

# Why Are the Outcomes in Patients With Schizophrenia So Poor?

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Despite many advances in the treatment of schizophrenia over the past 50 years, the outcomes for many patients with schizophrenia remain poor. While the majority of patients with a first episode of schizophrenia may be able to achieve and maintain a remission of symptoms, only 1 in 7 patients are likely to meet criteria for recovery. These findings could be easily reconciled if schizophrenia could be established to be a progressive brain disease. Results from longitudinal studies of brain structure, cognitive functioning, and clinical outcomes, however, do not support this view. The poor outcomes so commonly observed are likely best explained by poor access to treatment, poor engagement in ongoing care, poor treatment response, and poor adherence together with the cumulative negative impact of substance abuse, comorbid psychiatric disorders, cognitive deficits, and multiple social determinants of health.

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Over the past half century, the treatment of schizophrenia has been advanced by the introduction of antipsychotic medication, innovative models of community care, and most recently by the advent of early intervention initiatives. Despite these important developments, the outcomes for many patients with schizophrenia remain poor. Studies of patients receiving treatment for a first episode of schizophrenia have been consistent in demonstrating that a substantial majority of patients will achieve a remission of psychotic symptoms within the first year of treatment.<sup>1</sup> This contrasts with the very low rates of recovery found in individuals treated for a first episode of schizophrenia; when *recovery* is defined as social and clinical recovery lasting for at least 2 years together with symptoms that are no greater than mild, the percentage of patients found to meet these criteria in a recent meta-analysis of outcome studies was 13.5%.<sup>2</sup> Despite the presence of strong initial treatment outcomes, the long-term prognosis appears to be much less encouraging.

## IS SCHIZOPHRENIA A PROGRESSIVE OR A STABLE BRAIN DISEASE?

The findings of positive short-term outcomes and poor long-term outcomes could be easily reconciled by accepting that schizophrenia is a brain disease that is progressive in nature. It should then be possible to demonstrate that the brain abnormalities and cognitive deficits found in schizophrenia progress over the course of the illness and that clinical outcomes also worsen over time. This does not appear to be the case.<sup>1</sup>

Cognitive functioning in patients with schizophrenia is known to be associated with both structural brain measures<sup>3</sup> and measures of community functioning.<sup>4</sup> As a result, examining the course of cognitive deficits is of particular interest. Several studies have demonstrated consistent

cognitive differences in schizophrenia patients at the time of the first episode.<sup>5,6</sup> However, most of these differences were modest, with differences being smaller than those reported in more chronically ill patients. Furthermore, these deficits appeared to stay stable or improve across time after the first episode rather than showing deterioration.<sup>7–9</sup>

The structural brain abnormalities reported in patients with schizophrenia have also been described in patients experiencing their first episode of psychosis.<sup>1</sup> The magnitude of the deficits in gray matter volumes and increases in cerebrospinal fluid volumes have also been smaller than what has been observed in more chronically ill patients. These observations would seem to reinforce the likelihood that a progressive process is taking place. However, it has been more challenging to establish that the structural brain changes associated with schizophrenia worsen over time. Longitudinal magnetic resonance imaging (MRI) studies of brain volumes following a first episode of psychosis have been inconsistent in demonstrating loss of tissue volumes over time.<sup>10–13</sup> Some larger studies have substantiated reductions in brain tissue volumes in the years following a first episode of psychosis.<sup>12,13</sup> However, it has become increasingly clear from human<sup>14,15</sup> and animal studies<sup>16,17</sup> that exposure to antipsychotic medications is associated with changes on MRI. Other studies suggest that alcohol and cannabis use, smoking, and stress may also contribute to the increasing differences between patients and controls over time.<sup>1</sup> Effects of alcohol, drugs, and medications may also be reversible over time if their use is discontinued. As a result, it remains unclear whether the brain changes reported over time in patients with schizophrenia reflect the underlying pathophysiology of schizophrenia or potentially reversible effects of other non-illness-related factors.

## DO OUTCOMES FOR INDIVIDUAL PATIENTS WORSEN OVER TIME?

Given that the structural brain and cognitive deficits do not appear to worsen over the longer term, it is worth reexamining whether longitudinal clinical studies provide

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support for a progressive deteriorating course. A number of studies have reported that 70% to 80% of patients will achieve a remission of symptoms in their first year of treatment.<sup>18–20</sup> The question that arises from these results is why people with schizophrenia appear to do poorly in the long run if they are able to do quite well in the first year of follow-up. One important possibility is that relapses might explain the discrepancies found between short-term and long-term outcomes. In one of the first longitudinal studies of relapse rates in first-episode schizophrenia, Robinson et al<sup>21</sup> reported that 82% of patients who had achieved a remission went on to experience a relapse in the first 5 years of their illness course. Those who discontinued antipsychotic medications were 5 times more likely to relapse than those who stayed on medication; the absolute rate of relapse for those who were adherent with medication could not be determined from this study.

To investigate the risk of relapse off antipsychotic medication, my colleagues and I<sup>22</sup> carried out a systematic review of studies involving 209 remitted patients who stayed on their medication regimens for at least 6 months following a first episode of nonaffective psychosis. Studies were included if patients were followed for at least 6 months after discontinuing their medications. Results indicated that 77% of patients who discontinued medication relapsed in the first 12 months off medication compared to only 3% of those who continued maintenance doses of medication. Relapse rates approached 95% in the first 2 years for patients who had discontinued medications. These data strongly suggest that remitted first-episode schizophrenic patients who discontinue medications have an extraordinarily high rate of relapse in contrast with the very low rate of relapse found in those who remained adherent to medications. Relapse, while extremely common, should not be understood as an inevitable part of the course of schizophrenia but rather as a direct reflection of poor adherence to treatment.

If relapses can be prevented with maintenance antipsychotic medication in the early years following a first episode of psychosis, it is important to know just how long patients may be able to remain in remission. Girgis et al<sup>23</sup> carried out a longitudinal study of 160 treatment-naive individuals with a first episode of schizophrenia or schizophreniform disorder in Beijing, China, who were randomized to treatment with chlorpromazine or clozapine for up to 2 years. Patients were then followed for up to a total of 9 years to determine whether the remission status of the 2 groups differed over the follow-up period. The percentage of patients who were considered to be in remission remained stable at 78% throughout the 9-year follow-up period and did not differ in those treated with clozapine versus chlorpromazine. This study suggests that those patients who are able to achieve a remission early in their illness are likely to be able to sustain their remitted status over the longer term. This finding is consistent with the findings of Menezes et al who reported that the percentage of patients considered to have good outcomes and poor outcomes remains stable over time<sup>24</sup>; this stability would not be expected for a progressive disease.

## WHY DOES THE COURSE OF ILLNESS SEEM TO BE PROGRESSIVE AND THE OUTCOME SO POOR?

While sustained remission should be possible for most people with schizophrenia, this is not what is observed in specialized schizophrenia treatment services where poor outcomes seem to be the rule rather than the exception. Such specialized services, however, are much more likely to see individuals who have been ill for many years and have more severe and disabling forms of illness. Cohen and Cohen<sup>25</sup> identified this phenomenon, referred to as the *clinician's illusion*, that describes the misconception of practitioners who work in treatment centers (eg, emergency rooms, tertiary care clinics, inpatient units) and assume that the patients presenting in those settings are representative of the total population of people with a given illness. Patients who are more severely ill, less responsive to treatment, and have longer durations of illness are likely to be overrepresented in such treatment settings.

The impression that many clinicians have that outcomes from schizophrenia are very poor is also due in part to the concept referred to as *Berkson's fallacy*.<sup>25</sup> This phenomenon describes the situation in which patients who have other concurrent disabilities that are not causally connected to the condition being investigated (eg, schizophrenia) are more likely both to enter the treatment system and to have poor outcomes. For example, it is very common to admit patients with schizophrenia who have significant and sometimes multiple concurrent problems including substance use disorders, low intellectual functioning, depression, anxiety disorders, personality disorders, obsessive compulsive disorder, posttraumatic stress disorder, eating disorders, and a history of head injury. When such patients fare poorly in the community, it is often assumed that the schizophrenia explains their poor functioning. Individuals with any of these disorders or with combinations of them may have very poor outcomes irrespective of whether they have schizophrenia.

## WHAT FACTORS ACCOUNT FOR POOR OUTCOMES?

### Involvement and Engagement in Treatment

It is estimated that only 25% to 40% of individuals with schizophrenia receive stable ongoing treatment.<sup>26,27</sup> This quite likely reflects both the lack of adequate services and the challenges in engaging patients in ongoing treatment.<sup>28</sup>

### Poor Treatment Response

At the outset, it should be noted that 20% to 30% of patients do not respond well to first-line treatments and would not meet criteria for symptom remission.<sup>29</sup> These individuals do poorly in the short run and very likely make up a substantial percentage of the 25% of patients with schizophrenia who have been found to have poor outcomes in the longer term as well.<sup>24</sup> Of those who are poor responders, it would be expected that 30% to 60% would have a more substantial

response to clozapine.<sup>29</sup> This would still leave as many as 20% of all patients who do not respond well to antipsychotic medications.

### Poor Adherence

Among those who respond well to antipsychotic medication, nonadherence to medications results in relapse and rehospitalization. Rates of nonadherence for people with schizophrenia have been estimated at 50%.<sup>30</sup> Achieving social and vocational goals may be limited by recurrent and extended periods of illness.

### Cognitive Deficits

There has been much interest in the contribution of cognitive deficits to poor functioning in people with schizophrenia.<sup>4</sup> Whether cognitive remediation approaches may be able to address this problem is currently being intensively investigated.<sup>31</sup>

### Substance Use Disorders

The 12-month prevalence of substance use disorders in the United States is estimated at 3.8%.<sup>32</sup> Individuals with schizophrenia are believed to be at comparable risk to the general population for alcohol use disorders and at somewhat higher risk for problems with cannabis.<sup>33</sup> The poor outcomes experienced by many people with schizophrenia are likely due in part to concurrent substance use.

### Concurrent Mental Illness

Schizophrenia does not provide any protection from experiencing other mental disorders. On the contrary, the prevalence of other common mental disorders is believed to be high in people with schizophrenia, including depression, obsessive-compulsive disorder, anxiety disorders, and posttraumatic stress disorder.<sup>34</sup>

### Preexisting Developmental Problems

Significant deficits in intellectual and social functioning are known to occur in the premorbid phase of the illness dating back to early childhood.<sup>35</sup> While absolute scores on cognitive testing are not thought to decrease over time in patients with schizophrenia, the magnitude of the deficits relative to matched controls most likely increases over time as early difficulties may limit the successful acquisition of more advanced academic and social skills.

### Loss of Functioning Prior to Diagnosis

Once the symptoms of schizophrenia have remitted, it may be disappointing that the person is not able to easily return to normal functioning. It is clear, however, that most patients with schizophrenia experience ongoing deterioration in functioning for many years before the onset of psychotic symptoms. In the seminal work by Häfner et al,<sup>36,37</sup> deterioration in functioning was observed to take place an average of 5 years before the first experience of psychotic symptoms. Initiation of treatment is often delayed months and years from the initial development of psychotic

symptoms. That disability persists after the psychotic symptoms are largely resolved should not be surprising.

### Medication Effects

Many patients experience medication side effects as being disabling. These may include sedation, subjective cognitive dulling, weight gain, akathisia, parkinsonism, and tardive dyskinesia among others. Higher levels of dopamine D<sub>2</sub> receptor occupancy by antipsychotic medication are associated not only with improvement of psychotic symptoms, but also, paradoxically, with lower levels of subjective well-being.<sup>38,39</sup> Recent reports have suggested that patients who have discontinued antipsychotic medications are more likely to become employed; this has raised concerns that the effects of antipsychotic medication may interfere with vocational functioning.<sup>40,41</sup> While these studies are limited by their nonrandomized designs, it is not possible to rule out the possibility that, for some patients, medication effects interfere with achieving some functional outcomes.

### Social Determinants of Health

Many individuals with schizophrenia come from families that have been disadvantaged by poverty. Developing schizophrenia and the associated disability frequently interfere with the ability of patients to work. Living in impoverished communities, and frequently in very poor housing conditions, further limits opportunities for recovery. In some countries, income support is available for those with mental disabilities. This support is often critically important in allowing those with schizophrenia to avoid homelessness and to have access to health care services, safer housing, improved nutrition, and support for their transportation needs. There continues to be much debate about when in the course of schizophrenia disability income should be offered, with some experts expressing caution that the provision of income support for psychiatric disability too early in the course of the illness may interfere with the successful achievement of competitive employment.<sup>42</sup>

In order for an individual with remitted schizophrenia to achieve recovery, many conditions must be met. The availability of appropriate psychiatric care in the community and the necessary support for achieving educational, vocational, and social goals are critical as are access to optimal medications, decent and safe housing, income support, and family support. This support can contribute substantially to sustaining treatment engagement; their absence increases the likelihood that relapse will recur and that outcomes will remain poor.

### Accommodation to Disability and Shifting Expectations

Research into the outcomes in patients with schizophrenia has recently focused on how to best facilitate the return to a normal level of functioning, including the achievement of competitive employment and independent living. While these goals are often shared by mental health professionals, patients, and their families, it is not clear that all involved

prioritize them in the same way. For young people who experience schizophrenia, the great challenge that many face is how to develop a future life that is satisfying and meaningful given their ongoing need to manage a complex illness. Achieving competitive employment together with financial and social independence may not be their most important priorities. Davidson and colleagues<sup>43</sup> have described the distinction between the “rehabilitation model” of recovery versus the “medical model.” The “rehabilitation model” emphasizes having meaningful relationships with friends and family, developing satisfying vocational and recreational activities, and experiencing self-respect and hope. The “medical model,” on the other hand, emphasizes symptom control and the achievement of competitive employment and independence. That the outcomes most often measured by psychiatric researchers are not being achieved may in part reflect a disconnection between those outcomes that are important to patients and those that mental health professionals value most.

### CONCLUSIONS

Despite high rates of symptomatic remission following a first episode of psychosis, achieving long-term functional and symptomatic recovery is an elusive goal for the large majority of individuals with schizophrenia. Evidence to date does not support the view that these disappointing outcomes can be explained by progressive deterioration in brain structures or cognitive functioning. Nor do relapses appear to be an inevitable feature of the long-term course of treated schizophrenia. The cumulative impact of poor access to treatment, poor engagement in ongoing care, poor treatment response, and poor adherence most likely account for the poor outcomes so frequently observed. Substance abuse, comorbid psychiatric disorders, cognitive deficits, and the negative impact of multiple social determinants of health further limit the achievement of recovery for most people with schizophrenia. Future clinical and research efforts will need to be devoted to developing approaches that will address the full range of determinants of outcome if recovery from schizophrenia is to be achieved.

**Drug names:** clozapine (Clozaril, FazaClo, and others).

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