

# Predictors of long-term outcome in schizophrenia

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## Purpose of review

Further clarification of factors predicting the outcome in schizophrenia is needed. The present review examines recent research into some of these predictors, focusing on insight, duration of untreated psychosis, cognition and early treatment response. It also addresses the need for standard outcome measures.

## Recent findings

There is good evidence that poor insight predicts poor outcome, although perhaps not simply as a consequence of poor compliance. Further support is provided for a link between duration of untreated psychosis and long-term outcome. The relationship between cognition and outcome is complex, with specific cognitive deficits apparently predicting particular outcome domains. Early treatment response is closely related to long-term outcome. Outcome studies may be flawed by sample selection bias, and a lack of standardized outcome measures.

## Summary

Several predictors are potentially modifiable, indicating that they should be targets for therapeutic intervention. More carefully designed studies are needed. Recently proposed criteria for remission are helpful, and should facilitate cross-sample comparisons.

## Keywords

outcome, predictors, psychosis, schizophrenia

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## Introduction

Attempts have been made to identify predictors of treatment outcome in schizophrenia since the introduction of effective treatment more than 50 years ago. Identification of specific predictors of outcome would have considerable benefits in clinical practice. Early identification of poor-responders would allow timely adjustments to management programs. Additionally, as some predictors are modifiable, they may provide specific treatment targets. Since predictors are synonymous with risk and resilience factors, they might also provide a better understanding of the underlying pathophysiology of the illness. Until recently, factors influencing treatment outcome in schizophrenia were poorly understood, and results of studies were inconclusive and sometimes conflicting. Recent work, however, holds more promise due to improved study methodologies and refined outcome definitions. This paper looks at some of the outcome predictors that have received particular attention in the literature over the past 2 years.

## Insight as a predictor of outcome

While the determinants and psychopathological status of insight may be unclear, its clinical relevance in schizo-

phrenia is irrefutable. Poor insight is common in the illness, and is associated with poor compliance and poor outcome [1]. Studies have shown that between 50 and 80% of all patients with schizophrenia display impaired insight to the extent that they do not believe that they have an illness or disorder [2\*] (although insight was found to be good in a majority of first-episode patients [3\*]). Its importance as an outcome predictor is underpinned by its potential to be modified by both pharmacological and psychotherapeutic intervention [4\*\*]. In an important study, Drake *et al.* [5\*\*] investigated a first-episode cohort ( $n = 257$ ) followed up for 18 months. The effect of insight (defined according to a validated scale) on outcome (measured as time to relapse and readmission as well as level of symptoms and social function) was assessed. Poor insight significantly predicted relapse and rehospitalization. The aspect of insight that best related to poor outcome was poor recognition of symptoms. The authors went on to explore possible ways in which poor insight could contribute to poor outcome. The most obvious explanation would be that poor insight results in poor medication adherence, with ensuing relapse or incomplete treatment response. Although adherence was not directly assessed in this study, however, certain of their findings indicate that it might not be the most

important factor, insofar as patient attitudes towards medication were not found to be significantly associated with insight.

A systematic review of 88 studies [6\*\*] assessing insight and its impact on outcome reported that those investigating associations between insight and long-term outcome in schizophrenia have provided inconsistent results. While most studies support an association between insight and medication adherence during the acute treatment phase, the long-term association remains unclear. No link between poor insight, poor treatment adherence and poor outcome has been established. The authors also highlight an interesting and apparently paradoxical finding that better insight in schizophrenia is associated with higher levels of depression and hopelessness. They emphasize, however, that the causal direction of this relationship is unclear and that results are inconclusive [6\*\*].

A 2-year prospective study of 254 patients recovering from a first-episode of schizophrenia in which predictors of antipsychotic medication adherence were investigated found that subjects who do not believe strongly in the need for, or benefits of, treatment are more likely to become medication nonadherent. Changing these beliefs regarding treatment and the benefits of antipsychotic medication could improve the chances of long-term medication adherence [7\*\*].

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### More on duration of untreated psychosis and outcome

A plethora of studies have investigated the relationship between the duration of untreated psychosis (DUP) and outcome in schizophrenia. Taken together, there is firm evidence for an association between DUP and outcome, as concluded in two previous systematic reviews [8,9]. Again, DUP is a predictor of great interest because of its potential to be modified, raising the possibility of improving outcomes by shortening DUP. This finding has been an important driver of the development of early intervention programs. A study in Norway and Denmark involving 301 patients with a first episode of psychosis followed up over 1 year found that a shorter DUP was predictive of shorter time to remission, stable remission, fewer positive symptoms and better social functioning [10\*]. In a study conducted in Turkey predictors of 1-year outcome were investigated in a sample of 79 patients with a first episode of schizophrenia. Well defined outcome measures included relapse, rehospitalization, global level of functioning, employment status and severity of symptoms. DUP did not differ between patients who relapsed and those who did not, although DUP was longer in patients who had two relapses. It was also found that the period between discharge and rehospitalization

was shorter in those patients who had a longer DUP. Treatment compliance and premorbid adjustment were important predictors of relapse [11\*].

A study conducted in 81 patients with first-episode psychosis reported that longer DUP is associated with greater temporal gray matter reductions. These changes may represent a progressive morbid process prior to treatment initiation: evidence for psychosis being 'toxic'. The authors offer as an alternative explanation, however, the possibility that the gray matter changes may be associated with a more insidious onset of illness, resulting in later identification and treatment [12\*].

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### Cognitive performance as a predictor of outcome

The value of cognitive function as a predictor of outcome is not clear, and recent studies have done little to clarify the situation. Part of the controversy may be explained by findings suggesting a nonuniform rate of cognitive decline preceding first hospitalization. This was proposed by the authors of a study of 100 patients followed up for 10 years, in which it was found that functional outcome was associated with estimated premorbid intelligence quotient (IQ) and IQ at 10-year follow-up, but not with IQ assessed at first hospitalization [13\*].

An ongoing epidemiological study in Sweden, involving 211 patients, reported marked differences in cognitive ability between patients who were in remission and those who were not. This was a cross-sectional study, however, and the ability of pretreatment cognitive function to predict outcome was not assessed [14\*]. In a post-hoc analysis of 184 patients with chronic schizophrenia treated with ziprasidone over 6 months, baseline cognitive performance did not significantly predict remission status at endpoint [15\*]. In a well designed study involving 115 patients with recent-onset schizophrenia, Holthausen *et al.* [16\*\*] investigated whether baseline cognitive performance could predict outcome at 2-year follow-up. The authors correctly pointed out that, despite the fact that prediction of outcome in schizophrenia has most relevance at the time of initiation of first treatment, only a few of the previous prediction studies were conducted in first-episode patient cohorts. In this study, outcome was assessed in three different domains, namely psychopathology, social and occupational functioning, and need for care. Cognitive performance at baseline did not predict the number of relapses, activities of daily living, nor interpersonal functioning. The predictive value of cognition with regard to clinical outcome was statistically significant and cognitive performance most strongly predicted work performance (competitive employment status and vocational functioning).

Whether global cognitive impairment or discrete domains of impairment influence functional outcomes was investigated in 222 patients with schizophrenia by investigating predictive relationships between cognitive domains on the one hand, and functional competence, social competence, symptoms, and real-world behavior (work skills, interpersonal relationships, and community activities) on the other. While all cognitive domains predicted functional competence, only processing speed and attention/working memory predicted social competence. The attention/working memory domain was related to work skills and executive functions, and had a direct effect on interpersonal behaviors. These findings suggest that changes in specific cognitive skills might improve specific outcomes, rather than promoting global functional improvement [17\*\*].

In a separate study [18\*], the same group investigated the relationship between performance on neuropsychological testing and adaptive life skills in the real world. They examined cross-sectional data from a sample of 78 older (50–85 years) patients with schizophrenia. Supportive of previous research, they found neuropsychological performance predictive of functional capacity, which in turn predicted various domains of real-world functioning. When functional capacity was taken into account, however, neuropsychological scores only occasionally provided further predictive power in determining real-world outcome [18\*].

Taken together, these studies suggest that, while better cognitive performance is associated with a more favourable outcome, the predictive value of pretreatment cognitive function is more complex. Rather than global cognitive function being related to all aspects of outcome, baseline impairments in discrete cognitive domains may have predictive value for specific aspects of outcome.

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### Eliminating potential methodological pitfalls in outcome research

Interpreting and comparing findings in longitudinal outcome studies is hampered by the huge amount of variation regarding aspects such as sample selection and collection, assessment methods used, duration of study period and outcome measures employed. A meta-analysis of 37 longitudinal outcome studies of first-episode nonaffective psychosis highlighted several potential pitfalls. The authors failed to confirm previously reported variables such as DUP and age at onset as significant outcome predictors. Instead, variables found to be associated with a more favourable outcome were combined pharmacotherapeutic and psychosocial intervention, a developing country of origin, and sample populations with a diagnosis of schizophrenia only. The authors also found, however, that a lack of epidemiologic representation of the sample

was associated with favourable outcome, and studies with a prospective design were associated with poorer outcomes. These findings suggest that sample selection bias may significantly distort the results of outcome studies. Comparison of the studies was also hampered by substantial heterogeneity in definitions and study methodologies, leading the authors to appeal for a globally used definition of outcome for future research [19\*\*].

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### Remission as a standard measure of outcome

It is not surprising therefore that a definition of remission proposed by a Remission in Schizophrenia Working Group (RSWG) [20] has attracted considerable attention. In this definition remission is determined according to a threshold of symptom severity (mild or less) for selected rating scale items representing the ‘core features’ of the illness. Eight items on the *Positive and Negative Syndrome Scale* (PANSS) have been selected for this purpose. An additional requirement is that these criteria must be met for a minimum duration of 6 months. By utilizing a threshold of severity rather than a reduction from baseline score, comparisons across samples may be easier. Several studies have used this definition of remission, some in exploring predictors of outcome.

Our own group applied these criteria to two separate samples of patients with first-episode schizophrenia, and investigated possible predictors of remission. The first study investigated 57 subjects with first-episode psychosis who were treated with haloperidol according to a fixed protocol over 2 years. Forty percent of the subjects achieved RSWG criteria for remission. The predictive ability of various demographic, baseline clinical and early treatment response variables was examined by subjecting the data to discriminant analysis. The following significant predictors were identified: neurological soft signs, DUP, marital status, educational status, early treatment response (at 6 weeks) and high levels of excitement/hostility. Early treatment response was the strongest predictor. The combined model of these variables was able to correctly predict 89% of patients achieving remission and 86% of patients not achieving remission. These results suggest that a combination of baseline clinical and early treatment variables may be able to accurately predict outcome [21\*\*].

The other study comprised a post-hoc analysis of data from 462 patients with a first episode of psychosis who participated in a multinational, randomized clinical trial comparing oral risperidone and haloperidol over 2–4 years. RSWG remission criteria were met at some stage in the study by 23.6% of subjects. The two strongest predictors of remission were shorter DUP and greater treatment response at 6 weeks. A Cox regression model found that the significant effect for DUP was

independent of premorbid adjustment and baseline symptom severity. Another Cox regression equation found that early clinical response (defined as  $\geq 20\%$  reduction on PANSS at 6 weeks) could accurately predict remission [22\*\*].

### The relationship between early treatment response and later outcome

Compelling evidence now exists to challenge the belief that the onset of action of antipsychotics is delayed [23,24]. These findings of an early onset of antipsychotic action have rekindled interest in the possibility that the degree of response during the first weeks of treatment might predict which patients are likely to respond later in the course of treatment. Indeed, others have found a very strong association between early and later response to antipsychotic treatment [25,26\*]. These were short-term studies, however, investigating the value of early symptom changes 1 and 2 weeks after initiation of treatment in predicting nonresponse at 4 weeks. Of greater relevance would be to investigate the value of early response to treatment in predicting longer term outcome. The two studies mentioned above investigating predictors of remission in first-episode cohorts did just that, and found a strong association between treatment response at 6 weeks and later remission status [21\*\*,22\*\*].

### Other predictors

Several other studies investigated various other predictors of long-term outcome in schizophrenia. In a sample taken from a national register in Israel 129 schizophrenia patients with a poor treatment response were compared with a matched group of 29 patients who showed adequate response. Poor premorbid social functioning and individual autonomy predicted poor outcome, while intellectual functioning did not [27\*]. In a longitudinal study of 208 patients with schizophrenia, initial level of functioning, baseline symptoms, sex, educational status and duration of illness were found to be important predictors of long-term (2–8 years) functional outcome, with level of functioning at intake being the most reliable predictor of outcome [28\*\*]. Importantly, previously reported predictors of better premorbid adjustment, shorter DUP, better insight and lower baseline levels of symptoms were found to significantly predict remission in 319 patients with psychosis and comorbid substance abuse [29\*]. Lack of friends in childhood, high social class of father, poorer school performance and early age of onset of illness predicted poor outcome in a prospective study of patients derived from the Northern Finland 1966 Birth Cohort [30\*]. A 10-year follow-up study [31\*] of 3470 patients with schizophrenia found male sex, drug abuse, previous suicide attempts

and shorter duration of illness to be risk factors for suicide.

### Conclusion

Although research into outcome predictors in schizophrenia has yielded conflicting results, several consistent findings are now emerging. For example, insight, early treatment response and DUP appear to be particularly important predictors of long-term outcome. Because of the relative ease of assessing these predictors, they may be useful in the early identification of poor responders in clinical practice. Future studies should focus on eliminating methodological pitfalls and utilize standardized outcome measures.

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### References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 215).

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- 2 Dam J. Insight in schizophrenia: a review. *Nord J Psychiatry* 2006; 60:114–120.  
This paper reviews aspects of insight, with particular emphasis on phenomenology and assessment.
- 3 Saeedi H, Addington J, Addington D. The association of insight with psychotic symptoms, depression, and cognition in early psychosis: a 3-year follow-up. *Schizophr Res* 2007; 89:123–128.  
A good study assessing clinical factors associated with insight was limited by the use of a unidimensional measure of insight.
- 4 Buckley PF, Wirshing DA, Bhushan P, *et al.* Lack of insight in schizophrenia: poor insight on treatment adherence. *CNS Drugs* 2007; 21:129–141.  
This is an excellent review of insight in schizophrenia, and its impact on treatment adherence.
- 5 Drake RJ, Dunn G, Tarrier N, Bentall RP, *et al.* Insight as a predictor of the outcome of first-episode nonaffective psychosis in a prospective cohort study in England. *J Clin Psychiatry* 2007; 68:81–86.  
A very good study that looked at the predictive value of insight assessed by a standardized rating scale in a first-episode sample.
- 6 Lincoln TM, Lullmann E, Rief W. Correlates and long-term consequences of poor insight in patients with schizophrenia. A systematic review. *Schizophr Bull* 2007; 33:1324–1342.  
This is an excellent and balanced systematic review assessing the relationship between insight and outcome in schizophrenia.
- 7 Perkins DO, Johnson JL, Hamer RM, *et al.* Predictors of antipsychotic medication adherence in patients recovering from a first psychotic episode. *Schizophr Res* 2006; 83:53–63.  
A long-term study in a large sample of first-episode patients looked at the relationship between patient beliefs regarding medication and medication adherence.

- 8** Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry* 2005; 162:1785–1804.
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- 11** Uocok A, Polat A, Cakir S, Genc A. One year outcome in first episode schizophrenia predictors of relapse. *Eur Arch Psychiatry Clin Neurosci* 2006; 256:37–43.  
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This was a long-term (10-year) follow-up study. It identified pretreatment cognitive changes that may confound studies looking at association between cognition and outcome.
- 14** Helldin L, Kane JM, Karilampi U, *et al.* Remission and cognitive ability in a cohort of patients with schizophrenia. *J Psychiatr Res* 2006; 40:738–745.  
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- 15** Buckley PF, Harvey PD, Bowie CR, Loebel A. The relationship between symptomatic remission and neuropsychological improvement in schizophrenia patients switched to treatment with ziprasidone. *Schizophr Res* 2007; 94:99–106.  
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This was a cross-sectional study.
- 19** Menezes NM, Arenovich T, Zipursky RB. A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychol Med* 2006; 36:1349–1362.  
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- 25** Correll CU, Malhotra AK, Kaushik S, *et al.* Early prediction of antipsychotic response in schizophrenia. *Am J Psychiatry* 2003; 160:2063–2065.
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- 27** Caspi A, Reichenberg A, Weiser M, *et al.* Premorbid behavioral and intellectual functioning in schizophrenia patients with poor response to treatment with antipsychotic drugs. *Schizophr Res* 2007; 94:45–49.  
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- 30** Lauronen E, Miettunen J, Veijola J, *et al.* Outcome and its predictors in schizophrenia within the Northern Finland 1966 Birth Cohort. *Eur Psychiatry* 2007; 22:129–136.  
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- 31** Limosin F, Loze JY, Philippe A, *et al.* Ten-year prospective follow-up study of the mortality by suicide in schizophrenic patients. *Schizophr Res* 2007; 94:23–28.  
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