EBMH Notebook

Schizophrenia

The *EBMH* Notebook summarises key messages about schizophrenia, sourced from: *Clin Evid Concise* 2003;**10**: 235–7. For this review, *Clinical Evidence Concise* searched and appraised material published until December 2002.

DEFINITION

Schizophrenia is characterised by the positive symptoms of auditory hallucinations, delusions, and thought disorder, and by the negative symptoms of demotivation, self neglect, and reduced emotion.[1] People are defined as being resistant to standard antipsychotic drugs if, over the preceding 5 years, they have not had a clinically important improvement in symptoms after 2–3 regimens of treatment with standard antipsychotic drugs for at least 6 weeks (from at least 2 classes at doses equivalent to or greater than 1000 mg/day chlorpromazine) and they have had no period of good functioning.[2,3] Approximately 30% (10–45%) of people with schizophrenia meet these criteria.[3]

INCIDENCE/PREVALENCE

Onset of symptoms typically occurs in early adult life (average age 25 years) and is earlier in men than women.[4,5] Prevalence worldwide is 2–4/1000. One in 100 people will develop schizophrenia in their lifetime.

AETIOLOGY/RISK FACTORS

Risk factors include a family history (although no major genes have been identified); obstetric complications; developmental difficulties; central nervous system infections in childhood; cannabis use; and acute life events.[4] The precise contributions of these factors and ways in which they may interact are unclear.

PROGNOSIS

About three quarters of people suffer recurrent relapse and continued disability, although the proportion of people who improved significantly increased after the mid 1950s (mean 48.5% from 1956–1985 *v* 35.4% from 1895–1956).[6] Outcome may be worse in people with insidious onset and delayed initial treatment, social isolation, or a strong family history; in people living in industrialised countries; in men; and in people who misuse drugs.[5] Drug treatment is generally successful in treating positive symptoms, but up to a third of people derive little benefit and negative symptoms are notoriously difficult to treat. About half of people with schizophrenia do not adhere to treatment in the short term. The figure is even higher in the longer term.[7]

WHAT ARE THE EFFECTS OF TREATMENTS?

Most evidence is from systematic reviews of RCTs that report disparate outcomes. There is a need for larger RCTs, over longer periods, with well designed end points, including standardised, validated symptom scales. No intervention has been found to consistently reduce negative symptoms.

Beneficial

Continuation of antipsychotic drugs for 6–9 months after an acute episode to reduce relapse rates

Systematic reviews have found that continuing antipsychotic drugs for at least 6 months after an acute episode reduces relapse rates compared with no treatment or placebo, and that some benefit of continuing antipsychotics is apparent for up to 2 years.

Multiple session family interventions to reduce relapse rates

One systematic review found that multiple session family interventions reduced relapse rates at 12 months compared with usual care, single session family interventions, or psychoeducational interventions.

Psychoeducational interventions to reduce relapse rates

One systematic review has found that psychoeducation reduces relapse rates at 9–18 months compared with a control intervention.

Likely to be beneficial

Behavioural therapy to improve adherence

One RCT found that behavioural interventions improved adherence to antipsychotic medication over 3 months compared with usual treatment. Two RCTs found limited evidence that behavioural interventions may improve adherence more than psychoeducational therapy.

Compliance therapy to improve adherence

Two RCTs found limited evidence that compliance therapy may increase adherence to antipsychotic drugs at 6 and 18 months compared with non-specific counselling.

Psychoeducational interventions to improve adherence

One systematic review found limited evidence that psychoeducation improved adherence to antipsychotic medication compared with usual care. Two RCTs found limited evidence that psychoeducational therapy may improve adherence less than behavioural therapy.

Trade off between benefits and harms

Chlorpromazine

One systematic review has found that, compared with placebo, chlorpromazine reduces the proportion of people who have no improvement, or have marked or worse severity of illness at 6 months on a psychiatrist rated scale. The review found that chlorpromazine caused more adverse effects, such as sedation, acute dystonia, and parkinsonism, than placebo.

Clozapine

Two systematic reviews found that clozapine improved symptoms over 4–10 weeks compared with standard antipsychotic drugs. However, RCTs found that clozapine may be

associated with blood dyscrasias. Three systematic reviews of small RCTs provided insufficient evidence to compare clozapine versus other new antipsychotic drugs. One systematic review in people resistant to standard treatment found that clozapine improved symptoms after 12 weeks and after 2 years compared with standard antipsychotic drugs. RCTs provided insufficient evidence to compare clozapine versus other newer antipsychotics in people resistant to standard antipsychotic drugs.

Depot bromperidol decanoate
RCTs found no significant difference in the proportion of people who needed additional medication, left the trial early, or had movement disorders over 6–12 months between depot bromperidol decanoate and haloperidol or fluphenazine decanoate.

Depot haloperidol decanoate
One systematic review of one small RCT found no significant difference in global clinical state at 4 months between depot haloperidol decanoate and oral haloperidol, but it may have been too small to exclude a clinically important difference. Haloperidol is associated with acute dystonia, akathisia, and parkinsonism.

Haloperidol
One systematic review has found that haloperidol increases physician rated global improvement at 6 and 24 weeks compared with placebo but is associated with acute dystonia, akathisia, and parkinsonism.

Thioridazine
One systematic review has found that thioridazine improves global mental state over 3–12 months compared with placebo.

Amisulpride; loxapine; molindone; olanzapine; pimozide; quetiapine; risperidone; sulpiride; ziprasidone; zotepine
Systematic reviews have found that these newer antipsychotic drugs are as effective in improving symptoms as standard antipsychotic drugs, and have different profiles of adverse effects.

Unknown effectiveness

Cognitive behavioural therapy to reduce relapse rates
Limited evidence from a systematic review of two RCTs found no significant difference in relapse rates between cognitive behavioural therapy plus standard care and standard care alone.

Multiple session family interventions to improve adherence
One systematic review found that ''compliance with medication'' over 9–24 months was higher in people who received multiple family interventions compared with usual care, single family interventions, or psychoeducational interventions, but the difference did not quite reach significance.

Perazine
RCTs provided insufficient evidence to assess perazine.

Social skills training to reduce relapse rates
One systematic review of small RCTs provided insufficient evidence to assess social skills training.

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SL has been paid for speaking about critical appraisal by employees of the manufacturers of olanzapine, quetiapine, risperidone, and ziprasidone, and has been paid to speak about the management of schizophrenia by employees of the manufacturers of amisulpiride, olanzapine, risperidone, and clozapine. AM and ZN; none declared.

1 Andreasen NC. Symptoms, signs and diagnosis of schizophrenia. *Lancet* 1995;**346**:477–81.
2 Kane JM, Honigfeld G, Singer J, *et al*. Clozapine for the treatment-resistant schizophrenic. *Arch Gen Psychiatry* 1988;**45**:789–96.
3 Meltzer HY. Treatment-resistant schizophrenia: the role of clozapine. *Curr Med Res Opin* 1997;**14**:1–20.
4 Cannon M, Jones P. Neuroepidemiology: schizophrenia. *J Neurol Neurosurg Psychiatry* 1996;**61**:604–13.
5 Jablensky A, Sartorius N, Ernberg G, *et al*. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organisation ten-country study. *Psychol Med* 1992;**20**(Suppl):1–97.
6 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.
7 Johnstone EC. Schizophrenia: problems in clinical practice. *Lancet* 1993;**341**:536–8.

Other articles noted

The journals that are reviewed and the criteria for selecting articles from these journals for inclusion in *Evidence-Based Mental Health* are set out in the purpose and procedure in each issue. All articles that meet our criteria in the reviewed journals are cited in *Evidence-Based Mental Health,* but there is not enough space to abstract them all. The following articles passed all criteria but were not abstracted because, in the judgment of the editors, their findings were less widely applicable to clinical practice in the area of mental health.

THERAPEUTICS

Bell M, Bryson G, Wexler BE. Cognitive remediation of working memory deficits: durability of training effects in severely impaired and less severely impaired schizophrenia. *Acta Psychiatr Scand* 2003 Aug;**108**:101–9.

Ernst E. Serious psychiatric and neurological adverse effects of herbal medicines—a systematic review. *Acta Psychiatr Scand* 2003 Aug;**108**:83–91.

Gilbody S, Whitty P, Grimshaw J, *et al*. Educational and organizational interventions to improve the management of depression in primary care: a systematic review. *JAMA* 2003 Jun 18;**289**:3145–51

Januel D, Poirier MF, D'alche-Biree F, *et al*. Multicenter double-blind randomized parallel-group clinical trial of efficacy of the combination clomipramine (150 mg/day) plus lithium carbonate (750 mg/day) versus clomipramine (150 mg/day) plus placebo in the treatment of unipolar major depression. *J Affect Disord* 2003 Sep;**76**:191–200.

Jorm AF, Griffiths KM, Christensen H, *et al*. Providing information about the effectiveness of treatment options to

depressed people in the community: a randomized controlled trial of effects on mental health literacy, help-seeking and symptoms. *Psychol Med* 2003 Aug;**33**:1071–9.

Ludman E, Katon W, Bush T, *et al*. Behavioural factors associated with symptom outcomes in a primary care-based depression prevention intervention trial. *Psychol Med* 2003 Aug;**33**:1061–70.

Lyketsos CG, DelCampo L, Steinberg M, *et al*. Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. *Arch Gen Psychiatry* 2003 Jul;**60**:737–46.

Marder SR, Glynn SM, Wirshing WC, *et al*. Maintenance treatment of schizophrenia with risperidone or haloperidol: 2-year outcomes. *Am J Psychiatry* 2003 Aug;**160**:1405–12.

Nose M, Barbui C, Gray R, Tansella M. Clinical interventions for treatment non-adherence in psychosis: meta-analysis. *Br J Psychiatry* 2003 Sep;**183**:197–206.

Schneider LS, Nelson JC, Clary CM, *et al*. An 8-week multicenter, parallel-group, double-blind, placebo-controlled study of sertraline in elderly outpatients with major depression. *Am J Psychiatry* 2003 Jul;**160**:1277–85.

Seidman LJ, Schutt RK, Caplan B, *et al*. The effect of housing interventions on neuropsychological functioning among homeless persons with mental illness. *Psychiatr Serv* 2003 Jun;**54**:905–8.

AETIOLOGY

Blumenthal JA, Lett HS, Babyak MA, *et al*. Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet* 2003 Aug 23;**362**:604–9.

Kotimaa AJ, Moilanen I, Taanila A, *et al*. Maternal smoking and hyperactivity in 8-year-old children. *J Am Acad Child Adolesc Psychiatry* 2003 Jul;**42**:826–33.

Lieberman JA, Tollefson G, Tohen M, *et al*. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. *Am J Psychiatry* 2003 Aug;**160**:1396–404.

Osborn DP, Fletcher AE, Smeeth L, *et al*. Factors associated with depression in a representative sample of 14 217 people aged 75 and over in the United Kingdom: results from the MRC trial of assessment and management of older people in the community. *Int J Geriatr Psychiatry* 2003 Jul;**18**:623–30.

Ruo B, Rumsfeld JS, Hlatky MA, *et al*. Depressive symptoms and health-related quality of life: the Heart and Soul Study. *JAMA* 2003 Jul 9;**290**:215–21.

Verghese J, Lipton RB, Katz MJ, *et al*. Leisure activities and the risk of dementia in the elderly. *N Engl J Med* 2003 Jun 19;**348**:2508–16.

PROGNOSIS

DelBello MP, Carlson GA, Tohen M, *et al*. Rates and predictors of developing a manic or hypomanic episode 1 to 2 years following a first hospitalization for major depression with psychotic features. *J Child Adolesc Psychopharmacol* 2003 Summer;**13**:173–85.

Holtzer R, Wegesin DJ, Albert SM, *et al*. The rate of cognitive decline and risk of reaching clinical milestones in Alzheimer disease. *Arch Neurol* 2003 Aug;**60**:1137–42.