Review: longer duration of untreated psychosis is associated with worse outcome in people with first episode psychosis

Marshall M, Lewis S, Lockwood A, *et al.* Association between duration of untreated psychosis and in cohorts of first-episode outcome patients: a systematic review. *Arch Gen Psychiatry* 2005;**62**:975–83.

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Q Does duration of untreated psychosis affect outcome for people with first episode psychosis?

METHODS

Design: Systematic review with meta-analysis.

Data sources: CINAHL (January 1982 to May 2004), EMBASE (January 1980 to May 2004), MEDLINE (January 1966 to May 2004), PsychLIT (January 1967 to May 2004), and the Cochrane Schizophrenia Register (2004) plus hand searches of reference lists and reviews.

Study selection and analysis: Eligible studies were cohort studies of adults (16–60 years old) with first episode psychosis that assessed the association between duration of untreated psychosis and prognosis. Exclusions: follow up <50%; only assessing cognitive functioning or brain structure outcomes; not reporting duration of psychosis. Fisher Z transformation was used in calculating correlation coefficients (*r*) for all outcomes.

Outcomes: Primary outcomes: overall symptoms (positive, negative, and neurotic symptoms combined); depression/anxiety; negative and positive symptoms; overall functioning (combination of function scores from measures such as the Global Assessment Scale and Global Assessment of Functioning scale); remission.

MAIN RESULTS

Twenty six studies met inclusion criteria (4490 people; mean age 28 years; 61% male; mean duration of untreated psychosis 124 weeks). Twenty studies involved people with schizophrenia or schizophrenia-like disorders. A longer period of untreated first episode psychosis was not associated with worse overall symptoms or function at presentation, but was associated with worse depression/anxiety (see <http://www.ebmentalhealth.com/supplemental> for table). At 6 and 12 months, a longer period of untreated psychosis was associated with more severe overall symptoms, depression/anxiety, negative and positive symptoms, and worse overall function. People with longer duration of untreated psychosis were less likely to experience remission at 6, 12, or 24 months (OR for no remission at 6 months: 3.55, 95% CI 2.03 to 6.18; at 12 months: OR 2.75, 95% CI 1.14 to 6.64; at 24 months: OR 2.72, 95% CI 1.20 to 6.17).

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CONCLUSIONS

Longer duration of untreated psychosis is associated with worse symptoms and functioning, and less chance of remission in people with first episode psychosis.

Commentary

Historically the prognosis of schizophrenia has been attributed to the unalterable influence of genetics and environment on early brain development.¹ Antipsychotic treatment is proposed to address symptoms but not to alter the clinical course.² Over a decade's worth of longitudinal first episode schizophrenia cohort studies challenge this clinical pessimism, and "doomed from the womb" has been replaced with a belief that earlier treatment with antipsychotics may alter outcomes. Numerous specialty programmes now provide early identification and treatment services, although the controversy regarding the benefits of early intervention remains.

The meta-analysis by Marshall *et al* found a consistent but modest relationship between longer duration of untreated psychosis (DUP) and worse symptomatic and functional outcomes at 6–24 month follow up, but no relationship with baseline status. The relationship between DUP and outcome was not explained by treatment delays for individuals with a poor prognostic illness as indicated by poor premorbid adjustment. Another recent meta-analysis that evaluated DUP and clinical and functional outcomes using a somewhat different meta-analytic strategy came to very similar conclusions, except finding that longer DUP was associated with more severe negative symptoms at baseline.³

The mechanism by which early intervention may impact prognosis is not known, although these findings lend further support to the notion that psychosis is symptomatic of a potentially treatable neurodegenerative process. Thus, in addition to alleviating the obvious adverse impact of emerging psychosis on normal psychosocial and vocational development, early intervention may also impact the underlying disease process. While acknowledging the need for further research, this study lends strong support to the development of early intervention programmes.

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1 Weinberger DR, McClure RK. Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry: what is happening in the schizophrenic brain? *Arch Gen Psychiatry* 2002;**59**:553–8.

2 Hegarty JD, Baldessarini RJ, Tohen M, *et al.* One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Am J Psychiatry* 1994;**151**:1409–16.

3 Perkins DO, Gu H, Boteva K, *et al.* Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry* 2005;**162**:1785–804.