Improving outcome in schizophrenia: the case for early intervention

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The long-term course of schizophrenia, one of the world's most serious public health problems,[1] is generally regarded as one of chronicity and disability.[2–8] Despite the availability of treatment, more than 50% of patients continue to exhibit moderate levels of "positive symptoms" such as delusions, hallucinations, and disorganized thinking and behaviour, and "negative symptoms" such as poverty of thought, volition and affect, and social and interpersonal withdrawal, and require long-term support and periodic admission to hospital.[9,10] It is therefore important to find ways to improve long-term outcome. We reviewed the literature to examine the impact of strategies to improve long-term outcome, the factors that influence outcome and the evidence supporting early intervention as a means to improve outcome.

The difficulties inherent in defining outcome are well documented. For this review, we used the description of Hegarty and colleagues,[11] who stated that "patients considered improved in follow-up have been described as recovered, in remission, without symptoms, minimally or mildly symptomatic, improved without significant deficit, socially recovered, working or living independently."

Impact of treatment on outcome

The efficacy of pharmacotherapy with antipsychotic agents is now well established.[12,13] The limitations of neuroleptic therapy include a relative lack of efficacy in treating psychosis in a substantial minority of patients; the limited effect of these drugs on negative symptoms and cognitive deficits, such as those affecting verbal working memory and executive functioning; and the tendency of these drugs to induce disabling and distressing side effects, such as parkinsonism and tardive symptoms. The recent introduction of "atypical" antipsychotic agents such as clozapine,[14–16] risperidone,[17,18] olanzapine[19] and quetiapine[20,21] provides new hope for patients because of the lower incidence of extrapyramidal side effects associated with these compounds and their possible efficacy in treating negative and disorganization symptoms[22] and improving verbal working memory.[23] Clozapine in particular may be effective for patients in whom the standard neuroleptics have been ineffective.[14] Because cognitive functions[24] and symptoms[10,25] are most likely the major predictors of functional outcome in schizophrenia, these newer agents may alter the course of the illness; however, relevant long-term outcome data are not yet available.

There is strong evidence that family psychoeducational interventions,[26] social skills training[27] and supportive employment,[28] combined with medication, are associated with significantly lower risk of relapse than medication alone.[29] In addition, certain methods of delivering care, such as case management and assertive community treatment, have been shown to substantially improve patients' ability to live in the community[30,31] and to increase their quality of life.[32]

Despite acceptable levels of efficacy for drug treatment and psychosocial interventions, the overall outcome for patients with schizophrenia has improved to only a limited extent. Deterioration of functioning and progression of symptoms are not linear but tend to be worse for the first few years, often plateauing in subsequent years.[33,34] In addition, significantly better outcomes have been reported for patients in developing countries,[35–38] which indicates some influence of cultural factors.

The limited impact of available treatments on long-term outcome may be partly

due to poor use of combinations of optimal treatments. Although "model" community treatment programs have been consistently reported as superior to both short- and long-term institutional care,[39] these findings have failed to benefit the average patient.[40] Given that effective use of optimal combinations of treatments should produce more widespread positive results, the focus in clinical outcomes research should shift from demonstration of efficacy for individual interventions to the application of various combinations of efficacious treatments suited to the individual needs of unselected patients.[41] Successful application of treatment models derived from controlled trials in community settings has recently received some empirical support.[42]

Are there reliable predictors of outcome?

Given the extreme variation in outcome among patients with schizophrenia,[5,6] much effort has been expended in searching for reliable predictors of outcome. Better outcome has been reported in women[43–45] and in patients with later and sudden onset of the disease,[5,6] depressive symptoms,[7,46] a family history of affective disorders,[7] good initial response to medication,[10] and a low level of ambient tension in the family emotional atmosphere.[25,46,47] In contrast, male sex,[43–45] early age at onset,[5,6] predominantly negative symptoms,[7] poor premorbid social and cognitive functioning,[48] enlarged ventricles[49] and substance abuse[50] have been associated with less favourable outcomes. Previous employment, more social contacts, lower use of hospital services and shorter duration of untreated psychosis are strong predictors of good outcome.[13,51] The power of these predictors may vary with the stage of illness, the diagnostic criteria and the period of follow-up.[52]

One particularly noteworthy factor is the duration of untreated psychosis. Relevant studies are impressive in that they unanimously show that the duration of untreated psychosis is an independent predictor of and a possible influence on outcome. These findings strongly suggest that initiation of treatment soon after the onset of the first episode of psychosis could lead to better outcome. The studies have compared outcomes in patients whose condition was diagnosed before the introduction of neuroleptic drugs — and in whom effective treatment was therefore delayed — and patients who received treatment after the introduction of neuroleptics.[13,53] A study of 88 patients who lived in hospital for an average of 13 years before treatment with neuroleptics showed that cognitive deterioration was positively related to the length of the initial period of untreated illness, even after the effects of age and the duration and continuity of subsequent neuroleptic treatment were taken into account.[54] Clinical trials comparing neuroleptic drugs with placebos,[55] as well as follow-up studies,[56] also provide evidence of the importance of duration of untreated psychosis.

The most compelling evidence comes from a prospective study of 70 patients with schizophrenia and schizo-affective disorder treated for their first episode of psychosis.[57] The average duration of untreated psychosis was 51.9 weeks and the mean total pretreatment duration of any psychiatric symptoms was 150.8 weeks. A longer duration of untreated psychosis was associated with lower frequency of, and longer time to, remission. The duration of untreated psychosis was independent of other predictors, such as age at onset and MRI findings of abnormal brain morphology.

Although factors that predict outcome do not necessarily influence the course of the illness, they do indicate the most promising avenues for research. Family atmosphere, substance abuse and, most important, duration of untreated psychosis, are the only predictors of outcome that may be modifiable.

Improving outcome through early intervention

The evidence implies that intervention early in the development of psychosis may lead to complete, or almost complete, recovery in a much larger proportion of patients than is currently the case. The beneficial effects of early intervention are supported by the suggestions that untreated psychosis may have a noxious effect on brain functioning,[13] that patients experiencing their first episode of schizophrenic psychosis are much more responsive to antipsychotic medication than during subsequent episodes[58] and that relatively low doses of antipsychotic drugs are needed at this stage.[59] In addition, patients' social supports and insight, 2 important determinants of outcome,[60,61] are likely to still exist during the early stages. Outcome studies in schizophrenia show that the greatest decline in functioning occurs in the first few years of the illness.[7] A longer period of illness is associated with increasing negative symptoms and cognitive and behavioural deficits.[62] Medical and psychosocial interventions may be more effective when newer antipsychotics are used at a relatively early stage. The combination of better tolerance and greater brain plasticity associated with the new drugs could render the patient more amenable to psychosocial interventions. Therefore, evaluating the potential benefits of early intervention for psychosis must be a high priority.

McGorry and collaborators[63] have reported some encouraging results from their Early Psychosis Prevention and Intervention Centre (EPPIC). The program encourages referral at an early stage, combines treatment strategies effective in the treatment of psychosis and aims for early reintegration of patients into the community.[64,65] These authors compared outcomes of 51 patients with first-episode psychosis who were treated in the EPPIC program and those of a historical matched control group whose first episode was treated in a standard program (before the establishment of the EPPIC program).[63] At the end of 1 year, patients in

the EPPIC program had a lower number of hospital admissions, shorter length of stay in hospital, lower levels of negative symptoms, lower mean dose of neuroleptic drugs and higher scores on a measure of quality of life (all differences were statistically significant). Tentative, but not statistically significant, evidence indicated a reduction in the duration of untreated psychosis in the EPPIC group. There is, however, some ambiguity in interpreting these results because the EPPIC patients differed from the historical controls in the type and timing of treatment received.

The evidence suggests, therefore, that a change in the content and the timing of initial treatment of psychosis is likely to lead to better outcome for a number of dimensions. Findings on the impact of early intervention must be replicated, while controlling for treatment content. A study of this nature would probably require a quasi-experimental research design.[66] Ethical and other practical considerations would generally preclude a randomized controlled design. Given the widespread variation in systems for delivering mental health services across regions, a parallel control design in 2 jurisdictions would likely introduce more systemic confounders than would be encountered in a historical control design.

Challenges of early intervention

Although there is a clear rationale for early intervention, attempts to improve early detection and treatment face many challenges. The duration of untreated psychosis is probably influenced by many factors, such as pattern of onset of psychosis, tolerance of abnormal or eccentric behaviour in the patient's social network, social and cultural factors such as the stigma of mental illness, accessibility of appropriate care, the skills and knowledge of health care and counselling professionals in primary care settings, and the degree to which afflicted individuals and their families accept available treatment.

The onset of bizarre psychotic symptoms is the most readily identified aspect of such disorders, but psychosis often has a more subtle onset manifested in disturbances of mood, impaired concentration or nonspecific eccentricities that may be associated with other psychiatric problems or temporary circumstances. Family and friends may have difficulty recognizing early psychosis, and they may actively avoid such an interpretation. The social withdrawal and increased secretiveness that sometimes accompany the initial stages of psychosis may also interfere with early identification of the problem. Even experienced clinicians have difficulty identifying prodromes of psychosis because of the low sensitivity and specificity of behavioural changes during the period immediately preceding onset.[67-69] Also, the person may not be willing to reveal much about his or her inner experiences to physicians during routine assessments.

Systemic factors may also delay the initiation of treatment. These largely reflect the availability of appropriate professional services. Patients in whom a psychotic disorder is eventually diagnosed have frequently visited a physician for related problems, but the underlying illness remains undiagnosed.[70] As a result, most patients with schizophrenia are subject to the deleterious effects of delay in the initiation of treatment. Strategies for reducing the duration of untreated psychosis that could be evaluated include teaching better methods of case detection at the primary care level, increasing awareness of psychosis among the public and targeting high-risk populations for early case detection and intervention. It has been proposed that "indicated prevention" efforts[71] be directed toward people who are at high risk and who show minimal, yet detectable, signs and symptoms, but who do not meet the criteria for schizophrenia.[72] The definition of "caseness" — the point at which a patient can be regarded as suffering from psychosis and in need of treatment — would have to be adjusted, so that treatment for psychosis could be initiated even in the absence of a definitive diagnosis of schizophrenia.

Several attempts are under way to examine strategies to prevent schizophrenia in highly susceptible individuals.[73,74] However, we must await more definitive evidence from controlled trials of psychosocial and pharmacological interventions before such strategies can be implemented. For now, it may be more productive to improve detection of already established psychosis and initiate early treatment.

The objective of an early intervention program must be to establish an efficient system of providing care for patients early in the course of their illness, with quick and easy access to comprehensive, well-designed biological and psychosocial interventions. Future investigations should examine methods to reduce the duration of untreated psychosis through early case detection and diagnosis and should assess whether such methods actually reduce the severity and the duration of the initial episode of psychosis or lead to better long-term outcome (or both). The arguments for early and optimal intervention are compelling.

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