Schizophrenia Bulletin Advance Access published November 20, 2012
Schizophrenia Bulletin
doi:10.1093/schbul/sbs135

# The Myth of Schizophrenia as a Progressive Brain Disease

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**Schizophrenia has historically been considered to be a deteriorating disease, a view reinforced by recent MRI findings of progressive brain tissue loss over the early years of illness. On the other hand, the notion that recovery from schizophrenia is possible is increasingly embraced by consumer and family groups. This review critically examines the evidence from longitudinal studies of (1) clinical outcomes, (2) MRI brain volumes, and (3) cognitive functioning. First, the evidence shows that although approximately 25% of people with schizophrenia have a poor long-term outcome, few of these show the incremental loss of function that is characteristic of neurodegenerative illnesses. Second, MRI studies demonstrate subtle developmental abnormalities at first onset of psychosis and then further decreases in brain tissue volumes; however, these latter decreases are explicable by the effects of antipsychotic medication, substance abuse, and other secondary factors. Third, while patients do show cognitive deficits compared with controls, cognitive functioning does not appear to deteriorate over time. The majority of people with schizophrenia have the potential to achieve long-term remission and functional recovery. The fact that some experience deterioration in functioning over time may reflect poor access, or adherence, to treatment, the effects of concurrent conditions, and social and financial impoverishment. Mental health professionals need to join with patients and their families in understanding that schizophrenia is not a malignant disease that inevitably deteriorates over time but rather one from which most people can achieve a substantial degree of recovery.**

*Key words:* MRI/cognition/outcome/prognosis/remission/recovery

## Introduction

Schizophrenia is a leading cause of disability worldwide.[1] Kraepelin originally characterized the illness as having a course that led almost inevitably to severe cognitive and behavioral decline,[2] and many clinicians and neuroscientists still consider it to be a progressive brain disease that leads to chronicity and social incapacity.[3,4] This view has been reinforced by recent neuroimaging studies that have shown supposedly "progressive" changes in brain structure.[5,6] A progressive neuropathological process would provide a straightforward paradigm to understand the relationship between pathophysiology and a poor illness outcome.

This idea of schizophrenia as a progressive disease of the brain has also been an important part of the rationale for developing early intervention services. Indeed, the notion that psychosis itself may be toxic to the brain[7] provided a major impetus for programs designed to minimize the duration of untreated psychosis (DUP) in order to prevent further brain tissue loss.[8] However, the widespread development over the past 2 decades of specialized clinical programs to treat young people experiencing a first episode of psychosis (FEP) has also provided new opportunities to evaluate the outcome of the illness together with the course of structural brain differences and cognitive deficits. In this article, we will review the evidence concerning these 3 aspects of the illness in order to evaluate whether it is consistent with the view of schizophrenia as a progressive brain disease.

### *Definitions*

In order to characterize the outcome from schizophrenia, it is necessary to define the patient samples and measures of outcome found in different studies. Longitudinal studies that have followed patients after their FEP vary in their inclusion criteria. Some studies of first episode schizophrenia (FES) have included patients meeting criteria for schizophrenia or schizoaffective disorder,[9,10] while others have included those meeting criteria for schizophreniform disorder.[11] In this review, studies using these more narrow definitions will be referred to as studies of FES. Those studies that have included other psychotic disorders such as

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delusional disorder, brief psychotic disorder, and psychosis not otherwise specified, but excluded patients whose psychosis is due to a primary affective disorder, will be referred to as studies of FEP. Studies of FES and FEP also vary in the age range of subjects, the duration of time that the person has been ill prior to involvement in the study, and the duration of treatment prior to entering the study. In discussing the outcome from a FES or FEP, we have taken an inclusive approach because many studies do not provide specific details about age and duration criteria utilized.

Definitions for remission also vary considerably.[12,13] Remission criteria have typically required that positive symptoms be reduced to a mild level of severity, while criteria vary for the severity of negative symptoms and duration required to meet the threshold for remission.[9] The term "remission" will be used here to refer to patients whose positive symptoms have diminished to levels considered to be mild or lower in the presence of negative symptoms that are no greater than moderate in severity. The terms "functional recovery" and "recovery" are also used in this review. "Functional recovery" refers to the achievement of an adequate level of social and vocational functioning that involves appropriate role functioning, capacity for independent living, and social interactions at a regular frequency.[10] A range of definitions of the term "recovery" have been used in the schizophrenia literature and vary considerably between researchers, clinicians, and consumers.[12,14] The term "recovery" is used in this article to refer to levels of social and vocational functioning that are within the normal range together with a remission of psychiatric symptoms.[10,12]

## Outcome of Schizophrenia

Longitudinal follow-up studies of patients diagnosed as having schizophrenia have consistently found that about 40% achieve social or functional recovery.[15–17] While this finding in itself casts doubt on whether schizophrenia is inherently progressive, there is no question that schizophrenia can be a very disabling illness that causes many of those affected to suffer a substantial decline in their functioning and in their ability to realize their full potential. Two questions arise concerning this disability. First, does it result from stable deficits that are established early in the illness or from a progressive decline in functioning over the course of the illness? Second, does any functional decline reflect the impact of underlying biological disease mechanisms or rather the cumulative impact of adverse social factors and their interaction with the patient? To address these questions, it is instructive to begin by considering whether patients who experience a FES or FEP can achieve periods of remission and recovery over the course of their illness.

### *Remission*

With appropriate care, including the skillful prescription of antipsychotic medication, the early years following a FEP are not typically periods of decline but rather of substantial ongoing improvement in symptom severity and functioning.[17–19] Lieberman et al reported that 83% of patients with a FES experience a remission in psychotic symptoms within the first year of treatment.[9] This is comparable to estimates of rates of remission of 70%–74% for patients with a FEP.[18,20,21] These high rates of remission may in part reflect the effects of the assertive treatment received in research-intensive services and specialized FEP services, as well as the sampling approaches used. However, the evidence to date suggests that those patients who achieve remission after their first episode are, on average, able to maintain similar rates of remission over the longer term as well; ie, the proportion relapsing is matched by others remitting.[11] Thus, Girgis et al described the outcome of 160 Chinese patients with a FES who were randomized to clozapine or chlorpromazine for 2 years and then followed naturalistically for 7 years.[11] Between years 2 and 9, the percentage of patients rated as being in remission remained stable at 78% irrespective of their initial assignment to clozapine or chlorpromazine.

It is true that those who have had a FES run a high risk of relapse. Robinson et al reported that 82% of patients who achieved a remission from their FES experienced a relapse within 5 years, with comparable percentages of relapsed patients going on to have a second and third relapse.[22] Those who discontinue medications in the early years are at especially high risk with reports of the percentage relapsing within 1 year as high as 78%[23] compared with rates of 0%–12% for those who remain on antipsychotic medications.[24–27] Thus, while remitted patients who discontinue maintenance treatment have high relapse rates, those who are adherent have an equally high likelihood of remaining in remission. Adherence rates may be enhanced by efforts to better inform patients of the risk and consequences of relapse and by optimizing pharmacologic management to minimize bothersome side effects.

### *Functional Recovery*

Unfortunately, one cannot assume that patients who are in remission will have an adequate quality of life. Rates of functional recovery are lower than rates of remission.[10,15–17,28] In a systematic review of outcomes following a FEP, Menezes et al[16] found that approximately 40% of patients achieved functional recovery whether the follow-up period was less than, or greater than, 2 years. The percentage of patients considered to have a "poor outcome" was also estimated to remain stable at approximately 25%.[16] These estimates are in keeping with the results of Lambert et al[15] who carried out a 3-year follow-up study of 369 patients with a FES and found that the percentage considered to be in a "functional remission" (defined as the fulfillment of occupational status, independent living, and social relationships)



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remained stable at approximately 40% at 1-year and 3-year follow-up points. Similarly, Henry et al[29] found that 30.5% of 428 patients assessed a median of 7.4 years after their FEP met criteria for social-vocational recovery.

As with remission, however, the proportion recovered does not appear to either increase or decrease with time. Bertelsen et al found that only 17% of patients with a first episode of illness within the schizophrenia spectrum were considered recovered after 2 years, comparable to the rate of 18% found at 5 years.[19] Thus, while rates of recovery may vary across samples and with different criteria for recovery, they appear to remain stable within a given sample at least for the first 2–5 years of illness. The multicentre International Study of Schizophrenia supported by the World Health Organization found that the percentage time spent psychotic in the first 2 years of follow-up after a FES was the best predictor of symptom and disability scores at 15-year follow-up.[30] Thus patients who do not experience remission and are doing poorly in the first 2 years of illness are likely to be part of the 25% of patients reported to have a poor outcome over the longer term. In summary, rates of symptomatic and functional remission and rates of poor outcome appear to be relatively stable even over extended periods of follow-up. This pattern of stability would not occur in an illness that is by nature progressive.

There is little reason to believe that clinical deterioration that is often observed in patients with schizophrenia is an inevitability. Rather it may be a reflection not only of nonadherence and resulting relapses but also of the consequences of other critical determinants of health such as poverty, homelessness, unemployment, and lack of social support, as well as other comorbidities, that all too often complicate the course of schizophrenia.[31]

### *Why Do Clinicians Have Such a Pessimistic View?*

The view that most people with schizophrenia become markedly disabled continues to be held by many clinicians. In their seminal article, "The Clinician's Illusion", Cohen and Cohen[32] cited schizophrenia as an example of an illness for which the Clinician's Illusion is particularly relevant. The Clinician's Illusion is, "the attribution of the characteristics and course of those patients who are currently ill to the entire population contracting the illness." This illusion occurs because clinicians typically care for those patients currently suffering from the illness (ie, a prevalence sample), rather than of all those who have ever contracted the illness (ie, an incidence sample). Patients who are remitted or well stabilized are less likely to be seen in specialized psychiatric services, and if they are seen at all, it is more likely to be by their family doctor. Cohen and Cohen demonstrated that the likelihood that a patient will appear in such specialized clinics (ie, in a prevalence sample) is proportional to the duration of their illness. As a result, prevalence samples are greatly biased toward those who have been ill for many years, while those who have had brief periods of illness are underrepresented.

Cohen and Cohen also pointed out another important biasing artifact known as "Berkson's Fallacy": "those who have other disabilities that are not causally connected to the condition being investigated are more likely to enter the formal treatment system." As a result, patients may have clusters of problems that adversely contribute to their outcome but are not consequent upon the condition being treated. It is common in specialized schizophrenia clinics to see patients with concurrent problems of low intellectual functioning and developmental disabilities, as well as with mood, anxiety personality, and substance use disorders. The high prevalence of these problems in a specialized clinic does not argue for these difficulties being a direct consequence of schizophrenia. Rather, individuals with these problems in addition to having schizophrenia are more likely to find themselves sin such specialized clinics. Each of these conditions can be very disabling on their own, and when they occur together with schizophrenia, the net impact will be more severe disability. However, it may not be the natural course of schizophrenia, the principal factor responsible for the poor outcome. Thus, the fact that clinical researchers who write about schizophrenia mainly see patients who are profoundly disabled is more likely to reflect referral and sampling biases than the progressive nature of schizophrenia per se.

## The Search for Progressive Brain Changes

Researchers have sought to identify structural brain changes in schizophrenia since the time of Kraepelin.[2] Postmortem[33] and pneumoencephalographic studies[34,35] provided support for the presence of atrophic brain changes in some patients with chronic schizophrenia. However, the opportunity to systematically investigate brain structure emerged in the 1970s and 1980s. Computed tomography (CT) revealed that patients with schizophrenia on average had larger intracranial cerebrospinal fluid (CSF) volumes, including larger lateral ventricles[36,37] and cortical sulci.[38,39] Subsequent MRI studies demonstrated widespread deficits in gray matter volumes[40,41] and white matter volumes.[42] The magnitude of these group differences was observed to be greater for more chronically ill patients.[43] From the outset, both CT and MRI studies sought to demonstrate associations between illness duration and the magnitude of CSF and gray matter volumes, but with little success.[40,44]

MRI studies confirmed significant brain volume reductions in patients with chronic schizophrenia and also demonstrated their presence in patients presenting with their FES or FEP.[45,46] However, the magnitude of the effects observed for CSF increases and gray matter decreases in the early phase of the illness has been found to be

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modest relative to those observed in more chronically ill patients.[45–47] The possibility that this difference might be consistent with a progressive neuropathological process has been enticing. Alternative hypotheses, that this difference reflects a sampling bias or the effects of medications and other factors secondary to the illness, have received less attention to date. If patients who have more striking differences in CSF and gray matter volumes at the time of their first episode are more likely to have a poor outcome,[48–53] then such patients will have an increased likelihood of being represented in samples recruited from services for chronically ill patients.[54] Patients with a poor outcome may also be more likely to have neurodevelopmental problems and/or substance abuse that may independently be associated both with similar structural brain changes and with worse outcome. Whether the differences in the magnitude of structural brain changes observed in first episode compared with more chronically ill patients are due to progressive changes or sampling effects is best addressed through longitudinal studies.

### *Longitudinal Studies and the Effects of Antipsychotic Medication*

Longitudinal MRI studies have now shown that brain tissue volumes decrease and CSF volumes increase over time to a greater degree in patients with schizophrenia than control subjects.[47,55,56] However, there is now compelling evidence that antipsychotic medications have an important role in contributing to these "progressive" changes.[57,58] Lieberman et al[59] followed patients treated with either olanzapine or haloperidol for a FEP for 2 years; patients treated with haloperidol but not olanzapine had worsening deficits in gray matter volumes that were already apparent after 12 weeks of treatment. It was unclear whether the relative volume reductions seen in the haloperidol-treated group reflected a disease process that was ameliorated by olanzapine but not haloperidol, a drug effect caused by haloperidol but not olanzapine, an increase in relative tissue volume related to the weight gain and metabolic effects associated with olanzapine, or a statistical artifact caused by sample attrition.[60]

Ho et al[61] have now demonstrated an association between antipsychotic treatment and brain volume reductions in patients ascertained with a FES who were scanned longitudinally over an average of 7.2 years. Antipsychotics were associated with decreases in gray- and white matter volumes with higher doses resulting in greater decreases.[61]

That antipsychotic medications can result in reductions in brain tissue volumes has been put beyond doubt by animal studies.[62,63] Both haloperidol and olanzapine led to decreases in gray matter and white matter in macaque monkeys treated chronically for 17–27 months.[62] Like the brain changes described in schizophrenia, these deficits were diffusely distributed across the frontal, parietal, temporal, occipital, and cerebellar areas. Similar findings have been demonstrated using postmortem samples and ex vivo MRI using chronic doses of haloperidol and olanzapine in chronically treated rats.[63] Animal models provide the opportunity to better characterize the effects of antipsychotics on brain tissue and to determine the extent to which they may be progressive or reversible. Indeed, Vernon et al[64] have shown that MRI scans normalize in rats following withdrawal of the antipsychotic. Results from a longitudinal study of patients with a FES in Sao Paulo, Brazil, suggests that differences observed at the time of the first episode (after the initiation of antipsychotics) may also be reversible to some degree with medication discontinuation.[65]

### *Effects of Substance Use*

Recent studies have reported that cannabis[66–68] and cigarette smoking[69] are associated with MRI findings of diminished brain tissue volumes in psychotic and nonpsychotic populations. Rates of cannabis use and smoking are much higher in patients who develop schizophrenia and may contribute to the presence of brain volume differences at the time of the FEP.[70] Rais et al[67] found that cannabis-using patients who were followed for 5 years after a FES had greater losses in gray matter volumes and increases in lateral ventricle volumes than patients who were not abusing cannabis. Alcohol is also known to lead to reduction in brain tissue volumes[71–73] and to compound the differences observed in patients with schizophrenia.[71] That cannabis, alcohol, and smoking may all contribute to the magnitude of gray matter deficits observed in patients with schizophrenia is supported by recent findings by Stone et al[74] who found that at low to moderate levels, all were associated with lower gray matter volumes in individuals at high risk of psychosis and in healthy controls.

### *Effects of Lifestyle*

Many patients with schizophrenia have a sedentary lifestyle that may also contribute to the deficits in brain tissue volumes observed. Colcombe et al[75] found that aerobic exercise increased gray matter and white matter volumes in elderly community volunteers who had been sedentary. This is consistent with animal studies, which have demonstrated that exercise can increase new capillary formation, dendritic growth, and new cell production in the hippocampus.[76,77] Pajonk et al[78] carried out a randomized controlled trial of the effects of exercise and showed that increased physical activity leads to increases in hippocampal volumes in both patients with schizophrenia and healthy controls.

### *Stress and the Hypothalamic-Pituitary-Adrenal Axis*

The elevated glucocorticoid levels associated with chronic stress that patients with schizophrenia manifest may also contribute to the smaller brain tissue volumes observed.

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Effects of stress and glucocorticoids on hippocampal and ventricular volumes have been demonstrated in animal models and in humans with Cushing's syndrome,[79] and these are known to be at least partially reversible.[80,81] In patients with a FEP, cortisol levels have been found to be raised and to correlate inversely with hippocampal volumes.[82]

### *Duration of Untreated Psychosis*

If psychosis were in some way toxic to the brain, as Wyatt suggested,[7] then one would predict that there would be an association between the DUP and the magnitude of structural brain differences, particularly if the baseline MRI scans were obtained prior to treatment with antipsychotic medication. DUP has been found to be correlated with brain tissue volumes in some studies[8,83–86] but not in others.[44,45,87] Moreover, the direction of causality that underlies any association remains to be established because greater deficits in brain tissue volumes in those with greater DUP could reflect a more insidious onset of psychosis in those patients with greater longstanding deficits in brain tissue volumes.[84] Certainly, there has been no evidence to support the idea that longer DUP initiates a process of progressive and continuing brain change.

## Cognitive Studies

There is now an extensive literature characterizing the cognitive deficits of patients with schizophrenia. The deficits reported typically fall between 1 and 2 standard deviations below the mean of healthy controls.[88,89] Cognitive deficits in patients with schizophrenia are associated with inability to function in the community[90] and, as a result, have been the focus of specific clinical interventions.[91] Measures of cognitive functioning have been shown to correlate with measures of brain structure in patients with schizophrenia and healthy controls.[92–95] If progressive brain tissue loss occurs over the course of schizophrenia, one might predict that this would be accompanied by progressive deterioration in cognitive functioning. The latter does not appear to be the case.[96,97]

### *The Time Course of Cognitive Deficits*

When cognitive deficits are first present and whether there is some stage of the illness during which they progress have been areas of intensive study.[98,99] Cognitive deficits have been clearly demonstrated at the time of the FEP.[89,98,100] Cognition has been demonstrated to remain stable or improve[96,101–103] rather than deteriorate following a FEP. The improvement reported in some studies may reflect practice effects rather than real improvement.[104] Nevertheless, there is a consensus that this improvement plateaus following a FEP or FES, after which cognition does not worsen over time beyond what can be expected with normal aging.[97,99,102] Whether elderly patients with schizophrenia may experience a phase of cognitive decline that is of greater slope than that observed in otherwise healthy people[105,106] remains a possibility that requires further investigation.

Cognitive deficits are present in a proportion of children who later develop schizophrenia.[107–110] Meta-analyses have found that children who later develop schizophrenia are 0.4–0.5 standard deviations below the population average on intelligence quotient (IQ).[111,112] This is considerably smaller than the deficits described in patients at the time of their FES, and it raises the question of whether there is an active period prior to the first episode in which further decline occurs. Longitudinal data from a large US birth cohort have provided evidence that cognitive deficits are present when assessed at age 7 in children who have gone on to develop schizophrenia as adults, but were substantially larger on some measures when reassessed at age 35.[98] Using a follow-back design with patients presenting with a FES, Bilder et al[113] found that individuals who had a FES had deficits in school performance that were apparent in the first grade and increased substantially in magnitude when retested in the 12th grade. While these studies provide support for a relative decline in cognitive performance in individuals who subsequently develop schizophrenia compared with controls, it was not initially clear from these studies whether the increasing gap in cognitive performance reflects an absolute decline in those who go on to develop schizophrenia.

The Dunedin Multidisciplinary Health and Development Study provided the opportunity to investigate the trajectory of childhood cognitive functioning in individuals subsequently diagnosed with schizophrenia.[114] Cognitive testing was administered at age 7, 9, 11, and 13 years; results did not show any absolute decline in cognition but instead showed 2 interrelated problems, an early static deficit and then a developmental lag. Children destined to develop schizophrenia entered primary school struggling with verbal reasoning and then fell further behind their peers in attention and working memory as they got older. While it cannot be ruled out that the group differences may have been due to other comorbid disorders in the group of children who went on to develop schizophrenia as adults, the results do not suggest that this group experienced any absolute deterioration in cognitive functioning. This is consistent with the findings of Russell et al who demonstrated that individuals who had attended a child psychiatric clinic an average of 6 years before their FES had deficits in IQ when first seen but showed no additional deficit when followed up nearly 2 decades later.[115]

In accord with the above, individuals considered to be at clinical high risk for psychosis have been demonstrated to have significant cognitive deficits with those who eventually develop psychosis having greater deficits than those who do not.[116] However, studies by Keefe et al[117] and Becker et al[118] were not able to demonstrate any further deterioration in cognition in those at-risk subjects who

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subsequently transitioned to psychosis. The potential for such studies to identify significant deterioration in cognition has been limited by their small sample sizes and their identification of at-risk subjects late in the prodromal phase.

## Conclusions

The notion that schizophrenia is by nature a progressive deteriorating illness was central to the concept of dementia praecox as originally outlined by Kraepelin.[2] When structural brain abnormalities and cognitive deficits were demonstrated in the late 1970s these were taken as confirming that the illness was indeed a dementia of the young.[36]

It is true that people with schizophrenia as a group show modest decreases in certain brain tissue volumes at the time of the FEP but much research suggests that these, at least in part, reflect neurodevelopmental abnormalities.[119] In addition, MRI studies in the last decade have suggested a "progressive" component that can be detected after illness onset.[120] However, the pathological nature of these changes remains unclear.[121] There is no direct evidence for a toxic effect of psychosis on brain tissue, and emerging evidence from human and animal studies suggests that these changes are in part consequent upon antipsychotic medication.[57,58] Furthermore, there is evidence that cannabis, alcohol, smoking, stress-related hypercortisolemia, and low physical activity also contribute to the changes in cortical and ventricular volumes observed over the course of schizophrenia. Together with the effects of antipsychotic medications, these factors appear to account for the majority of the so-called "progressive" brain changes. Their importance lies in the fact that at least some may be reversible.

The findings from neuropsychology consistently contradict the idea of schizophrenia as a progressive dementia. Cognitive deficits are present at a young age in some children who later develop schizophrenia together with slower cognitive development in a range of domains, which results in further divergence in cognitive ability by the time psychosis develops. However, there is no evidence that lasting cognitive decline occurs during the transition to psychosis or following its onset.

Thus, the idea that schizophrenia is a progressive brain disease is not supported by the weight of longitudinal neuroimaging and cognitive studies, and it is not consistent with what is now known about the clinical course of schizophrenia. It is important for optimum clinical care that the idea that underlying schizophrenia there exists an intrinsically malignant process be reconsidered. It has contributed to an undue pessimism among mental health professionals and their consequent alienation from sufferers and their representatives, who increasingly advocate for the "recovery model."[14,122]

Furthermore, etiological and clinical research suggests that schizophrenia is not a discrete illness with a single cause or course, rather it appears to be a syndrome with multiple interacting causes, both genetic and environmental, and a heterogeneous outcome.[123] Thus we can better conceive individuals diagnosed with schizophrenia as having a vulnerability to psychotic reactions to a range of biological[124] and social risk factors.[125] The greater the cumulative load of risk factors before onset, and also incurred subsequently, the more likely the individual is to have a poor outcome. Some individuals, especially those with developmental impairment, start their journey through illness with considerable impairment of their ability to cope with further stressors and show deterioration in their social functioning; others may start with less vulnerability but are exposed to repeated social adversities that prevent their recovery.

Rejecting the concept of schizophrenia as a progressive brain disease does not negate the serious and disabling problems that many patients with schizophrenia experience. No doubt, many patients experience a decline in many spheres of functioning. Further research is certainly required to determine whether there is an active period of developmental or degenerative changes that take place prior to the syndrome being expressed and diagnosed. However, it is important for patients, family members, clinicians, and the public more broadly to recognize that the deterioration that many patients experience over the long-term is not an inevitable part of the illness course. Sadly, many people with schizophrenia do not have access to the skilled mental health services and social supports that are needed for them to achieve recovery and a good quality of life. It is crucial to appreciate that the terrible social sequelae of schizophrenia such as homelessness, poverty, unemployment, hospitalization, and imprisonment are not the inevitable outcomes of a progressive brain disease but highlight the challenges we face in providing the needed services and supports, and in engaging ill people in models of care which they are likely to accept and appreciate.

## Funding

This work was supported by the Morgan Firestone Chair in Psychiatry at McMaster University.

## Acknowledgments

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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