Critical Period and Duration of Untreated Psychosis

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Introduction

The paradigm of early intervention in psychosis has been highly promoted due to the growing body of evidence from prospective studies and randomised controlled trials that the specific interventions in early phase of psychosis induce better clinical and functional outcomes (1). Thus, early intervention services have become an important area of the Community Mental Health development in recent years (WHO, 2004). The large number of clinical and research programmes focusing on early psychosis have now been established (2-8). Early intervention can be conceptualized as a series of preventive strategies, comprising three components, interconnected with each other: 1) early detection of emerging psychosis; 2) reducing delay in the initiation of treatment; 3) providing continuous intervention during the early phase of psychosis or so called "critical period" (9). The potential benefits of early intervention also include: reduced morbidity, more rapid recovery, better prognosis, preservation of social skills, family and social supports and decreased need for hospitalization (10). The aim of early intervention in first-episode psychosis is the shortening of the course and decreasing the severity of an initial psychotic episode, which by turn minimizes many complications following untreated psychosis (11).

The Critical Period

The concept of critical period proposes the rapid progression of symptomatic, cognitive and psychosocial decline during the early phase of psychosis including the period of untreated psychosis. Afterwards, progression of morbidity slows or stops, and the level of disability sustained or recovery attained (10).

The critical period hypothesis has sustained the development of early intervention services for treatment of patients with recent onset of psychosis all over the world. The critical period concept was also underpinned by the neurobiological findings elucidating schizophrenia as a progressive neurodegenerative illness. Based on the results of Northwick Park longitudinal studies and referring to the past outcome studies, Birchwood (10) suggested that the major changes in psychosocial functioning of patients with schizophrenia and schizophrenia spectrum disorders occur in the early course of the disorder, specifically within first 3 years. As Birchwood (12) argued, "the course of psychosis is the most stormy at its onset and early in its manifest course…the first three years of treated or untreated illness offer a window of opportunity to prevent, or limit the potential decline in outcome." Subsequently, prospective studies have shown that for many subjects, there is a rapid period of progression of psychosis prior to the onset and following the first episode of psychosis (13;14).

However, according to the subsequent findings the process of deterioration appeared to be quite active 2-3 years before the onset and sometimes for 1-2 years after onset until a stable plateau is reached in the course of the disorder (15). However, in an 11-year follow-up study Carpenter & Strauss (16) demonstrated that a global measure of outcome at 11 years remained consistent with outcome assessed at 2 and 5 years, providing evidence of neither marked deterioration nor improvement over the 6 to 9-year period suggesting that symptom severity, duration of hospitalization, and work and social functioning constituted "loosely linked" domains of functioning, with level of functioning in each domain at or prior to index admission being most predictive of outcome in that domain findings at both 2- and 5-year follow-up. The investigators suggested that these findings of a lack of deterioration and consistency in outcome indicate that psychopathology tends to plateau early in the course of illness following an initial deterioration, with later-course improvement more likely than progressive deterioration.

According to McGorry (1), the critical period is a period of maximum risk for disengagement, relapse and suicide, as well as coinciding with the major developmental challenges of forming a stable identity, peer network, vocational training and intimate relationships. Hence, all attempts of early intervention services should be focused on maximizing the patient's chances of engagement, in maintaining of treatment and adherence to therapy, facilitating family engagement and support, rebounding functional recovery.

The Duration of Untreated Psychosis

Duration of untreated psychosis is defined as the interval between the first onset of psychotic symptoms and the administration of the first adequate pharmacological treatment. Within this hypothesis lies the evidence, which was derived from previous and reaffirmed in recent studies that untreated psychosis results in alterations to brain tissue and structural deficits become more severe after the first episode. (17- 21). The results of these studies are consistent with a notion that cerebral volume deficits in a complex network of cortical and subcortical regions occurring in schizophrenia, irreversibly limit the individual abilities of recovery in schizophrenia. As a consequence, there may be an important therapeutic opportunity to ameliorate the long-term course by minimizing post-diagnosis neurodegenerative progression of the illness in reduction of the DUP. Therefore, the goal of early intervention is to start treating the psychosis before this process of toxicity occurs. However, despite the growing evidence for "neurotoxicity" of untreated psychosis it is still debatable whether cognitive dysfunction is a neurotoxic consequence of delayed treatment, as cognitive impairment occurs prior to the onset of psychosis and is poorly affected by available antipsychotics (22). Supporting this view, Goldberg et al (23) found no relationship between longer DUP and worse cognition.

The relationship of the duration of untreated psychosis and poor clinical outcome is a keystone of the concept of early intervention. Numerous retrospective and several prospective studies have found that the longer a person remained psychotic before treatment initiation, the higher the relapse rates, less beneficial is the maintenance of anti-psychotic medication. Due to these findings, treatment should begin as soon as the first positive symptoms occur, but it also may be possible to intervene during the prodromal phase. The program for intervention at high-risk mental state has already been included in the British Guidelines, although there is a lack of support from evidence-based research into the standards of care, for instance management of medication dosages prescribed to the individuals experiencing at risk mental states (24).

Within the early intervention concept it has been proposed that among the most established predictors of outcome, duration of untreated psychosis is exceptional and potentially modifiable. In order to indicate the impact of DUP in outcome measures, a systematic meta-analysis of 43 studies investigated the relationship between DUP and outcome in first-episode schizophrenics, and showed that a prolonged DUP was associated with lower levels of symptomatic and functional recovery from the first episode and with the severity of negative symptoms, while there was no association between the DUP and the severity of positive symptoms (25). In another systematic review Marshall et al. (26) indicated a moderately strong association between DUP and a range of outcomes at 6 and 12 months of the follow-up. At 24 months the evidence of the association was weaker, although the data from a single 15 year follow-up study provided support for an association between DUP and positive and affective symptoms as well as overall functioning. Moreover, there were no differences in outcome between long and short DUP groups. Interestingly, lack of association between DUP and outcome measures during time, according to the authors support the hypothesis that the long-term harm caused by psychosis occurs principally in the first few months or even weeks following the onset, proposed by Drake et al. (27).

Conclusion

Critical period in the long trajectory of psychosis has supported the concept of early intervention and initiated a process of health service reforms and development of new approaches for management of psychosis, including prodromal phase (1). There is evidence that courses of long-term outcome in schizophrenia may be identified and determined within the first 2-5 years of illness and the outcomes are better, the earlier treatment initiated. There is however, a genuine uncertainty about how long intensive early intervention should be provided and whether all cases should receive the input at the same fixed period. There is a debate regarding the duration of intervention required for benefits in the long term trajectory of illness. Several 5-year studies have indicated that although interventions may show effect immediately after treatment, the benefits are lost at 5-year follow up (28).

Effectively reducing treatment delay requires an understanding of the nature and source of this delay and finding effective interventions to reduce it. Management and treatment approaches during the critical period in psychosis should be aimed to minimize the development of disability and maximize functioning.

GP comment

What have I learned from this paper?

1. Although there is debate about whether early treatment of schizophrenia affects long-term outcome, the evidence seems to favour early treatment.

2. Early treatment is likely to decrease distress and might improve outcome; therefore I would refer a patient with a likely diagnosis of schizophrenia promptly to a specialist for treatment.

3. I am sure early intervention will have a positive effect on patient well-being but the early detection will invariably be happening in the primary care and therefore it is important to bring GPs on board and educate them about the prodromal/critical phase of the illness. By doing that the rates of undetected critical period would drop.

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