there is minimal impact on occupational functioning. Because external factors may impact employment such as availability of employment and stigma, early intervention is unlikely to bring about improvement in occupational outcome. It may be necessary to begin specific interventions such as supported employment early in the illness for specific
subgroups of FE patients. Rinaldi et al. demonstrated that an individual placement and support model was effective with FE clients. In this study, over a 12-month period, unemployment dropped from 55% to 5% and competitive employment rose from 10% to 41%.

A meta-analysis of the schizophrenia literature demonstrated that only 40.2% of patients improved after follow-up averaging 5.6 years. However, a recent meta-analysis examined 37 studies that represented 4100 FE subjects with a mean follow-up of 35 (±6) months. Good outcomes were reported in 42.2% of the cases and poor outcomes in 27.1% of cases, suggesting that good and intermediate outcomes were more common than previous studies have reported. Predictors of good outcome included a combination of pharmacotherapy and psychosocial treatment. The authors rightly point out the limitations in conducting a meta-analysis with such a relatively small and recent body of literature. This meta-analysis draws out the inconsistencies in the literature and emphasizes the importance of having consistent definitions and measures that will permit the future collaboration of smaller studies.

Family work

Families play an important role in recovery for young people experiencing an FEP. Equally family work may be especially important during the FE as families tend to experience the greatest amount of distress during these early years. To design an optimal family programme within an FE service, we need to be sensitive to the phase of the illness. In a study with 187 families from the Calgary Early Psychosis Program, a longitudinal cohort design was used to test the real-life acceptability and effectiveness of a family intervention embedded within a multidisciplinary treatment approach. Assessments were conducted over a 3-year period. Over time, families demonstrated improved ratings on measures of psychological well-being and experience of caregiving. The most significant predictor of poor psychological well-being was the family’s appraisal of the impact of the illness on themselves and not the severity of symptoms or impaired functioning of the patient. Seventy per cent of families remained involved throughout the 3 years and the maximum average number of sessions in any 1 year was seven suggesting that it is not the number of sessions that are important but rather that they are spread over a longer period. This family intervention embedded within a treatment programme proved to be highly acceptable and effective. The intervention was based on a recovery model and offers suggestions for goals and both individual family and family group interventions at different stages of the recovery process after an FE psychosis. Other work is appearing in the literature describing family approaches that may be useful in setting up FE programmes and services.

The one RCT family study by Linszen’s group in the Netherlands was a phase specific intervention. Ninety-eight patients, aged 15–26 years were randomly assigned to an individual orientated psychosocial intervention or an identical programme plus a behavioural family intervention. The treatment was a 3-month inpatient stay plus a 12-month follow-up outpatient intervention. Seventy-three completed the follow-up. Overall, relapse rates during the 12 month outpatient intervention phase were low (16%). However, once patients were referred to other agencies after the end of the treatment, the relapse rate could not be retained with a total of 64% relapsing during the follow-up period. Fifty-two per cent had one or more psychotic relapses, 25% developed chronic positive symptoms and 23% did not have another psychotic episode. Additionally, in this follow-up, it was observed that as a group these young people had poor skills for independent living and working. However, for the younger patients, parents certainly appeared to play a significant role in supporting their offspring and those who had received the family intervention spent fewer months in institutions. The intervention condition had no impact on relapse rate or level of family expressed emotion between the groups at follow-up.

CBT

Despite advocating CBT as a valuable treatment in FEP, the only RCT of CBT with an FE sample is the Study of Cognitive Realignment Therapy in Early Schizophrenia (SoCRATES) trial in the UK, a multisite methodologically rigorous trial with a large representative sample (n = 315; 83% FE). This trial compared a 5-week treatment package of CBT plus routine care (RC), to supportive therapy (ST) plus RC and to RC alone during the acute phase of a psychotic illness. At 70 days, there were trends towards faster improvement of positive symptoms in the CBT group compared with ST and RC. By 18 months, both the CBT and ST groups demonstrated significant advantages over RC but there were no significant differences between the impact of CBT and ST on symptoms, relapse, or rehospitalization. The one exception was that auditory hallucinations responded better to CBT relative to SC. Importantly, there are significant limitations to this study.
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study. The CBT was delivered over an insufficient period to make an impact (5 weeks). A high recovery rate in the acute phase under RC is to be expected because we know that up to 85% of patients recover from an FE under a standardized drug regime. In this context, there is little room for CBT to impact positive symptoms at the acute phase. Unfortunately, this is disappointing as SoCRATES was clearly a step in the right direction.

Jackson et al., in a sample of 80 FE patients, used Cognitively Oriented Psychotherapy for Early Psychosis (COPE), aimed at promoting adjustment to psychosis. At 1-year follow-up, those who received COPE compared with a historical control and those who had refused to participate in groups differed only on a measure of integration versus sealing-over. In a subsequent non-randomized, COPE intervention study with 91 FE subjects, there were no differences between the groups on all outcome measures. Study limitations included alternate subject assignment and poor measurement of non-compliance to medication.

Pharmacological treatments

Studies with FE populations that examine the effectiveness and side effects of medications offer the unique opportunity to examine the impact of medications often without the confounding effects of prior medication use. Interested readers are directed to a recent comprehensive review by Robinson et al. that focuses upon studies of pharmacological treatment of the initial episode. Studies that consider maintenance treatment issues, recovery, and side effects are also reviewed. Although response rates for the initial episode are high with both first generation antipsychotics and SGAs, data addressing those who are less responsive to treatment are limited. Unfortunately, the metabolic side effects associated with SGAs, in particular, are of great concern for these young patients particularly as there are risks for longer-term medical problems. Although data are reported that supports maintenance treatment to prevent relapse, the optimal duration of such maintenance treatment and how that fits with potential long-term side effects of antipsychotics is unclear.

Little is known about any differences in effectiveness of the SGAs for FE patients. A recent 52-week RCT comparing the effectiveness of olanzapine, risperidone and quetiapine (mean doses were 11.7 mg day, 2.4 mg day and 506 mg day, respectively) in 400 FE subjects reported that these three medications had similar all-cause treatment discontinuation rates and were comparable in their effects on general psychopathology. In this study, ongoing substance abuse and depression and treatment response failure were identified as predictors of medication non-adherence. Being African American, having higher baseline performance on cognitive tests and reaching remission status also predicted non-adherence.

The long-term phase of an FE risperidone vs. haloperidol comparison trial demonstrated no significant difference between groups in symptom improvement although there was a significant difference in relapse with 42% of the risperidone treated group compared with 55% of the haloperidol group relapsing. There was also significantly less risk for tardive dyskinesia in the risperidone group. In a large double-blind study comparing olanzapine to haloperidol, both drugs were associated with substantial and comparable baseline to endpoint reductions in symptom severity. Advantages for olanzapine were greater retention in the study and less treatment emergent Parkinsonism and akathisia although there was more weight gain. It remains to be seen if SGAs as a class improve outcome in FE subjects.

Relapse

One of the first groups to study recovery during the early phase of schizophrenia was the Hillside group. This longitudinal study demonstrated that 5 years after initial recovery the cumulative first relapse rate was 81.9%, the second relapse rate was 78% and by 4 years after recovery from a second relapse the third relapse rate was 86.2%. Risk of relapse was increased by discontinuing medication. Furthermore, those with poor premorbid school adaptation and premorbid social withdrawal had an earlier relapse. After 5 years, only 47.2% achieved symptom remission and 25.5% had adequate social functioning. Only 13.7% of the patients actually met full recovery criteria for 2 years or longer. In the risperidone-haloperidol trial discussed above, although 70% of the sample had a reduction to mild or less on key remission symptoms on the Positive and Negative Syndrome Scale, only 23.6% were able to maintain this status for at least 6 months to meet remission criteria. However, it is unknown what treatments beyond pharmacotherapy they were receiving and the majority were not part of any organized FE programme. The meta-analysis described above reported 44.5% relapse over an average of 36 months.

However, improved rates of relapse in specialized FE programmes have been reported. The LEO study reported 30% relapsing at 18 months, in the
Calgary FE programme 29.5% at 2 years\textsuperscript{129} and in the FE programme in Hong Kong, after year one 21% relapsed, 33% relapsed by year two but 40% by year three.\textsuperscript{130}

**Suicide**

For those suffering from schizophrenia, the life time risk of suicide and parasuicide is high and the first year of psychosis has been reported as a particularly high risk period.\textsuperscript{5,131–136} However, within specialized FE programmes, lower rates are being reported. The OPUS trial reported rates of 11% for parasuicide over 1 year, which was associated with hopelessness, hallucinations, parasuicide at baseline and being female. One suicide occurred in the group receiving integrated treatment with a rate of 0.3% for the entire sample.\textsuperscript{84} In the TIPS project, the rate of severe suicidality (plans or attempts) was significantly higher in subjects from communities without the early detection programme relative to those from the early detection communities.\textsuperscript{74} In a cohort study of 238 FE patients in the Calgary Early Psychosis Program, although 15.1% attempted suicide before programme entry, only 2.9% made an attempt in the year after programme entry and 0.4% completed suicide. No further attempts in the first year were seen in those with previous parasuicide.\textsuperscript{137} In EPPIC, LifeSPAN was an RCT of CBT plus standard care versus standard care for those FE patients who were seen as being at high risk of suicidal. Although the treatment group had a decrease in suicidal ideation, this was not significantly different. However, those receiving the therapy demonstrated greater improvements on hopelessness an important correlate of depression and risk factor for suicide.\textsuperscript{138}

**Substance use**

The abuse of alcohol and drugs is an important and clinically challenging aspect of FEP with prevalence being significantly higher than in the general population.\textsuperscript{139–141} In a large Canadian sample,\textsuperscript{142} 51% met criteria for substance abuse and/or dependence most of whom used alcohol (35%) or cannabis (33%). Substance use was significantly associated with male gender, young age and young age of onset and cannabis use with increased positive symptoms. Similar figures were reported in Melbourne (53%) where over a 15-month follow-up substance misuse was independently associated with increased risk for inpatient admission, relapse of positive symptoms and shorter time to relapse.\textsuperscript{143} Furthermore, those with heavy use had poorer social functioning and more severe positive symptoms.\textsuperscript{144} Similarly in Cambridge, UK cannabis use was reported in 51% of patients and alcohol abuse in 43%\textsuperscript{145} and in London, UK alcohol misuse in 30% and cannabis misuse in 32%.\textsuperscript{146} Lower levels were observed in the TIPS sample with 23% abusing drugs and 15% abusing alcohol. The abusing group were more often male, younger with higher premorbid social functioning and poorer premorbid academic achievement.\textsuperscript{147}

Interestingly, in these FE samples who are part of specialized treatment services rates decline over time. In the Calgary programme, over 3 years those with an alcohol substance use diagnosis (SUD) declined considerably by 1 year to 20% and did not decline further and for cannabis SUD by 2 years to 7%.\textsuperscript{142} In EPPIC, 62% had an SUD at baseline, which was reduced to 36% in the patients who completed 18 months of treatment.\textsuperscript{146} In London, only 15% were misusing alcohol and 18.5% misusing cannabis at 14-month follow-up.\textsuperscript{146}

There is one RCT comparing a 10-session cannabis focused intervention with 10 sessions of psychoeducation (nature of psychosis, treatments, relapse prevention and stigma but avoided explicit discussion of cannabis).\textsuperscript{149} There was a significant decrease in cannabis use at the end of treatment, which was sustained at the 6-month follow-up but the specialized intervention was no more effective than the provision of regular FE psychosis education. This supports the above findings that simple interventions in specialized FE services may be worth considering before intensive specialized therapeutic efforts.

**SUMMARY**

In summary, there is a tremendous growth in the literature addressing FE psychosis. From the literature reviewed here, we have learned that these young people already are experiencing impairments in cognition, social functioning and social cognition at their first presentation. Although correlational, the DUP literature is suggestive that a long DUP is associated although at moderate levels with poorer outcome. TIPS was one quasi-experimental effort to reduce DUP demonstrating that more work is required in understanding not only DUP better but also pathways to care where there may be the opportunity for further improvement.

There are many outcome studies, several with positive results suggesting improvement in recovery, outcome and relapse rates after treatment in FE programmes, particularly those offering a range of
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comprehensive treatments. However, RCTs are rare. The two published from Denmark and the UK demonstrated some improvement in functional and symptomatic outcome and decreased suicide rates. Although there are some positive outcomes in working with families, the Dutch RCT by Linszen et al., suggested that once treatment ends, it is difficult to maintain the good results in the longer term. RCTs of individual treatments are so rare that it is difficult to draw conclusions, especially if methodological concerns are taken into account.

**PROGRESS**

The clinical and research practice in FEP accomplished to date constitutes a major reform in the treatment of schizophrenia. Tremendous shifts have been made worldwide to identify and treat young people at the very beginning of their illness. Programmes have and are continuing to be developed world wide and one, as an example, has only to review the multitude of endeavors in the UK such as the National Evaluation of Early Intervention for Psychosis Services (EDEN) project, the EDEN National project and First Episode Research Network (FERN) to see the impact of national reform. The FEP field demands that treatments for people newly diagnosed with a psychotic illness should be available right at the beginning of the illness and that such treatment needs to be of the highest quality aiming for the best recovery possible.

Typically, criticisms of early intervention reflect the notion that although it is a well-established approach in many countries it is unclear how much early detection, phase specific treatments and early intervention teams are supported by evidence of effectiveness. This review has demonstrated that there are successful reports of reduction in DUP. Pathways to care are being explored with the intent of better understanding and subsequently improving referral systems. Traditionally, outcome in schizophrenia has had a major focus on psychopathology; however, increasingly occupational and social functioning and the person’s quality of life are being seen as important measures of the impact of the illness and/or its treatment. Once diagnosed, we now have concerns about how these young people adapt to the illness and the impact it has on their development, and are striving to lessen the impact. Substance use, medication side effects and relapse rates are being studied and addressed. Successful work with families to help the families themselves with their distress is being reported. RCTs are rare but the effectiveness studies are highly promising and the OPUS trial has some positive results. We have a range of evidence of improved adherence and decreased attrition, reduction in positive and negative symptoms, reductions in depression, hopelessness, suicide rates and relapse rates.

**THE FUTURE: INTERVENE EARLY BUT INTERVENE WELL**

The past has been promising and there has been good progress. What do we need to do to maintain the hope for the future? The potential for improving outcome through earlier timing of interventions is likely to be limited unless it is combined with improved treatment that is specifically designed for the earlier phase of illness and for a younger patient population. We need to ensure that FE programmes are properly implemented. We have determined the feasibility and cost effectiveness of identifying performance measures for early psychosis treatment services and have begun to develop a comprehensive set of performance measures suitable for people with an FEP. Such measures need to be used by services to establish standards and norms for routine clinical practice. Intervention at the FE has to be seen as a complex intervention of early engagement, maintaining engagement, reducing DUP and offering well-developed phase specific interventions. Thus, we have to intervene early and intervene well by continuing to develop and evaluate interventions that better meet the needs of patients and their families.

In designing and assessing treatment outcomes, researchers and clinicians need to take into account impairments that may already be present at the FE. Further research needs to understand better the delay in treatment both from the ‘seeking’ perspective of the client, the referral perspective of gatekeepers and the delivery of treatment. Cultural, social and political issues should also be considered. The impact of treatments needs to be monitored for quality of delivery and effectiveness. There is a need for many more RCTs to determine not just if a treatment such as CBT is effective but for whom it may be effective and at what stage of the recovery process it will have most impact.

There is to date no good outcome data demonstrating how long treatment should continue. A legitimate concern is that FE programmes may be offering an intensive treatment that is no longer available after discharge from the programme. Just referring to other agencies may not be enough; we have to determine who needs what level of care.
There has to be ongoing connections between FE programmes and those offering continuous care. After early identification and treatment, key issues are continuity of patient care and family support and the management of the illness, medication, stress and other concerns that may arise. It remains questionable whether early intervention programmes can offer the prospect of altering the course of schizophrenia without a sustained comprehensive treatment programme.110

It is not enough to state that further research is needed; there are many specific requirements. There has to be longer-term data from large cohorts of FEP patients that includes uniform assessment procedures and clearly defined multidimensional criteria for outcome. Large epidemiologically representative samples are required with a minimum of 2- to 3-year follow-up. Non-adherence with treatment and relapse rates are crucial issues. We have to find ways to understand the different trajectories of outcome so that we can better define patient subgroups that follow different trajectories. Such empirical trials can further establish what treatments are necessary at what stage of the illness and when it is cost effective to provide them. Difficulties in obtaining long-term research funding and limited access to large cohorts of patients, especially in single centers may be additional obstacles that will need to be resolved.

Without a doubt, there is an active and dedicated network of clinicians and researchers working in early psychosis who are interested in sharing information, resources and data to ensure the future of service developments. To further inform and accelerate more progress, not only do our research efforts need to be of the highest quality, but have to continue to be accompanied by political pressure and community demand.

REFERENCES

The promise of early Intervention

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