



Is earlier better? At the beginning of schizophrenia: timing and opportunities for early intervention

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The clinical course and outcome of schizophrenia have been the subject of extensive investigation throughout the twentieth century. Although these studies consistently show marked heterogeneity in the course of the disorder [1–6], as a group, patients with schizophrenia continue to exhibit a poorer outcome compared with patients with other psychotic disorders [7]. For about 50% of patients, the illness has a lifelong chronic disabling course [8], and 10% die by suicide [9]. It is yet to be determined if recent advances in pharmacological, psychosocial, and rehabilitative treatments have improved the human and economic outcome of schizophrenia [10–12].

In schizophrenia, many factors influence outcome, some of which are fixed (eg, gender) and some of which are potentially modifiable. It has been proposed that the outcome of the disorder can be improved by intervening earlier in the psychosis [13–16]. This proposal sounds logical, the principles are ethical, and there are some data to support the hypothesis, but how much?

Background

The drive toward early intervention has been influenced by several factors:

1. Research reports indicating a correlation between the duration of untreated psychosis (DUP) and outcome [17–21]

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2. The hypothesis that the active psychotic process may be biologically toxic [20,22,23]
3. The introduction of novel antipsychotics with their reduced side-effect profile [24]
4. A move in general medicine toward preventive interventions

Outcome and duration of untreated psychosis

Many early long-term follow-up studies showed that most of the deterioration in schizophrenia occurs in the first 5 years after diagnosis [13,25,26]. Bleuler's [25] follow-up study indicated that patients reached a plateau of disability early in the course of the disorder. These findings were supported by some of the results from the Washington cohort, which showed that 75% of patients showed no change in outcome measures between the 2-year and 11-year follow-up [27]. More recent longitudinal first-episode follow-up studies from India and England support the notion of deterioration plateauing in the first 2 years after presentation [28–31]. Evidence now exists, however, that in some cases the decline process may start *before* presentation because first-episode studies have shown that many patients have significant deficits in social, occupational, and biologic functioning at the time of first presentation [32–35].

Despite the distressing changes that frequently accompany a first episode of psychosis, the average time from onset of first symptoms to presentation and treatment is long. Studies from North America, Canada, Australia, and Europe consistently have reported a mean DUP, or treatment lag time, of approximately 1 year in schizophrenia [14,17,33,37]. Although this figure is influenced by outliers who have exceptionally long DUP, the median values reported from the study average at around 26 weeks [17,37,38].

One of the first studies to highlight delay to treatment as a major problem was the Northwick Park study [39]. In this cohort of 253 first-episode psychosis patients, the delay between the onset of psychosis and treatment was more than 1 year in approximately one quarter of the group. Loebel and colleagues [17] measured treatment delay in 70 patients who had a diagnosis of schizophrenia or schizoaffective disorder. The mean duration of psychotic symptoms was 52 weeks, and on average the prodrome lasted 99 weeks. Similarly, Beiser and coworkers [36] showed an average DUP of about 1 year for schizophrenia. Some evidence exists that a longer DUP may be associated with a poorer outcome, and it has been hypothesized that an active untreated psychotic process may be biologically toxic [20] and psychosocially [40] toxic.

Evidence—for and against

The biologic toxicity hypothesis proposes a causal relationship between a longer DUP and a poorer outcome [20]. If this were true, reducing the DUP

should improve the outcome of the disorder. Retrospective studies have provided indirect evidence that a longer DUP generally is associated with an inferior longitudinal course [41–44]. These findings are substantiated by prospective studies that have produced evidence in favor of a “toxic psychosis” process [17,20,30,45–49]; however, other data suggest that this is not always the case.

First, studies from the preneuroleptic era showed that a percentage of individuals have a reasonable outcome despite the lack of neuroleptic medication. Kraepelin [50] concluded that 17% of his patients had good social adjustment at follow-up. Mayer-Gross [51] reported good social recovery in 30% of patients after 16 years. Bleuler [25] followed 208 patients who had been admitted to the hospital in Switzerland between 1942 and 1943; 20 years after admission, 20% had recovered, and a further 20% showed long-term symptoms of only mild severity. Bleuler [25] considered that these outcome figures had changed little despite the advances in treatment.

Second, more recent prospective studies that examined the relationship between DUP and outcome produced negative findings [52–55]. Robinson and associates [52] did not find that DUP influenced relapse rates in a sample of 104 first-episode patients with schizophrenia or schizoaffective disorder over a 5-year period. Ho and colleagues [53] found that the duration of untreated initial psychosis did not impair significantly subsequent quality of life, symptom severity, or remission of positive symptoms in their group of 74 patients with schizophrenia meeting DSM IV criteria. Similarly, Craig and colleagues [55] found that the DUP was not associated significantly with 24-month illness course or clinical outcomes in a large sample of 349 first-episode psychosis patients. Barnes and colleagues [54] showed that there were no differences in decline in IQ, memory, or executive functions or symptoms and social function in a sample of 53 first-episode patients. Another study failed to show a relationship between DUP and decline in cognitive function in an epidemiologic sample of 113 first-episode patients [56]. Hoff and associates [57] found no significant correlations between DUP and the severity of either cognitive or structural brain deficits at baseline. Amminger and colleagues [49] showed an association, however, between a longer DUP and some aspects of cognitive function in a sample of 47 first-episode patients with schizophrenia or schizophreniform disorder while controlling for other prognostic variables.

The inconsistencies between some of these findings could be explained at least partially by the possibility that the DUP/outcome relationship may be an epiphenomenon of a real relationship between another prognostic variable and outcome. This variable may be responsible for the lengthy DUP and the poor outcome. This suggestion has been given some credence by the associations that have been reported between DUP and negative symptoms [18,37,44,58,59], premorbid adjustment [54,59], and a more insidious onset [37]. These findings have not been universally replicated, however [17,53].

Interpretation of these conflicting results is hampered by varying study methods, including sampling differences [60], mixed diagnostic groups, and diverse concepts of outcome [30]. Nonetheless a long DUP could be conceptualized on a continuum from a poor premorbid adjustment, an insidious onset, a longer DUP, and more negative symptoms. This disease subtype may present more silently and may be a more malignant form of the disorder with an inherently poor outcome. Alternatively a longer DUP perhaps in combination with other risk factors could exert an independent influence on some aspects of outcome but not others. Malla and colleagues [56], in a sample of 106 first-episode nonaffective patients who completed 1 year of treatment, showed that DUP was the only independent predictor of the level of remission and the reality distortion syndrome, whereas negative symptoms, disorganization, and anxiety were more likely to be influenced by characteristics such as premorbid adjustment, age of onset, and length of the prodromal period.

In the studies that reported positive results, DUP alone was shown to explain only a modest (8% to 15%) proportion of the variance in 1-year outcome [14,56]. Maybe prediction could be improved by incorporating other risk factors [56]. This situation could be compared with the relationship between blood pressure and cardiovascular disease. High blood pressure is a direct and independent risk factor for cardiovascular disease, but it is only one of the many risk factors that determine the absolute risk of cardiovascular disease. Blood pressure alone is a poor predictor of cardiovascular events, and conventional treatment even when effective prevents only 25% of expected events [61]. Incorporating blood pressure as part of absolute cardiovascular risk may allow more accurate prediction of adverse cardiovascular events and guide treatment more effectively.

The evidence linking a longer DUP with a poorer outcome is inconsistent, and even the positive studies have not provided direct evidence of neurotoxicity. It has been proposed, however, that the unchecked psychotic process may be psychosocially toxic [40] and that damage to an individual's social and vocational network may occur after the onset of psychosis that may be difficult to recover from and that may set limits on future rehabilitation [40,62]. This period of untreated psychosis has been associated with considerable difficulties for the patients and their families, including suicidal behavior and other potentially life-threatening conduct [39,63–66]. These ideas, the availability of medication with a reduced side-effect profile [67], and a general medical trend for prevention and early intervention have formed the basis for several preventive or early intervention programs that now exist worldwide.

Prevention

A preventive intervention in psychosis, if successful, could improve the course and outcome of the disorder, alleviate human suffering, and save

millions of dollars in direct and indirect hospital costs. Illness prevention traditionally has been conceptualized into three phases: primary, secondary, and tertiary. Primary prevention aims to prevent the occurrence of a disease and reduce the incidence of a disorder. Secondary prevention involves early intervention to reduce the duration or severity of the disorder. Tertiary prevention includes rehabilitation aimed at restoring or partially restoring the lost function and prevention of complications and disability arising from the illness. Another model developed by Gordon [68] classifies prevention according to the target population, distinguishing between interventions focused at the general population (universal), at risk subgroups of the general population (selective), and asymptomatic individuals with a risk factor for a particular disease (indicated). It has been proposed that for psychiatric disorders, indicated prevention could include individuals who are minimally symptomatic but do not reach diagnostic criteria [40,69]. This approach would allow prodromal or preonset intervention to be classified as indicated prevention. At present, there is a considerable degree of uncertainty over prodromal intervention, and it is difficult to know where to classify it. This discussion briefly examines the opportunities for primary prevention and prodromal and early-onset interventions.

Primary prevention

Primary prevention in any illness involves identifying causative factors, estimating the degree of risk posed by each of these factors, and intervening to eliminate or modify these risk factors. Such an intervention should be feasible, safe, effective, and economic. There has been a considerable degree of success in reducing the incidence of many other illnesses that in the past were misdiagnosed as schizophrenia (general paralysis of the insane, pellagra-associated dementia, and “myxedema madness” of endemic goiter) [70]. Primary prevention of schizophrenia is a considerable challenge, however, because the cause of the disorder is complex, almost certainly multifactorial, and still poorly understood [71]. Identified risk factors in schizophrenia include a family history of the disorder [72], spring or winter birth [73,74], urban birth [75,76], nutritional deficiencies during pregnancy [77], in utero infections [78,79], and rhesus incompatibility [80].

Several authors suggested that modifying obstetric risk factors provides a potential opportunity to prevent some cases of schizophrenia [81,82]. Possibilities include targeting high-risk cases (ie, individuals with a family history of the disorder) with educational programs aimed at improving obstetric care. Although such an intervention is theoretically feasible and likely to be safe, its effectiveness would be questionable.

Early intervention

In contrast to primary prevention, many early intervention centers have been established in schizophrenia. These can be divided into programs that

target the period before the onset of the psychosis and programs that intervene as early as possible after the onset of frank psychosis.

Prodromal detection and intervention

For any disorder, preonset intervention supposes the existence of some form of disease process that manifests before the full clinical syndrome. The *prodrome* refers to nonspecific signs and symptoms, such as poor concentration; lack of initiative, interest, or energy; impairment in role functioning; and feelings of unease, that represent a change from the person's premorbid functioning and may be present for an unspecified period before the onset of schizophrenia [17,36,83,84].

At present, the prodrome is a retrospective concept that is derived exclusively from patients with schizophrenia, and its definition is subject to bias and potential distortion [85]. Prospective research of the prodromal stage is at an early stage, and so it is unclear whether these symptoms are also predictive of other disorders or whether in some cases they resolve spontaneously without evolving into schizophrenia or any other psychiatric illness.

One study evaluated prodromal symptoms in a sample of 657 schoolchildren and found that 10% to 50% (depending on the time frame used) fulfilled the criteria for a prodromal state [86]. The uncertainty over the definition of the prodrome is reflected in the fact that the criteria used in DSM III-R [87] to characterize the prodrome have been removed from DSM IV [88]. Alternative definitions of the prodrome have been developed and are being evaluated in early intervention programs [89–91].

Prodromal intervention studies

One of the first prodromal intervention studies was based in Buckinghamshire, United Kingdom. Between 1984 and 1988, the research team worked with primary health care providers to screen the population using a checklist for prodromal symptoms derived from DSM III-R criteria [92]. When cases were identified, the intervention consisted of family intervention, social skills training, stress management, and in some cases low-dose medication. On the basis of comparison with a historical control group, it was concluded that their intervention had resulted in a 10-fold reduction in the incidence of schizophrenia [93]. Methodologic limitations to the study include the sample size, uncertainty over diagnostic reliability, lack of follow-up, and the validity of the comparison with the historical control group.

Groups in Australia, North America, and Europe have developed prodromal intervention centers which focus on developing more specific diagnostic criteria for the prodrome and implementing therapeutic interventions that consist of psychosocial treatments sometimes combined with low-dose neuroleptic medication.

In Melbourne, Australia, McGorry and colleagues [14,94] set up the Personal Assistance and Crisis Evaluation service (PACE), which is located at a

general outpatient service and health promotion center for adolescents. Noting that the term *prodromal* implies that psychosis inevitably follows, they introduced the concept of the *at-risk* mental state [84]. They outlined criteria to characterize three high-risk prodromal groups [84,96]:

1. Patients with attenuated positive psychotic symptoms
2. Individuals experiencing brief psychotic episodes in which the symptoms resolve within 1 week
3. Individuals with genetic risk and recent marked deterioration in functioning equivalent to a drop of 30 points on the Global Assessment of Functioning scale

Their first sample ($n=21$) registered an annual conversion rate to psychosis of 21% by 12 months and 33% by 24 months [90,95,97]. A later sample ($n=49$) using amended criteria had a conversion rate of 41% at 12 months and 54% at 24 months [96]. A further larger sample ($n=104$) using the same criteria registered a similar rate of 35% [90]. These transition rates occurred despite intensive psychosocial intervention, and it has been speculated that these rates may have been substantially higher with monitoring alone [90]. These studies formed the basis of the PACE randomized open interventional study comparing psychosocial intervention versus low-dose antipsychotic medication and psychosocial intervention in 59 patients.

This study, performed between 1996 and 1999, showed a reduction in the transition rate from 35.7% to 9.7% over the treatment phase of 6 months [98]. Individuals not making the transition showed significant improvements in symptoms and functioning with similar benefits occurring in individuals who received the antipsychotic.

The at-risk criteria of the Australian group were incorporated into the Structured Interview for Prodromal Symptoms (SIPS) and Severity Scale of Prodromal Symptoms (SOPS) [99]. These scales were developed to identify prodromal individuals in the PRIME study (Prevention through Risk Identification, Management and Education). The PRIME center is based at Yale University, and the group is testing in a double-blind, placebo design whether early treatment with an atypical antipsychotic can prevent or delay the onset of psychosis. The intervention consists of 1 year of treatment and 1-year follow-up. All patients receive psychosocial intervention, which consists of problem-solving training and stress management. The preliminary results on 29 patients indicate a conversion rate of 46% at 6 months and 54% at 12 months [100]. The group reported interrater reliability figures of 93% [100]. The fact that most of the patients convert within 6 months of initial assessment suggests that they are being identified in the late prodromal phase of the illness.

A Norwegian version of the SIPS and SOPS is being used in Stavanger, Norway, in the early Treatment of Prepsychosis project. The intervention consists of supportive psychotherapy without the use of antipsychotics, and

the follow-up period is 5 years. The group reported a conversion rate of 40% on 10 patients over a 1-year follow-up period [89].

The instrument with one of the highest demonstrated specificities and sensitivities is the 66-item Bonn Scale for Assessment of Basic Symptoms (*basic symptoms* is the term used to denote prodromal symptoms) [101]. This scale was used in the Cologne Bonn Early Recognition project [102]. The study aimed to record longitudinally the transition rate to psychosis rather than provide any intervention. The study population consisted of outpatients attending clinics in three university departments in Germany, who were referred for diagnostic evaluation between 1987 and 1991. A total of 160 patients (110 with prodromal symptoms and 50 without) were followed for a mean of 9.6 years. The instrument showed a high sensitivity (0.98) and a reasonable specificity (0.59) [103]. The presence of certain symptoms or symptom complexes, mainly disturbances of thought, speech, and perception, increased the predictive accuracy (specificity, 0.71 to 0.91; false-positive predictions, 1.9% to 7.5%) [103].

Analysis

Two of the key determinants of the success of a preonset intervention program are the predictive accuracy of the diagnostic instrument and the effectiveness of the interventions. In this regard, there are some issues that should be considered, such as:

1. The uncertainty whether treatment for a first episode of psychosis is suitable or effective treatment for a prepsychotic state
2. The false-positive rate of case identification
3. The potential physical and psychological side effects of being identified incorrectly and treated as an at-risk mental state
4. The lack of epidemiologic data on conversion rates to psychosis in a naturalistic setting

Appropriate treatment

It seems to be generally assumed that antipsychotic medication would be the most effective pharmacologic method of preventing prodromal individuals from becoming psychotic. Although there is a fairly clear consensus on the effectiveness of such treatment in a first-episode psychosis, there are few data on the effectiveness or safety of such interventions in the prodromal state.

Treatments developed for an acute stage of a disorder may not be safe or effective as prophylactic therapy. A person who has a family history of diabetes mellitus and who is overweight usually is given dietary advice rather than treated with an oral hypoglycemic agent. It is difficult to know whether

antipsychotic medication has the potential to prevent prodromal symptoms from evolving into psychosis. It has been suggested that medications such as antidepressants and mood stabilizers may reduce the risk of psychotic deterioration in vulnerable individuals [104,105].

False-positive identification rate

A percentage of any sample diagnosed as prodromal or at risk for schizophrenia never develops the disorder. It is likely that the predictive accuracy of the diagnostic instrument used can be increased by considering factors such as genetic loading, targeting people who are treatment seeking, and including brief psychotic symptoms in the prodromal criteria. The latter strategy may improve the conversion rate, but it could be argued that it implies treatment early in the psychosis rather than in a true prodromal state. Individuals who have psychotic symptoms for less than 1 week are classified in DSM IV as a brief psychotic episode or psychosis not otherwise specified rather than prodromal.

Although it is acknowledged by the early intervention groups that the approaches used are applicable only to a specialist setting, it is useful to consider the relevance of such measures to general population screening; otherwise, it is likely that many individuals who have the illness will remain undetected in the community. Difficulties with the current approaches are the fact that only one third of individuals who present with schizophrenia have a family history of the disorder [106], and one quarter of individuals do not exhibit a prodrome [107].

Attenuated negative symptoms, such as deficits in social functioning, are an important characteristic of the prodromal phase of the illness [108,109]. Prospective birth cohort studies have identified deficits in social functioning long before the onset of frank psychotic symptoms [62,110]. Most individuals with schizophrenia develop negative symptoms before positive symptoms yet in practice most scales focus only on positive symptoms or their derivatives. A combination of both may improve the predictive accuracy.

Side effects

The intervention studies using pharmacotherapy are prescribing atypical antipsychotics in low doses. Although atypical antipsychotics have a reduced motor side-effect profile compared with the older neuroleptics, they are relatively new and there are few data on potential long-term side effects. As with any new medication, it is often many years before the entire side-effect profile—acute and long-term—becomes fully known. Evidence is accumulating that some atypical antipsychotics may be associated with sedation, weight gain, and undesirable metabolic side effects [111,112].

The benefits of these medications in psychosis outweigh the possible adverse effects. In the prodromal state, the long term benefits are unknown; however, side effects can be anticipated. However, atypical antipsychotics are being researched as treatment for many other conditions that do not involve the presence of any psychotic symptoms [113].

Apart from potential physical side effects, there is concern about the psychological effects of being identified incorrectly of being at risk of developing psychosis—for the individual involved and family members. A considerable degree of stigma still is associated with psychiatric illness that can be difficult to overcome [114]. Initial experience from prodromal clinics indicates that the risk of stigma can be managed [115]. McGorry and colleagues [90] cited high levels of attendance at the clinic, suggesting that a nonpsychiatric setting can decrease stigmatization. There is some concern that people who are identified incorrectly as prodromal may “downgrade” their life expectations unnecessarily [82], and that this may lead to failure to achieve their social and vocational potential.

Assessing the effectiveness of the intervention

The absence of baseline rates of conversion to schizophrenia in general population samples makes it difficult to assess whether the interventions used are preventing individuals from developing schizophrenia. Does a low conversion rate mean that the intervention is effective, or is the baseline rate of conversion low? Although the programs are using a double-blind, placebo-controlled design, in the absence of baseline rates, the placebo group would need to be of substantial size and randomly ascertained [104].

Early detection and treatment

As outlined earlier, the factors that determine the DUP are complex and not fully understood [116]. The delay likely is influenced by disease-related and sociocultural factors. Disease-related factors include poor premorbid functioning, insidious onset, more negative symptoms, and diminished insight [58]. These factors may account for only a small percent of the variance in DUP, however. Sociocultural factors are poorly understood and scarcely studied. Yet, it is almost inconceivable that such factors do not influence the presentation of the disorder. Although a relationship between DUP and poor social support has been shown [54,58], this relationship may be a result of the psychosis rather than causal. Attempting to reduce the DUP presents a challenge when so little is known about its determinants, and it is likely that only some of the influencing factors will be amenable

to change through education and alternative interventions. The following measures may have some effect in reducing the DUP:

1. Enhancing the accessibility and acceptability of the treatment system
2. Improving general community awareness of the signs, symptoms, and nature of a psychotic illness, particularly in schools and third-level institutions
3. Optimizing the detection and diagnostic skills of primary health care professionals

Pathways to care

Studies have shown that most patients with psychiatric illness present to their general practitioner at some stage in their illness [117]. The Northwick park study was one of the first studies to focus on the pathways to initial treatment in first-episode psychosis. In this group of 253 first-episode patients, the study found that treatment delays of 1 year were common. Although nearly 30% of cases were admitted after no more than three contacts, in 46 cases (18.2% of the sample), at least nine contacts were required before admission was organized [39]. Similar findings were reported by a sample of 62 first-episode patients from Australia, where the mean number of helping contacts with professionals and nonprofessionals was 4.9 (SD, 2.8). About half the patients had four to six contacts, and 16% had more than six contacts [118]. The data indicated the pivotal role the patient's general practitioner plays in recognizing the psychosis because more than one third (36%) of the patients initially sought help with a general practitioner, and 50% had consulted a general practitioner.

Illness recognition

Research has shown that general practitioners may have difficulty recognizing psychiatric illness (mostly based on nonpsychotic disorders) [117,119]. Many aspects of a psychotic illness may hinder recognition. First, subjectively experienced symptoms, such as hallucinations, may not be readily apparent to others [120]. Second, some of the initial symptoms may be subtle, and because the onset of schizophrenia is usually in adolescence or early adulthood, it may be difficult to distinguish these symptoms from developmental adjustment behaviors. Third, patients who are paranoid may be reluctant to visit a physician, let alone discuss their symptoms. Fourth, comorbid substance misuse may confound the diagnostic picture. It reasonably could be anticipated that educating general practitioners and health care professionals about the various presentations and signs of a psychotic disorder would increase awareness and optimize detection skills [121]. There is some evidence, however, that this education may require a specific

targeted approach [122]. There is little point, however, in implementing such programs unless there is easy and quick access to a treatment service that is tailored to the needs of individuals with a first-episode psychosis.

Early intervention services

In Melbourne, Australia, McGorry and colleagues [14] initiated early intervention studies with a first-generation project in 1984, followed by much broader programs beginning in 1991 involving the Early Psychosis Prevention and Intervention Center (EPPIC) and the PACE clinic (discussed earlier). The EPPIC treatment model is based on low-dose medication, individual case management, cognitive therapy, vocational rehabilitation, and family support and education. To improve engagement within the service, the Early Psychosis Assessment Team offers extended hours of assessment and flexibility in the site of assessment. The team also is involved in community education programs targeted at the general population and at general practitioners and other people in the community who have contact with adolescents.

Baseline characteristics and 1-year course and outcome were compared between the EPPIC sample and a historical control group, drawn from the same region but treated within a different service model. The results showed that the mean DUP was not reduced significantly by the intervention. The median DUP was increased from 30 weeks to 52 weeks [48]. Closer examination of the data using log transformation to minimize the effect of outliers with extremely long DUP confirmed that the DUP was longer in the EPPIC sample. This effect may be due to the detection of a group of patients who under the old system might never have been treated [123]. During the 1-year follow-up study, the EPPIC sample experienced significantly fewer admissions, spent less time in the hospital, and required lower doses of medication. When a subgroup of patients with a DUP of 1 to 6 months were compared (pre-EPPIC, $n = 42$; EPPIC, $n = 31$), the EPPIC sample showed a significant improvement in quality of life and had fewer negative symptoms [48].

Contrasting results are reported from the Early Treatment and Intervention in Psychosis (TIPS) project in Norway. This is a multicenter study that prospectively evaluates the effect of early detection and treatment on the natural course of the disorder. The intervention center is based in Rogaland County catchment area in Stavanger, where an extensive community education and early treatment programs are in operation. The educational program is targeted at several levels—general populations, health professionals, and schools—and attempts to alter the help-seeking behavior of the population by information campaigns that educate, focusing on the positive outcomes and the treatment available, and reduce stigma. Two control sectors in Denmark and Norway rely on existing methods to detect and refer first-episode cases. Patients in each sector are treated with a standard pharmacologic and psychosocial protocol [91,124].

Initially the early detection group has been compared with an historical control group drawn from the same catchment area 4 years before the intervention program. The results indicate that the TIPS program has reduced the DUP significantly from 114 weeks (median, 26 weeks) ($n=43$) to 26 weeks (median, 5 weeks) ($n=51$). The patient profile of the two groups was different in that the early detection group was younger, with better premorbid adjustment and less severe psychopathology, and the percentage with a diagnosis of schizophrenia at baseline was reduced [89].

The findings from the Norwegian study are generally encouraging; however, one would expect that the early detection program would pick up the undetected patients with schizophrenia in the community with long DUP that characterize most first-episode samples and may have influenced some of the results of the Australian study. One possibility is that such patients may not be willing to enter such studies [125,126]. If this were the case, the exclusion of such patients would influence significantly the validity of the study's findings.

In this vein, it could be argued further that early detection biases toward the inclusion of cases with better prognostic indicators and a shorter DUP, who would have a better outcome anyway. Alternatively the reasons for the improvement in outcome could be related to the treatment package per se rather than the early detection [82]. It is hoped that the results from some of the multicenter comparison studies will answer this question.

The term *clinical equipoise* has been used to describe the state of the scientific field with regard to benefits of prodromal intervention [115]. In this situation, *equipoise* refers to a position of genuine uncertainty between the benefits of prodromal intervention or continuing with the current treatment approaches. The term *equipoise* could be applied equally, however, to the question of whether reducing the DUP can improve outcome. Although at present early detection may not deliver all that is promised or hoped, it is worthwhile to consider the general principles underpinning the intervention programs. The available evidence suggests that achieving a reduction in DUP may not be as simple as it sounds [127]. It may be difficult to refine detection strategies when there is still so much uncertainty over the determinants of the DUP, and its sociocultural influences in particular remain largely unknown and underresearched. There is a concern that the detection programs may not pick up the cases most in need of detection, a situation that has been encountered in other areas of medicine, particularly in relation to general medical screening. In such screening programs, lead time bias is another important confounder, and the question of whether such early detection merely diagnoses the disorder earlier but does not improve outcome needs to be addressed.

Because early intervention approaches are still evolving and the benefits of such intervention in confirmed cases of psychosis are still uncertain, making a case in favor of prodromal intervention becomes more challenging. There are many legitimate concerns related to intervening in prepsychotic individuals, particularly with regard to unnecessary or premature labeling,

stigma, and side effects of treatment. It reasonably could be argued that investing time in developing a more accurate screening instrument for prodromal symptoms might be an important first step. Then screening in a general population setting with longitudinal follow-up could ensue. This screening might generate useful population-based rates of prevalence of prodromal symptoms and naturalistic conversion rates. This information could aid in evaluating the risk-to-benefit ratio of intervening in the prodromal period, which at present is unclear.

Early intervention offers some hope that schizophrenia can be identified earlier and treated more effectively with better outcomes for the individuals and families. In this emerging era of evidence-based medicine and “value for money” health care, the facts and the figures influence how treatment is provided. At present, the development of early intervention programs can be justified on the basis of the services they aspire to provide. It is hoped that careful evaluation of these interventions will provide direct evidence that these measures are cost-effective and have the potential to improve outcome. If this were the case, perhaps shifting the emphasis from the treatment of established disorders to prodromal interventions could be considered. Primary prevention may be within reach.

Summary

The fundamental tenet is treating psychotic patients as quickly and as effectively as possible. Few would oppose this idea. Increasing community awareness of the services, enhancing accessibility, optimizing the treatment approaches, improving compliance, and addressing substance misuse should hopefully translate into improved outcomes for the patients and their families and are extremely encouraging and welcome developments. However, the field urgently needs properly designed randomized controlled trials to definitively determine their efficacy. If they are shown to be efficacious the emphasis should then shift to randomized controlled trials of prodromal intervention. If prodromal intervention is proven to be successful then earlier might indeed be better and primary prevention within reach.

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