ClinicalEvidence

Schizophrenia (maintenance treatment)

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ABSTRACT

INTRODUCTION: One in a hundred people will develop schizophrenia; about 75% of people have relapses and continued disability, and a third fail to respond to standard treatment. Positive symptoms include auditory hallucinations, delusions, and thought disorder. Negative symptoms (demotivation, self-neglect, and reduced emotion) have not been consistently improved by any treatment. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: Which interventions reduce relapse; and improve adherence rates? Which interventions are effective in people resistant to standard antipsychotic drugs? We searched: Medline, Embase, The Cochrane Library, and other important databases up to October 2007 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 45 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: behavioural therapy, clozapine, cognitive behavioural therapy (CBT), compliance therapy, continuation of antipsychotic drugs (reduce relapse rates), first-generation antipsychotic drugs in treatment-resistant people, multiple-session family interventions, psychoeducational interventions, second-generation antipsychotic drugs in treatment-resistant people, and social-skills training.

QUESTIONS

INTERVENTIONS

Key points

- One in 100 people will develop schizophrenia; about 75% of people have relapses and continued disability, and a third fail to respond to standard treatment.

  Positive symptoms include auditory hallucinations, delusions, and thought disorder. Negative symptoms (anhedonia, asociality, flattening of affect, and demotivation) and cognitive dysfunction have not been consistently improved by any treatment.

- Continuation of antipsychotic drugs for at least 6 months after an acute attack reduces the risk of relapse compared with no treatment, although no one drug seems to be more effective than the others at preventing relapse.

The definition of relapse varies widely among studies, and in many cases is synonymous with re-hospitalisation, although this reflects social variables as well as symptom exacerbation.

- Where available, multiple sessions of family interventions or psychoeducational interventions can reduce relapse rates compared with usual care.

  We don't know whether CBT or social-skills training are also beneficial.

- In people resistant to standard antipsychotic drugs, clozapine may improve symptoms compared with first generation antipsychotic agents, but there is limited evidence on its effectiveness compared with other second generation antipsychotic agents.

  There is limited evidence to indicate that any antipsychotic other than clozapine is effective in people with treatment-resistant schizophrenia.

  We don't know how second generation agents other than clozapine compare with each other or first generation antipsychotic agents.

- Behavioural interventions, compliance therapy, and psychoeducational interventions may improve adherence to antipsychotic medication compared with usual care.

DEFINITION

Schizophrenia is characterised by three semi-independent symptom domains: positive symptoms, such as auditory hallucinations, delusions, and thought disorder; negative symptoms, including anhedonia, social withdrawal, affective flattening, and demotivation; and cognitive dysfunction, particularly in the domains of attention, working memory, and executive function. [1] Schizophrenia is typically a life-long condition characterised by acute symptom exacerbations and widely varying degrees of functional disability. Maintenance antipsychotic drug regimens for schizophrenia are intended to limit the frequency and severity of relapses, maximise effects of treatment for persistent symptoms, and enhance adherence to recommended regimens. Antipsychotic medications are primarily effective for positive symptoms, and most people require psychosocial interventions to manage the disability that often results from negative symptoms and cognitive dysfunction. [2] Adherence to prescribed antipsychotic regimens is typically low, and several psychosocial interventions have been developed to enhance adherence. About 20% of people with schizophrenia are resistant to standard antipsychotics, as defined by lack of clinically important improvement in symptoms after 2–3 regimens of treatment with standard antipsychotic drugs for at least 6 weeks; an additional 30–40% of people improve but are residually symptomatic despite antipsychotic treatment. [3] Several pharmacological strategies have been explored for these people. This review focuses on these three key aspects of the management of schizophrenia.

INCIDENCE/ PREVALENCE

One in 100 people will develop schizophrenia, and worldwide 1-year prevalence rates vary from 2 to 7 per 1000. [2] [4] Onset of symptoms typically occurs in early adult life (average age 25 years), and occurs earlier in men than in women. [5]

AETIOLOGY/ RISK FACTORS

Risk factors for schizophrenia include a family history, 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 with schizophrenia 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; people living in industrialised countries; men; and in people who misuse drugs. [7] 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. [8]

AIMS OF INTERVENTION

To prevent relapse and to improve quality of life, with minimal adverse effects of treatment.

OUTCOMES

Severity of positive and negative symptoms; global clinical improvement; global clinical impression (a composite measure of symptoms and everyday functioning); rate of relapse; adherence to treatment (compliance/adherence; pill counting; clinical improvement; reduction in psychotic symptoms); adverse effects of treatment. Some systematic reviews calculate effect sizes to meta-analyse primary studies that use different outcome measures. Effect size is a difficult measure to interpret clinically, so we have given lower priority to analyses that use this measure.

METHODS

Clinical Evidence search and appraisal October 2007. The following databases were used to identify studies for this review: Medline 1966 to October 2007, Embase 1980 to October 2007, PsycINFO 1967 to October 2007, and The Cochrane Database of Systematic Reviews and Cochrane

Central Register of Controlled Clinical Trials 2007, Issue 3. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. There was a large number of good systematic reviews. Most RCTs completed before 2000 were small, short term, had high withdrawal rates, and employed many different outcome measures. [9] There were, however, many RCTs published between 2004 and 2007 that incorporated large sample sizes and good design features. We included both systematic reviews and RCTs, focusing on outcomes thought to be most clinically relevant. Because each treatment is associated with different benefits and harms, we used estimates of global effectiveness if they were available. We searched for placebo-controlled RCTs of standard antipsychotic medication and comparative RCTs of newer antipsychotic drugs. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded, unless blinding was impossible. The criteria for inclusion of studies in this review are stringent by design and we have maintained them for historical necessity. Consequently, a number of published studies relevant to the topic areas reviewed were excluded. Results from studies excluded from this review do not substantially alter the conclusions reached, but provide additional information pertinent to the topics reviewed. We have reported some of these studies in the Comments sections. Wherever possible, we have reported SRs in people with schizophrenia alone. However, some reviews, particularly of psychological treatments in preventing relapse and improving adherence, also included RCTs in people with schizophrenia-related disorders (e.g. schizoaffective disorder, schizophreniform disorder and psychotic disorders). We have reported reviews including studies with people with schizophrenia-related disorders, but have explicitly stated the trials included a mixed population: the proportion of people with schizophrenia-related disorders was not always clear. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 21).

QUESTION What are the effects of treatments to reduce relapse rates in people with schizophrenia?

OPTION CONTINUED TREATMENT WITH ANTIPSYCHOTIC DRUGS

Relapse rates

Continuation of treatment with first-generation antipsychotic drugs compared with placebo or no treatment Continuing treatment with chlorpromazine may be more effective at reducing relapse rates at 6–24 months in people with schizophrenia. Continued treatment with haloperidol or fluphenazine decanoate may be more effective at reducing relapse rates at 12 months (low-quality evidence).

Continuation of treatment with second-generation antipsychotic drugs compared with placebo Continuing treatment with olanzapine, ziprasidone, or zotepine may be more effective at reducing relapse rates over 6–12 months (low-quality evidence).

Different antipsychotic drugs compared with each other Antipsychotic drugs seem to be as equally effective as each other at preventing relapse (moderate-quality evidence).

For GRADE evaluation of interventions for schizophrenia, see table, p 21 .

Benefits:

Continued treatment with first-generation antipsychotic drugs versus no treatment or placebo:

We found four systematic reviews. [10] [11] [12] [13] The first review (search date 2007, 8 RCTs, 1341 people with schizophrenia) found that continuing chlorpromazine significantly reduced relapse rates over the short, medium, and long term compared with placebo (short term: 0–8 weeks; 2 RCTs, 74 people: 4/36 [11%] with chlorpromazine *v* 16/38 [42%] with placebo; RR 0.29, 95% CI 0.11 to 0.75; medium term: 9 weeks to 6 months; 4 RCTs, 809 people: 87/495 [18%] with chlorpromazine *v* 144/314 [46%] with placebo; RR 0.49, 95% CI 0.41 to 0.60; long term: 6–24 months and 2–5 years: 6–24 months: 3 RCTs; 106/264 [40%] with chlorpromazine *v* 176/248 [71%] with placebo; RR 0.57, 95% CI 0.48 to 0.67; NNT 3, 95% CI 3 to 4; 2–5 years: 2 RCTs; 108/202 [53%] with chlorpromazine *v* 159/192 [83%] with placebo; RR 0.65, 95% CI 0.56 to 0.75). [10] However, the review found significant heterogeneity (defined as I^2 of 75% or more) between RCTs included

in the analysis of relapse rates over 2–5 years of treatment with chlorpromazine. The review did not discuss possible reasons for observed heterogeneity. The duration of previous antipsychotic treatment was not clear for some of the identified RCTs.

The second systematic review (search date 2006, 10 RCTs, 1042 people stable on chlorpromazine for 8 weeks to 18 months) assessed the effects on relapse rates of cessation of chlorpromazine treatment. [11] The review found that, compared with no treatment, continuing with chlorpromazine significantly reduced relapse rates over the short, medium, and long term (short term: 0–8 weeks: 3 RCTs, 376 people: 8/143 [6%] with continued treatment *v* 74/233 [32%] with cessation; RR [for cessation *v* continuation] 6.76, 95% CI 3.37 to 13.54; medium term: 8 weeks to 6 months: 6 RCTs, 850 people: 33/388 [8%] with continued treatment *v* 161/462 [35%] with cessation; RR [for cessation *v* continuation] 4.04, 95% CI 2.81 to 5.81; long term: 6–24 months: 3 RCTs, 510 people: 99/261 [38%] with continued treatment *v* 160/249 [64%] with cessation; RR [for cessation *v* continuation] 1.70, 95% CI 1.44 to 2.01). The review included RCTs in people with schizophrenia-like psychoses (2 RCTs, 270 people; proportion of people within these 2 RCTs with schizophrenia not clear).

The third systematic review (search date 2005, 2 RCTs, 70 people with schizophrenia currently in remission) compared haloperidol versus placebo over 1 year. [12] It found that haloperidol significantly reduced relapse over 1 year compared with placebo (32/47 [68%] with haloperidol *v* 23/23 [100%] with placebo; RR 0.69, 95% CI 0.57 to 0.83; NNT 4, 95% CI 2 to 5).

The fourth review (search date 2002, 4 RCTs, 250 people with schizophrenia) assessed the effects of continuing treatment with fluphenazine decanoate (depot) versus placebo. [13] The review found that fluphenazine significantly reduced relapse rates in the longer term (defined as longer than 1 year) compared with placebo (1 RCT, 54 people with schizophrenia: 8/27 [30%] with fluphenazine *v* 23/27 [85%] with placebo; RR 0.35, 95% CI 0.19 to 0.64). However, there was no significant difference between groups in relapse rates in the shorter term (6–12 months) (3 RCTs, 196 people with schizophrenia: 42/98 [43%] with fluphenazine *v* 66/98 [67%] with placebo; RR 0.62, 95% CI 0.24 to 1.60). The duration of previous antipsychotic treatment was not clear for some of the identified RCTs.

Continued treatment with second-generation antipsychotic drugs versus placebo:
We found one systematic review (search date 2002, 6 RCTs, 983 people) comparing continued treatment with second-generation antipsychotic drugs (amisulpride, olanzapine, ziprasidone, and zotepine) versus placebo. [14] Two of the identified RCTs included people responding to treatment after an acute episode, and the other RCTs included people stable on their medication. The review found that, as a class, second-generation antipsychotics significantly reduced relapse rates over 6–12 months compared with placebo (6 RCTs: 104/653 [16%] with antipsychotic *v* 109/330 [33%] with placebo: ARR –0.21, 95% CI –0.34 to –0.08; P = 0.001). However, there was significant heterogeneity among studies (P = 0.0001). One RCT included in the analysis included people with residual schizophrenia and predominantly negative symptoms, which was thought to be the cause of the observed heterogeneity. The review carried out subgroup analysis for the individual second-generation antipsychotics. The review found that olanzapine, ziprasidone, and zotepine significantly reduced relapse rates over 6–12 months compared with placebo (olanzapine: 3 RCTs, 446 people; 25/317 [8%] with olanzapine *v* 40/129 [31%] with placebo; ARR –0.24, 95% CI –0.33 to –0.16; P less than 0.0001; ziprasidone: 1 RCT, 277 people; 71/206 [34%] with ziprasidone *v* 43/71 [61%] with placebo; ARR –0.26, 95% CI –0.39 to –0.13; P less than 0.0001; zotepine: 1 RCT, 119 people; 4/61 [7%] with zotepine *v* 21/58 [36%] with placebo; ARR –0.30, 95% CI –0.43 to –0.16; P less than 0.0001). However, there was no significant difference between amisulpride and placebo for this outcome (1 RCT, 141 people: 4/69 [6%] with amisulpride *v* 5/72 [7%] with placebo: ARR –0.01, 95% CI –0.09 to +0.07; P = 0.80). The review reported that some RCTs included people with schizoaffective disorder or schizophreniform disorder, but most RCTs looked at people with schizophrenia (number of studies/people included not specified).

Choice of drug:
We found 13 systematic reviews [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] comparing the effects of newer versus older antipsychotic drugs, newer antipsychotic drugs versus each other, and oral versus intramuscular administration of antipsychotic drugs on relapse rates (see table 1, p 18).

Eight reviews found no significant difference between antipsychotic drugs in relapse rates, [13] [15] [18] [19] [20] [22] [23] [24] but in two of the reviews [19] [20] the number of people studied was too small to detect a clinically important difference.

One review (search date 1998) found that significantly fewer people taking depot zuclopenthixol decanoate relapsed over 12 weeks to 1 year compared with people taking other depot preparations. [25] A second review (search date 2003) found that bromperidol significantly increased the proportion

of people who relapsed compared with haloperidol or fluphenazine. [17] A third review (search date 1999) found that clozapine significantly reduced relapse rates in the short (0–12 weeks) and long term (over 26 weeks) compared with first-generation antipsychotic drugs. [16]

Two reviews compared first- versus second-generation antipsychotic medications. [21] [14] One review (search date 2002) found that risperidone (a second-generation antipsychotic) significantly reduced relapse rates at 1 year compared with first-generation antipsychotic drugs (see table 1, p 18). [21] The second review (search date 2002, 11 RCTs, 2032 people) found that second-generation antipsychotic agents (amisulpride, clozapine, olanzapine, risperidone, or sertindole) significantly reduced relapse rates over 26–130 weeks' treatment compared with first-generation antipsychotic agents (haloperidol [10 RCTs], and chlorpromazine) (see table 1, p 18). [14] The review carried out a subgroup analysis for the individual second-generation antipsychotics. It found that the difference between groups was significant for only risperidone and sertindole (see table 1, p 18). Although there was no significant difference between clozapine, olanzapine, and amisulpride and first-generation antipsychotics, relapse rates were lower with the second-generation antipsychotics.

Harms:

Continued treatment with first-generation antipsychotic drugs versus no treatment or placebo:
The reviews gave no information on adverse effects of continuing treatment with antipsychotic drugs. [10] [11] [12] [13]

Continued treatment with second-generation antipsychotic drugs versus placebo:
The review gave no information on adverse effects specifically associated with continuing treatment with antipsychotic drugs. [14]

Choice of drug:
The withdrawal and adverse-event rates for 13 systematic reviews are described in table 1, p 18 . [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] The review comparing different depot antipsychotic drugs found that the annual incidence of tardive dyskinesia was 5%. [25]

Comment:

Clinical guide:
Discontinuation rates with different first- or second-generation antipsychotics:
One large RCT (Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE], 1493 people) was designed to compare several second-generation antipsychotic medications versus a first-generation agent (perphenazine) and versus each other over an 18-month treatment period. [26] This RCT did not meet *Clinical Evidence* inclusion criteria for reporting (loss to follow-up of more than 20%) because it used a primary outcome measure of “all cause” medication discontinuation. The RCT found that time to medication discontinuation due to lack of efficacy was significantly longer for people taking olanzapine compared with those taking quetiapine (P less than 0.001) or risperidone (P = 0.002), but not those taking perphenazine (P = 0.02) or ziprasidone (P = 0.03) (ziprasidone was added to the RCT after enrollment of about 40% of people).

Hospitalisation for exacerbation with different first- or second-generation antipsychotics:
CATIE found that people taking olanzapine had a lower rate of hospitalisation for an exacerbation of schizophrenia compared with people taking perphenazine, quetiapine, risperidone, or ziprasidone (P less than 0.001 for comparison among 4 groups). [26]

Relapse rates with first- versus second-generation antipsychotics:
Three large RCTs that did not meet *Clinical Evidence* criteria for inclusion reported relapse rates for people with schizophrenia taking different antipsychotic medications. Results from the three RCTs suggested that haloperidol is associated with higher relapse rates compared with the second-generation antipsychotics olanzapine, risperidone, and quetiapine. [27] [28] [29]

Relapse rates after change of second-generation antipsychotic:
In separate analyses of the CATIE RCT, people who discontinued treatment were randomly assigned to a second-generation agent. People who received a second-generation antipsychotic after discontinuing treatment with the first-generation antipsychotic perphenazine had similar relapse rates regardless of the second-generation agent used (risperidone, olanzapine, or quetiapine; P = 0.79 for comparison among 4 groups). [30] However, analyses of people who switched from one second-generation agent to another second-generation agent (olanzapine, quetiapine, risperidone, or ziprasidone) found that olanzapine and risperidone were associated with lower relapse rates compared with quetiapine and ziprasidone (P = 0.02 for comparison among 4 groups). [31]

Although some studies suggest that second-generation antipsychotics may be more effective than first-generation agents in reducing relapse rates, overall the evidence suggests that no class of antipsychotic is substantially more effective than another class at lowering relapse rates in people

with schizophrenia. Many years of experience using antipsychotic medications to prevent relapse in schizophrenia have led to the consensus that they are effective.

OPTION FAMILY INTERVENTIONS (PREVENTION OF RELAPSE)

Relapse rate

Compared with usual care, single family intervention or psychoeducational interventions Multiple family interventions or family-based psychosocial interventions may be more effective than usual care, single family intervention, or psychoeducational interventions at reducing relapse rates at 24 months (very low-quality evidence).

For GRADE evaluation of interventions for schizophrenia, see table, p 21 .

Benefits:

We found two systematic reviews [32] [33] and one subsequent RCT [34] assessing the effects of multiple family interventions.

In the first review, [32] family interventions consisted mainly of education about the illness and training in problem solving over at least six weekly sessions. The review found that multiple family interventions significantly reduced relapse rates at 12 months compared with other interventions (usual care, single family interventions, or psychoeducational interventions) (11 RCTs, 729 people with schizophrenia; OR 0.52, 95% CI 0.31 to 0.89; absolute numbers not reported). On average, eight families would have to be treated to avoid one additional relapse (and likely admission to hospital) at 12 months in the family member with schizophrenia (NNT 8, 95% CI 6 to 18). [32] The review included studies in people with schizophrenia-related disorders (including delusional disorders, schizophreniform disorder, or schizoaffective disorder), but only if the data were reported separately for people with schizophrenia.

The second review (search date 2005) assessed all types of family-based psychosocial intervention that required more than five sessions: [33] it identified 16 RCTs identified by the first review, but the meta-analyses carried out by the reviews included different RCTs. [32] [33] The second review found that family-based psychosocial interventions were significantly more effective at reducing relapse rates compared with usual care at 7–12 months and 19–24 months (7–12 months: 16 RCTs, 857 people: 149/446 [33%] with family intervention *v* 191/411 [46%] with usual care; RR 0.71, 95% CI 0.60 to 0.83; 19–24 months: 6 RCTs, 348 people; 104/184 [57%] with family intervention *v* 111/164 [68%] with usual care; RR 0.82, 95% CI 0.68 to 0.98). [33] However, in the shorter term (0–6 months) and longer term (25–36 months), there was no significant difference between groups in relapse rates (0–6 months: 3 RCTs, 213 people: 26/109 [24%] with family intervention *v* 35/104 [34%] with usual care; RR 0.71, 95% CI 0.46 to 1.09; 25–36 months, 2 RCTs, 147 people: 72/91 [79%] with family intervention *v* 41/56 [73%] with usual care; RR 1.08, 95% CI 0.88 to 1.32). The review included quasi-randomised RCTs and RCTs that included people with schizophrenia-related disorders (5 RCTs, 344 people: proportion of people within these 5 RCTs with schizophrenia not clear).

The subsequent RCT (96 relatives of people with schizophrenia, and who were the primary care giver) compared a family mutual-support group (32 people) versus a family psychoeducation group (33 people) versus usual care (31 people). [34] The RCT found no significant difference between the three groups in the mean number of hospital readmissions at 12 months and 18 months (12 months: ITT analysis: 1.4 with mutual support *v* 1.9 with psychoeducation *v* 2.0 with usual care; 18 months: 1.1 with mutual support *v* 1.5 with psychoeducation *v* 2.0 with usual care; reported as not significant; P values not reported for any comparison). People with schizophrenia were excluded from the mutual-support group sessions, which comprised 12 bi-weekly 2-hour sessions (over 6 months). Each session was led by an elected family carer, and focused on the principles of strengthening a mutual-support group (e.g. disclosing personal information, and problem solving). Psychoeducation included patients and comprised 12 bi-weekly 2-hour sessions (over 6 months) led by two trained psychiatric nurses.

Harms:

The reviews and subsequent RCT gave no information on adverse effects. [32] [33] [34]

Comment:

Clinical guide:
The mechanism for the effects of family intervention remains unclear. It is thought to work by reducing “expressed emotion” (hostility and criticism) in the relatives of people with schizophrenia. There is evidence of benefit for family therapy in reducing relapse rates in schizophrenia. The time-consuming nature of this intervention can limit its availability. It cannot be applied to people who have little contact with home-based carers.

OPTION PSYCHOEDUCATIONAL INTERVENTIONS (PREVENTION OF RELAPSE)

Relapse rate
Compared with usual care Both brief and standard-length group psychoeducational interventions may be more effective at reducing relapse rates at 9–18 months (very low-quality evidence).

Compared with social-skills training We don't know whether psychoeducation is more effective at reducing relapse rates (low-quality evidence).

For GRADE evaluation of interventions for schizophrenia, see table, p 21 .

Benefits:

Psychoeducational interventions versus usual treatment:
We found one systematic review (search date 2002) [35] and one subsequent RCT. [34]

The review identified one RCT of a brief individual intervention (maximum of 10 sessions), six RCTs of brief group psychoeducational interventions, and four RCTs of standard-length group psychoeducational interventions (11 sessions or more). It found that standard-length group psychoeducational interventions were significantly more effective than usual care in preventing relapse without readmission over 9–18 months (2 RCTs; 14/57 [25%] with psychoeducation *v* 24/57 [42%] with usual care; RR 0.58, 95% CI 0.34 to 0.99). It also found that brief group psychoeducational interventions were significantly more effective than usual care in preventing relapse or readmission over 1 year (5 RCTs; 153/326 [47%] with psychoeducation *v* 162/296 [55%] with usual care; RR 0.85, 95% CI 0.74 to 0.98; NNT 12, CI 6 to 83). The review found that any form of psychoeducation significantly reduced relapse with or without readmission to hospital over 9–18 months compared with usual care (6 RCTs; 176/383 [46%] with psychoeducation *v* 192/337 [57%] with usual care; RR 0.78, 95% CI 0.62 to 0.98; NNT 9, 95% CI 6 to 22; see comment below). [35] The review included people with schizophrenia-related disorders (2 RCTs, 318 people: proportion of people within these 2 RCTs with schizophrenia not clear).

The subsequent RCT (96 relatives of people with schizophrenia and who were the primary care giver) compared a family mutual-support group (32 people) versus a family psychoeducation group (33 people) versus usual care (31 people). [34] The RCT found no significant difference between the three groups in the mean number of hospital readmissions at 12 months and 18 months: this RCT is reported in full in the family interventions section (see benefits of family interventions for the prevention of relapse section, p 6).

Psychoeducational interventions versus social-skills training:
See benefits of social-skills training, p 8 .

Harms:

Psychoeducational interventions versus usual treatment:
The systematic review and RCT gave no information on adverse effects. [35] [34]

Psychoeducational interventions versus social-skills training:
See harms of social-skills training, p 8 .

Comment:

Clinical guide:
There are few well-designed RCTs focusing on psychoeducation and relapse prevention, with current studies showing substantial heterogeneity of both interventions and outcomes. The specific mechanisms by which psychoeducation leads to relapse reduction remain unclear, but probably involve enhanced compliance with prescribed treatments. There is limited evidence that psychoeducation strategies alone diminish relapse rates in schizophrenia.

OPTION CBT

Relapse rates
CBT plus standard care compared with standard care alone We don't know whether CBT plus standard care is more effective at reducing relapse rates at up to 60 months (very low-quality evidence).

For GRADE evaluation of interventions for schizophrenia, see table, p 21 .

Benefits:

We found one systematic review (search date 2004) [36] and one subsequent RCT [37] assessing the effects of CBT on relapse rates.

CBT plus standard care versus standard care alone:
The review searched for RCTs using standard CBT techniques including challenging key beliefs, problem solving, and enhancement of coping. The review found no significant difference between CBT plus standard care and standard care alone in relapse or readmission to hospital over 10

weeks or over 9–60 months (10 weeks, 1 RCT: 0/33 [0%] with CBT plus standard care *v* 4/28 [14%] with standard care alone, RR 0.09, 95% CI 0.01 to 1.69 [reported in review as not significant]; 9–60 months, 4 RCTs: 47/182 [26%] with CBT plus standard care *v* 56/175 [32%] with standard care alone, RR 0.86, 95% CI 0.50 to 1.49). [36] The review included RCTs in people with schizophrenia-like disorders (3 RCTs, 239 people: proportion of people within these 3 RCTs with schizophrenia not clear).

The subsequent RCT (422 people with chronic schizophrenia) compared CBT delivered by mental-health nurses plus standard care versus usual care alone. [37] It found that nurse-led CBT significantly reduced relapse rates compared with usual care at 12 months' follow-up (ITT analysis: 36/257 [14%] with CBT *v* 38/165 [23%] with usual care; P less than 0.05). CBT comprised 6 nurse-led one-to-one sessions held over 2–3 months. To improve recruitment, people were randomised to give a ratio of nurse-led CBT to usual care of 2:1. CBT was administered by mental-health nurses who had undergone intensive training in CBT techniques but who were not recruited from community-health teams, which the RCT noted may affect generalisability.

Harms:

CBT plus standard care versus standard care alone:
The systematic review and RCT gave no information on adverse effects. [36] [37]

Comment:

Clinical guide:
There is limited evidence that CBT diminishes relapse rates in schizophrenia.

OPTION SOCIAL-SKILLS TRAINING

Relapse rates
Compared with standard care Social-skills training over 2 years of treatment seems to be more effective at reducing relapse rates (moderate-quality evidence).

Compared with psychoeducational interventions We don't know whether social-skills training is more effective at reducing relapse rates at 1 year (low-quality evidence).

Compared with supportive group discussion We don't know whether social-skills training is more effective at reducing relapse rates at 6 months (low-quality evidence).

For GRADE evaluation of interventions for schizophrenia, see table, p 21 .

Benefits:

We found one systematic review (search date 1999) [38] and two subsequent RCTs studying the effects of social-skills training on relapse rates. [39] [40] The review identified nine RCTs (471 people) comparing the effect on relapse rates of social-skills training versus standard care or psychoeducational interventions. [38]

Social-skills training versus standard care:
The systematic review found that social-skills training significantly reduced relapse rates over 2 years of treatment compared with standard care (2 RCTs, 264 people with schizophrenia; OR 3.03, 95% CI 1.11 to 8.33; absolute numbers not reported). [38] The review included studies in people with schizophrenia-related disorders (including delusional disorders, schizophreniform disorder, or schizoaffective disorder), but only if the data were reported separately for people with schizophrenia.

Social-skills training versus psychoeducational interventions:
The systematic review found no significant difference in relapse rates over 1 year of treatment between social-skills training and other psychoeducational interventions (4 RCTs, 125 people; OR 0.74, 95% CI 0.43 to 1.29; absolute numbers not reported). [38]

One subsequent RCT (103 people with schizophrenia recently discharged from hospital, clinically stable for at least 1 month before recruitment) compared a community re-entry social-skills programme versus group psychoeducation. [39] The RCT found that the social-skills training programme significantly reduced relapse rates at 24 months compared with group psychoeducation (10/49 [20%] with skills training *v* 23/45 [51%] with psychoeducation; P = 0.002). The community re-entry programme is primarily designed to equip inpatients with the social skills necessary for successful transition from hospital into the community. The programme comprised 16 1-hour sessions. Method of randomisation was unclear.

Social-skills training versus supportive group discussion:
We found one RCT (36 hospital inpatients with schizophrenia) that found that similar proportions of people in the two treatment groups relapsed at 6 months (4/17 [24%] with social-skills training *v* 2/18 [11%] with supportive group discussion; significance not assessed). Social-skills training

and supportive group-discussion programmes were designed to deliver 30–32 hours of treatment over 8 weeks (bi-weekly session of 1.5–2.0 hours in length). [40]

Harms: The review and RCTs gave no information on adverse effects. [38] [39] [40]

Comment: **Clinical guide:**
There is limited evidence that social-skills training diminishes relapse rates in schizophrenia. The time-consuming nature of this intervention can limit its availability.

QUESTION What are the effects of interventions in people with schizophrenia who are resistant to standard antipsychotic drugs?

OPTION CLOZAPINE VERSUS FIRST-GENERATION ANTIPSYCHOTIC DRUGS (TREATMENT-RESISTANT DISEASE)

Symptom improvement
Compared with first-generation antipsychotic drugs Clozapine may be more effective at increasing the proportion of people who improve at 6–12 weeks and at 12–24 months in people with treatment-resistant schizophrenia (low-quality evidence).

Adverse effects.
Clozapine has been associated with agranulocytosis.

For GRADE evaluation of interventions for schizophrenia, see table, p 21 .

Benefits: **Clozapine versus first-generation antipsychotic drugs:**
We found one systematic review (search date 1999, 6 RCTs) comparing clozapine versus first-generation antipsychotic drugs in people resistant to standard treatment. [16] It found that, compared with standard antipsychotic drugs, clozapine significantly increased the proportion of people who improved at 6–12 weeks and at 12–24 months (6–12 weeks: 4 RCTs, 370 people, RR for no improvement compared with standard antipsychotic drugs 0.71, 95% CI 0.64 to 0.79; 12–24 months: 2 RCTs, 648 people, RR 0.83, 95% CI 0.76 to 0.91). Some RCTs in the review included people who were partial responders to neuroleptic drugs and people unable to take some neuroleptic medications because of adverse effects. [16]

Harms: **Clozapine versus first-generation antipsychotic drugs:**
The review gave no information on adverse effects (see harms of clozapine versus second-generation antipsychotics, p 9). [16]

Comment: **Clinical guide:**
Because of the risk of agranulocytosis associated with clozapine, it is recommended that clozapine be limited to people who are treatment resistant (defined as patients who are not responsive to adequate trials of two or more antipsychotics or who are intolerant of their adverse effects). The second-generation antipsychotic agents clozapine, olanzapine, and quetiapine seem to be associated with a higher risk of cardiometabolic adverse effects compared with first- and other second-generation antipsychotic agents. [41]

OPTION CLOZAPINE VERSUS OTHER SECOND-GENERATION ANTIPSYCHOTIC DRUGS (TREATMENT-RESISTANT DISEASE)

Symptom improvement
Compared with olanzapine, risperidone, zotepine Clozapine and other second-generation antipsychotic drugs (olanzapine, risperidone, zotepine) seem equally effective at improving symptoms in people with treatment-resistant schizophrenia (moderate-quality evidence).

Compared with olanzapine Clozapine and olanzapine seem to be equally effective at improving symptoms in people with treatment-resistant schizophrenia (high-quality evidence).

For GRADE evaluation of interventions for schizophrenia, see table, p 21 .

Benefits: **Clozapine versus olanzapine, risperidone, and zotepine:**
We found one systematic review (search date 1999, 8 RCTs, 5 in people with treatment-resistant schizophrenia, 595 people) comparing clozapine versus olanzapine, risperidone, and zotepine. [42] It found no significant difference between clozapine and other second-generation antipsychotic drugs in Clinical Global Impression Scale (CGIS) (4 RCTs, 315 people; WMD –0.10, 95% CI –0.34 to +0.15) or mental state (Brief Psychiatric Rating Scale [BPRS] or Positive and Negative Syndrome

Scale [PANSS]; less than 20% improved: 5 RCTs, 351 people; 83/173 [48%] with clozapine *v* 81/178 [46%] with olanzapine or risperidone; RR 0.93, 95% CI 0.75 to 1.16). However, the number of people studied was too small to detect a clinically important difference.

Clozapine versus olanzapine:
We found one systematic review (search date 2004, 2 RCTs, 330 people; including 1 RCT identified by the previous review [42]) [19] and one subsequent RCT comparing clozapine versus olanzapine. [43] The review found no significant difference between treatments in improvement in psychotic symptoms over 18 weeks (86/166 [52%] with olanzapine *v* 96/164 [59%] with clozapine; RR for no important clinical response [defined as a 40% reduction on CGIS] 0.89, 95% CI 0.73 to 1.08). [19]

The subsequent RCT (25 children and adolescents aged 7–16 years with onset of symptoms of schizophrenia before age 13 years and no response to treatment with 2 antipsychotic medications) also found no significant difference between clozapine and olanzapine at 8 weeks in change-in-symptom scores using various scales, although the RCT reported a trend in improved symptoms that favoured clozapine (mean change in score from baseline: BPRS: –9 with clozapine *v* –1 with olanzapine; P = 0.12; Schedule for the Assessment of Negative symptoms: –22 with clozapine *v* –8 with olanzapine; P = 0.08; Schedule for the Assessment of Positive symptoms; –12 with clozapine *v* +3 with olanzapine; P = 0.14; Clinical Global Impression of Severity of Symptoms scale: –1.1 with clozapine *v* –0.5 with olanzapine; P = 0.39). [43]

Harms:

Clozapine versus olanzapine, risperidone, and zotepine:
The review found that, compared with other second-generation antipsychotic agents (mainly olanzapine and risperidone), clozapine was significantly less likely to cause extrapyramidal adverse effects (305 people; RR 0.3, 95% CI 0.1 to 0.6; NNT 6, 95% CI 4 to 9; absolute numbers not reported). [42] It also found that clozapine may be less likely to cause dry mouth, but more likely to cause fatigue, nausea, dizziness, hypersalivation, and hypersomnia than other new antipsychotic drugs; however, these findings were from one or, at most, two RCTs. It found no significant difference in rates of blood dyscrasias between clozapine and other second-generation antipsychotic drugs (4 RCTs, 558 people: 7/281 [3%] with clozapine *v* 5/277 [2%] with second-generation antipsychotic; RR 0.76, 95% CI 0.27 to 2.18); but the number of people studied was too small to detect a clinically important difference. The review found that people taking clozapine tended to be more satisfied with their treatment compared with those taking other second-generation antipsychotic drugs, but that they also tended to withdraw from RCTs more often.

Clozapine versus olanzapine:
The review gave no information on adverse effects. [19] The subsequent RCT found that clozapine was associated with a significantly higher incidence of hypertension and tachycardia (more than 100 beats/minute) compared with olanzapine (hypertension: 7/11 [64%] with clozapine *v* 1/11 [9%] with olanzapine; P = 0.02; tachycardia: 7/10 [70%] with clozapine *v* 2/12 [17%] with olanzapine; P = 0.03). [43] It also found that a significantly higher proportion of treatment-related adverse effects were reported in the clozapine group compared with the olanzapine group (proportion of total number of adverse effects reported: 55/386 [14%] with clozapine *v* 28/418 [7%] with olanzapine; P less than 0.001). [43]

Comment:

Some of the studies included patients who were intolerant of the adverse effects of previous treatments. Inclusion of intolerant patients can bias the results such that the effect size of clozapine is smaller than the actual effect size: patients who are intolerant often have a higher response rate in terms of symptom improvement to treatments that they could tolerate compared with previous treatments that were discontinued because of adverse effects. Therefore, it is possible that the effectiveness of clozapine in true treatment-resistant people is larger than reported in this review.

Clinical guide:
The standard measure for improvement in many of the studies reviewed here is defined as at least 20% reduction in BPRS or PANSS total score. This improvement in BPRS and PANSS scores correlates with at least minimal improvement in severity of clinical symptoms. [44] In treatment-resistant patients, who by definition have shown no improvement in clinical symptoms with prior treatments, even minimal improvement is significant.

OPTION SECOND-GENERATION ANTIPSYCHOTICS (OTHER THAN CLOZAPINE) VERSUS FIRST-GENERATION ANTIPSYCHOTICS (TREATMENT-RESISTANT DISEASE)

Symptom improvement
Olanzapine versus chlorpromazine We don't know whether olanzapine is more effective at improving psychotic symptoms at 8 weeks in people with treatment-resistant schizophrenia (very low-quality evidence).

Ziprasidone versus chlorpromazine We don't know whether ziprasidone is more effective at improving psychotic symptoms at 6–12 weeks in people with treatment-resistant schizophrenia (very low-quality evidence).

Aripiprazole versus perphenazine: We don't know whether aripiprazole is more effective at improving psychotic symptoms at 6 weeks in people with treatment-resistant schizophrenia (low-quality evidence).

Note
We found no clinically important results from RCTs about the effects of other interventions on relapse rates in people with treatment-resistant schizophrenia.

For GRADE evaluation of interventions for schizophrenia, see table, p 21 .

Benefits:

Olanzapine versus chlorpromazine:
One systematic review (search date 2004, 1 RCT, 84 people with schizophrenia) found no significant difference in persistence of psychotic symptoms over 8 weeks between olanzapine 25 mg daily and chlorpromazine (no important response defined as less than 20% reduction on the Clinical Global Impression scale [CGIS]; AR for no important response: 39/42 [93%] with olanzapine *v* 42/42 [100%] with chlorpromazine; RR 0.93, 95% CI 0.85 to 1.01). [19] The RCT is likely to have been too small to detect a clinically important difference. The RCT identified by the review included people who were partial responders to neuroleptic drugs and people unable to take some neuroleptic medications because of adverse effects. [19] The review did not specify the duration of treatment-resistant illness of the people included in the RCT.

Ziprasidone versus chlorpromazine:
We found one RCT (306 treatment-resistant people). [45] It found that ziprasidone (80–160 mg/day) significantly improved Clinical Global Impression (CGI)-Severity scores at 6 weeks and Positive and Negative Symptom Severity (PANSS) Negative Subscale scores at 12 weeks compared with chlorpromazine (200–1200 mg/day) (CGI-Severity scale: P = 0.05 or less; absolute numbers not reported: PANSS Negative Subscale: P less than 0.05; data presented graphically; absolute numbers not reported). However, there was no significant difference between groups in proportion of people with a reduction in Brief Psychotic Rating Scale (BPRS) score of 20% or more or PANNS total score at 12 weeks (proportion of people with reduction in BPRS score of 20% or more: 58% with ziprasidone *v* 55% with chlorpromazine; absolute numbers not reported; no data available for PANSS total scores; P values not reported; reported as not significant for both comparisons). Before randomisation, people were enrolled in a 6-week open-label phase of treatment with haloperidol. Only those showing no response to treatment were randomised to further treatment. It was not clear whether there was a wash-out period after the 6-week haloperidol-treatment phase.

Aripiprazole versus perphenazine:
We found one RCT (300 treatment-resistant people). [46] At 6 weeks, the RCT found no significant difference between aripiprazole and perphenazine in PANSS total score (–9.8 with aripiprazole *v* –10.5 with perphenazine), BPRS score (–2.0 with aripiprazole *v* –2.0 with perphenazine), or CGI-Severity scores (–0.3 with aripiprazole *v* –0.3 with perphenazine; changes reported are mean change in score from baseline [LOCF analysis]; differences between groups reported as not significant; P values not reported). At 6 weeks, the RCT found that similar numbers of people in each group were classed as responders (defined as a 30% or greater decrease in PANSS total score: 40/150 [27%] with aripiprazole *v* 36/144 [25%] with perphenazine; significance not assessed).

Harms:

Olanzapine versus chlorpromazine:
The review found no significant difference between olanzapine and chlorpromazine in extrapyramidal adverse effects or in nausea and vomiting at 8 weeks (any extrapyramidal adverse effect: 12/42 [29%] with olanzapine *v* 21/42 [50%] with chlorpromazine; RR 0.57, 95% CI 0.32 to 1.01: nausea and vomiting: 5/42 [12%] with olanzapine *v* 8/42 [19%] with chlorpromazine; RR 0.63, 95% CI 0.22 to 1.75). [19]

Ziprasidone versus chlorpromazine:
The RCT found that the most common treatment-emergent adverse effects were extrapyramidal symptoms, with similar proportions of people reporting these effects in both groups (49/152 [32%] with ziprasidone *v* 54/154 [35%] with chlorpromazine; significance not assessed). [45]

Aripiprazole versus perphenazine:
The RCT found that a significantly smaller proportion of people had clinically significant high levels of prolactin after treatment with aripiprazole compared with perphenazine (6/135 [4%] with aripiprazole *v* 79/137 [58%] with perphenazine; P less than 0.001). [46] Aripiprazole was also associated with a lower incidence of extrapyramidal symptoms compared with perphenazine (21/153 [14%] with aripiprazole *v* 28/144 [19%] with perphenazine; significance not assessed). The RCT found that the most common adverse effect reported was insomnia, with a similar proportion of people

affected in both groups (37/153 [24%] with aripiprazole *v* 30/144 [21%] with perphenazine; significance not assessed). [46]

Comment: **Clinical guide:**
The data for treatment of people resistant to first-generation antipsychotics do not provide clear evidence of benefit of one drug over another. Current evidence seems to suggest that treatment with a second-generation antipsychotic, including clozapine, provides some benefits over continued treatment with first-generation antipsychotics in people resistant to another first-generation antipsychotic.

OPTION SECOND-GENERATION ANTIPSYCHOTICS (OTHER THAN CLOZAPINE) VERSUS EACH OTHER (TREATMENT-RESISTANT DISEASE)

We found no clinically important results from RCTs about second-generation antipsychotics (other than clozapine) compared with each other in people with treatment-resistant schizophrenia. For GRADE evaluation of interventions for schizophrenia, see table, p 21 .

Benefits: We found no reviews or RCTs comparing second-generation antipsychotic agents (other than clozapine) versus each other in people with treatment-resistant schizophrenia that met criteria for inclusion in this report.

Harms: We found no review or RCTs.

Comment: **Clinical guide:**
Other than clozapine, there is insufficient evidence to conclude that any second-generation antipsychotic agent is more effective than other second-generation agents.

QUESTION What are the effects of interventions to improve adherence to antipsychotic medication in people with schizophrenia?

OPTION BEHAVIOURAL THERAPY

Adherence to treatment
Compared with usual treatment We don't know whether behavioural therapies are more effective at increasing adherence to antipsychotic medication at 3 months (very low-quality evidence).

Compared with psychoeducational therapy We don't know whether behavioural therapies are more effective at improving adherence to antipsychotic medication at 2–3 months (very low-quality evidence).

For GRADE evaluation of interventions for schizophrenia, see table, p 21 .

Benefits: **Behavioural therapy versus usual treatment:**
We found no systematic review but found one RCT (36 men with schizophrenia) that compared three interventions: psychoeducation versus behavioural therapy versus usual treatment. [47] The behavioural training method consisted of being told the importance of adhering to antipsychotic medication and instructions on how to take it. Each patient was given a self-monitoring spiral calendar, which featured a dated slip of paper for each dose of antipsychotic drug. Adherence was estimated by pill counts (see comment below). After 3 months, the RCT reported fewer people had high pill adherence after usual treatment compared with behavioural therapy (figures not reported; significance for between group comparison not assessed).

Behavioural therapy versus psychoeducational therapy:
See benefits of psychoeducational interventions, p 13 .

Harms: **Behavioural therapy versus usual treatment:**
The RCT gave no information on adverse effects. [47]

Behavioural therapy versus psychoeducational therapy:
See harms of psychoeducational interventions, p 13 .

Comment: **Clinical guide:**
Assessing adherence by pill count has potential confounders, in that people may throw pills away. [47] There is limited evidence that behavioural therapy is effective in improving adherence.

OPTION PSYCHOEDUCATIONAL INTERVENTIONS (IMPROVING ADHERENCE)

Adherence to treatment

Compared with usual treatment A brief group psychoeducational intervention may be more effective at increasing adherence to antipsychotic medication, but we don't know whether brief individual or standard-group psychoeducational interventions improve adherence (measured by "medication concordance") compared with usual care (very low-quality evidence).

Compared with behavioural therapy We don't know whether psychoeducational therapies are more effective at improving adherence to antipsychotic medication at 2–3 months (very low-quality evidence).

For GRADE evaluation of interventions for schizophrenia, see table, p 21 .

Benefits:

Psychoeducational interventions versus usual treatment:

We found one systematic review (search date 2002, 3 RCTs) [35] and one subsequent RCT [48] assessing adherence to medication. The RCTs compared an individual or group psychoeducational intervention of either standard length (11 sessions or more) or brief length (maximum of 10 sessions) versus usual care. The review found that a brief group psychoeducational intervention significantly improved adherence compared with usual care over 1 year (measured on a continuous scale of "medication concordance"; 1 RCT, 163 people: WMD –0.40, 95% CI –0.62 to –0.18). [35] However, the review found no significant difference in adherence between brief individual psychoeducation and usual care, measured on a continuous scale of medication compliance (1 RCT, 67 people: reported to be not significant; absolute numbers not reported). The review found no significant difference in adherence over 18 months between standard-length group interventions and usual care (1 RCT, 82 people: 7/41 [17%] with psychoeducation *v* 2/41 [5%] with usual care; RR 3.50, 95% CI 0.77 to 15.85; P = 0.1). The review included RCTs that included people with schizophrenia-related disorders (2 RCTs, 318 people: proportion of people within these 2 RCTs with schizophrenia not clear).

The subsequent RCT (107 people with schizophrenia) found no significant difference between an individual psychoeducational programme and usual care in the proportion of people showing "good compliance" to their pharmaceutical regimen at 6 months (16/39 [41%] with psychoeducational programme *v* 26/47 [55%] with usual care; P greater than 0.05). [48] Compliance was measured from data that were dichotomised from physician- and patient-rated assessments (using different scales), and the concentration of drug in patients' plasma. In the psychoeducational programme, the treating clinician provided the person with information on different antipsychotics available and their adverse effects (through discussion and decision aids) to assist in decisions regarding future treatment.

Psychoeducational interventions versus behavioural therapy:

We found no systematic review but found two RCTs. [47] [49] The first RCT (36 men with schizophrenia) compared three interventions: psychoeducation, behavioural therapy, or usual treatment. [47] During behavioural training, the importance of complying with antipsychotic medication was emphasised and people were given instruction on how to take their medication. Each patient was given a self-monitoring spiral calendar, featuring a dated slip of paper for each dose of antipsychotic drug. Adherence was estimated by pill counts (see comment below). The RCT found no significant difference between groups after 3 months, although fewer people had high pill adherence after psychoeducation compared with behavioural therapy (pill adherence scores of 80% measured by pill counts: 3/11 [27%] with psychoeducation *v* 8/11 [73%] with behavioural therapy; RR of high pill adherence score 0.37, 95% CI 0.13 to 1.05). The RCT is likely to have been too small to detect a clinically important difference. [47]

The second RCT (39 people with schizophrenia) compared a psychoeducational intervention, an individual behavioural intervention, and a behavioural intervention involving the person with schizophrenia and their family. [49] The individual behavioural intervention consisted of specific written guidelines and oral instructions on how to use a pill box consisting of 28 compartments for every medication occasion during 1 week. The family-based behavioural intervention contained additional instructions for family members to compliment the person with schizophrenia for taking their prescribed medication. The primary outcome measure was pill count at 2 months (see comment below). The RCT found that medication adherence was significantly more likely with behavioural interventions than with psychoeducation (greater than 90% adherence at 2 months: 25/26 [96%] with behavioural interventions *v* 6/13 [46%] with psychoeducation; RR 2.08, 95% CI 1.15 to 3.77; NNT 2, 95% CI 2 to 5).

Harms:

Psychoeducational interventions versus usual treatment:

The review and subsequent RCT gave no information on adverse effects. [35] [48]

Psychoeducational interventions versus behavioural therapy:
The RCTs gave no information on adverse effects. [47] [49]

Comment: Assessing adherence by pill count has potential confounders, as people may throw pills away. [47] [49] Each psychoeducational intervention varied in the protocol used, and few employed the same outcome measurements.

Clinical guide:
Most clinicians believe that psychoeducation is an important element of a comprehensive treatment plan. However, to ensure adherence with antipsychotic medication, psychoeducation strategies are best used in combination with other interventions.

OPTION COMPLIANCE THERAPY

Adherence to treatment
Compared with non-specific therapy Compliance therapy seems to be as effective as non-specific therapy or health education at increasing adherence to antipsychotic medication at 12 months (moderate-quality evidence).

For GRADE evaluation of interventions for schizophrenia, see table, p 21 .

Benefits: We found one systematic review [50] and one subsequent RCT [51] assessing compliance therapy. The review (search date 2005, 1 RCT, 56 people with schizophrenia admitted to hospital and followed post-discharge) found no significant difference in the proportion of people who were non-compliant (compliance measured on a 4-point scale where 4 was classified as optimal compliance) between those receiving compliance therapy and those receiving non-specific counselling therapy over 1 year (non-compliant: 16/28 [57%] with compliance therapy *v* 13/28 [46%] with non-specific therapy; RR 1.23, 95% CI 0.74 to 2.05). [50]

The subsequent RCT (409 people with schizophrenia) compared adherence therapy versus health education. [51] At 12 months, the RCT found no significant difference between groups in either patient-rated or keyworker-rated measures of compliance (ITT analysis: change in scores from baseline: patient-rated compliance; 2.98 to 3.20 with adherence therapy *v* 2.97 to 3.33 with health education; AR –0.13, CI –0.35 to +0.08; P = 0.23; keyworker-rated: 5.04 to 5.22 with adherence therapy *v* 4.73 to 5.03 with health education; AR +0.19, CI –0.12 to +0.52; P = 0.24; CI not reported). Adherence therapy and health education comprised a maximum of 8 once-weekly 30–50 minute sessions. Patient-rated adherence was assessed using the Medication Adherence Questionnaire and keyworker-rated adherence was measured using the Schedule for the Assessment of Insight scale (where 1 = complete refusal and 7 = active participation in treatment).

Harms: The review and RCT gave no information on adverse effects. [50] [51]

Comment: **Clinical guide:**
There are limited studies on the effectiveness of compliance therapy. The RCT identified by the review [50] and a subsequent RCT [51] failed to document the effectiveness of compliance therapy. However, other RCTs with methodological issues (e.g. did not use a standardised measure of adherence or were open label in design) suggest that compliance therapy may be effective in improving adherence. Further studies are needed in this area.

OPTION FAMILY INTERVENTIONS (IMPROVING ADHERENCE)

Adherence to treatment
Compared with usual care, single-session family intervention, or psychoeducational intervention We don't know whether multiple-session family interventions are more effective at improving adherence to antipsychotic medication (very low-quality evidence).

For GRADE evaluation of interventions for schizophrenia, see table, p 21 .

Benefits: We found two systematic reviews. [32] [33] The first review (search date 1999) compared multiple-session family interventions versus usual care, single-session family interventions, or psychoeducational interventions. [32] Family interventions mainly consisted of education about the illness and training in problem solving over at least 6 weekly sessions. The review found no significant difference between multiple family interventions compared with other interventions in "compliance with medication" over 9–24 months, but compliance was higher in people who received family interventions (5 RCTs, 393 people with schizophrenia; OR 0.63, 95% CI 0.40 to 1.01; absolute numbers not reported). [32] The review included studies in people with schizophrenia-related disorders (including delusional disorders, schizophreniform disorder, or schizoaffective disorder), but only if the data were reported separately for people with schizophrenia.

The second review (search date 2005) focused on all types of family-based psychosocial intervention that required more than five sessions: [33] the second review identified 16 RCTs identified by the first review, but the meta-analyses carried out by the reviews included different RCTs. [32] [33] The second review found that family-based psychosocial interventions significantly improved compliance with medication (expressed as proportion of people with poor compliance) compared with usual care (poor compliance: 7 RCTs, 369 people: 78/177 [44%] with family intervention *v* 114/192 [59%] with usual care; RR [for poor compliance] 0.74, 95% CI 0.61 to 0.91). [33] The review included quasi-randomised RCTs and RCTs that included people with schizophrenia-related disorders (2 RCTs, 121 people: proportion of people within these 2 RCTs with schizophrenia not clear).

Harms: The reviews gave no information on harms. [32] [33]

Comment: **Clinical guide:**
The mechanism for the effects of family intervention remains unclear. It is thought to work by reducing "expressed emotion" (hostility and criticism) in relatives of people with schizophrenia. There is strong evidence of benefit for family therapy in improving antipsychotic medication adherence in schizophrenia. The time-consuming nature of this intervention can limit its availability. It cannot be applied to people who have little contact with home-based carers.

GLOSSARY

Negative symptoms This generally refers to qualities that are abnormal by their absence (e.g. loss of drive, motivation, and self care).
Positive symptoms This refers to symptoms that characterise the onset or relapse of schizophrenia, usually hallucinations and delusions, but sometimes including thought disorder.
Psychoeducational intervention Intervention programmes aimed at the education of a person with psychiatric disorder in subject areas that serve the goals of treatment and rehabilitation. The terms "patient education", "patient teaching", and "patient instruction" have also been used for this process.
Clinical Global Impression Scale is a one-item, observer-rated scale for measuring the severity of a condition. It has been investigated for validity and reliability. It is scored on a scale from 0 (not ill at all) to 7 (severely ill).
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

CBT (to reduce relapse rates) One RCT added found that nurse-led CBT significantly reduced relapse rates compared with usual care at 12 months' follow-up. [37] Categorisation unchanged (Unknown effectiveness).
Clozapine versus other second-generation antipsychotic drugs (treatment-resistant disease) One RCT added comparing olanzapine versus clozapine in children and adolescents aged 7–16 years who had not responded to treatment with 2 antipsychotic medications found no significant difference between treatments at 8 weeks in change-in-symptom scores using various scales, although the RCT reported that there was a trend in improved symptoms that favoured clozapine. [43] Categorisation unchanged (Unknown effectiveness).
Continuation of antipsychotic drugs (to reduce relapse rates) One systematic review added found that, in the longer term (longer than 1 year), depot fluphenazine decanoate reduced relapse rates compared with placebo. [13] However, the review found no significant difference between groups in relapse rates in the shorter term (6–12 months). One systematic review added found that, compared with cessation of treatment, continued treatment with chlorpromazine for people already stable on medication for 8 weeks to 18 months reduced relapse rates for all time frames assessed (0 weeks to 24 months). [11] One review added found continued treatment with second-generation antipsychotic drugs (olanzapine, ziprasidone, and zotepine) reduced relapse rates over 6–12 months compared with placebo. [14] The also found that second-generation antipsychotic agents reduced relapse rates over 26–130 weeks' treatment compared with first-generation antipsychotic agents (predominantly haloperidol). Categorisation unchanged (Beneficial).
Family interventions (to reduce relapse rates) One review added found that family-based psychosocial interventions reduced relapse rates compared with usual care at 7–12 months and at 19–24 months. [33] However, there was no significant difference between groups in the shorter term (0–6 months) and longer term (25–36 months). One RCT added found no significant difference between a family mutual support group, a family psychoeducation group, and usual care in the mean number of hospital readmissions at 12 months and 18 months. [34] Categorisation unchanged (Beneficial).
Multiple-session family interventions (to improve adherence) One systematic review added found that family-based psychosocial interventions improved compliance with medication compared with usual care. [33] However, the review included quasi-randomised RCTs and RCTs in people with schizoaffective disorder. Categorisation unchanged (Unknown effectiveness).

Psychoeducational interventions (to improve adherence) One small RCT added found no significant difference between an individual psychoeducational programme and usual care in the proportion of people showing "good compliance" to their pharmaceutical regimen at 6 months. [48] Categorisation unchanged (Likely to be beneficial).
Psychoeducational interventions (to reduce relapse rates) One RCT added found no significant difference in the mean number of hospital readmissions at 12 months and 18 months between a family psychoeducation group, a family mutual-support group, and usual care. [34] Categorisation unchanged (Beneficial).
Second-generation antipsychotics (other than clozapine) versus first-generation antipsychotics (treatment-resistant disease) One RCT added found that ziprasidone improved Clinical Global Impression (CGI)-Severity scores at 6 weeks and Positive and Negative Symptom Severity (PANSS) Negative Subscale scores at 12 weeks compared with chlorpromazine, but found no difference between groups in proportion of people classed as responders. [45] A second RCT added found no significant difference between aripiprazole and perphenazine at 6 weeks in various scales used to assess symptoms of schizophrenia. [46]
Social-skills training One RCT found that a social-skills training programme reduced relapse rates at 24 months compared with group psychoeducation. [39] One small RCT added compared social-skills training versus a supportive group-discussion programme. [40] The RCT found similar rates of relapse in the treatment groups at 6 months. Categorisation unchanged (Unknown effectiveness).
Compliance therapy One systematic review added found no significant difference in the proportion of non-compliant people between those receiving compliance therapy and those receiving non-specific counselling therapy over 1 year. [50] One RCT comparing adherence therapy versus health education found no significant difference between groups in either patient-rated or keyworker-rated measures of compliance at 12 months. [51] Reassessment of evidence resulted in change of categorisation from Likely to be beneficial to Unknown effectiveness.

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TABLE 1 **Continued treatment with antipsychotic drugs: choice of drugs (see text, p 3).**

Ref	Search date	Number of RCTs	Comparisons	Results	Main conclusion
[13]	2002	9	Fluphenazine decanoate versus oral antipsychotics (pimozide, penfluridol, and fluphenazine hydrochloride)	Relapse (6–12 months; 6 RCTs, 417 people): 103/211 [49%] with fluphenazine decanoate *v* 88/208 [42%] with oral antipsychotics; RR 1.46, 95% CI 0.75 to 2.83 Adverse effects: movement disorders: 3 RCTs, 159 people: 9/135 [7%] with fluphenazine *v* 17/124 [14%] with oral antipsychotics; RR 0.47, 95% CI 0.24 to 0.91	No significant difference in relapse rates
[13]	2002	14	Fluphenazine decanoate versus other depot antipsychotics	Relapse (6–12 months; 11 RCTs, 581 people): 38/290 [13%] with fluphenazine decanoate *v* 47/291 [16%] with other depot antipsychotics; RR 0.82, 95% CI 0.56 to 1.18 Relapse (at more than one year; 4 RCTs, 252 people): 30/124 [24%] with fluphenazine decanoate *v* 26/128 [20%] with other depot antipsychotics; RR 1.22, 95% CI 0.77 to 1.92 Adverse effects: general movement disorders (6–12 months; 4 RCTs, 234 people): 56/119 [47%] with fluphenazine *v* 49/115 [43%] with other depot antipsychotics; RR 1.08, 95% CI 0.86 to 1.34	No significant difference
[13]	2002	2	Fluphenazine enanthate versus other depot antipsychotics	Relapse (6–12 months; 1 RCT, 32 people): 1/16 [6%] with fluphenazine enanthate *v* 3/16 [19%] with other depot antipsychotics; RR 0.33, 95% CI 0.04 to 2.87 Adverse effects: general movement disorders (6–12 months; 2 RCTs 63 people): 10/26 [38%] with fluphenazine enanthate *v* 7/37 [19%] with other depot antipsychotics; RR 1.52, 95% CI 0.75 to 3.07	No significant difference
[15]	2003	16	Pipotiazine (pipothiazine) palmitate *v* other depots	Relapse (6 months–longer than 1 year; 7 RCTs, 417 people): 41/212 [19%] with pipotiazine *v* 39/205 [19%] with other depots; RR 0.97, 95% CI 0.66 to 1.41 Withdrawal: 11 RCTs, 608 people: 82/304 [27%] with pipotiazine *v* 57/304 [19%] with other depots; RR 1.38, 95% CI 1.04 to 1.83 Adverse effects (3 RCTs, 157 people): 33/77 [43%] with pipotiazine *v* 44/80 [55%] with other depots; RR 0.80, 95% CI 0.61 to 1.04	No significant difference
[15]	2003	3	Pipotiazine (pipothiazine) palmitate *v* oral antipsychotic drugs	Relapse (1 RCT, 124 people): 15/61 [25%] with pipotiazine *v* 10/63 [16%] with oral antipsychotic drugs; RR 1.55, 95% CI 0.76 to 3.18 Withdrawal: 3 RCTs, 219 people: 22/112 [20%] with pipotiazine *v* 15/107 [14%] with oral antipsychotic drugs; RR 1.37, 95% CI 0.77 to 2.44 Extrapyramidal adverse effects: 1 RCT, 53 people (data reported for combined effects of dystonia, stiff gait, and tremor): 17/81 [21%] with pipotiazine *v* 18/78 [23%] with oral antipsychotic drugs; RR 0.91, 95% CI 0.52 to 1.61	No significant difference
[18]	1998	8	Haloperidol decanoate *v* other depots (1 RCT [38 people] included people with schizoaffective disorder)	Relapse (7 RCTs, 317 people): 26/155 [17%] with haloperidol decanoate *v* 23/162 [23%] with other depots; RR 1.17, 95% CI 0.73 to 1.85	No significant difference

Ref	Search date	Number of RCTs	Comparisons	Results	Main conclusion
				Adverse effects: needing anticholinergic drugs: 5 RCTs, 257 people: 73/124 [59%] with haloperidol *v* 80/133 [60%] with other depots; RR 0.94, 95% CI 0.80 to 1.11	
[19]	2004	29	Olanzapine *v* first-generation antipsychotic drugs	Relapse/hospitalisation at 1 year(2 RCTs, 495 people): 202/340 [59%] with olanzapine *v* 94/155 [61%] with first-generation; RR 0.68, 95% CI 0.18 to 2.38	No significant difference
[20]	2005	31	Pimozide *v* first-generation antipsychotic drugs	Medium-term relapse (3–12 months; 11 RCTs, 377 people): 3/190 [38%] with pimozide *v* 75/187 [40%] with typical antipsychotic; RR 0.92, 95% CI 0.79 to 1.08	No significant difference
				Adverse effects: no significant differences reported between groups for various adverse effects (e.g. tremor, cardiovascular effects, central nervous system effects) in the medium term	
[22]	1999	11	Flupenthixol decanoate *v* other depots	Relapse (6–24 months; 8 RCTs, 376 people): 47/179 [26%] with flupenthixol decanoate *v* 48/197 [24%] with other depots; RR 1.11, 95% CI 0.79 to 1.54	No significant difference
				Withdrawal: 6 RCTs, 284 people: 35/137 [25.5%] with flupenthixol decanoate *v* 38/147 [25.8%] with other depots; RR 1.00, 95% CI 0.68 to 1.47	
[23]	2005	1	Fluspirilene decanoate *v* oral antipsychotics	Relapse (up to 5 months; 2 RCTs, 64 people): 2/31 [6%] with fluspirilene decanoate *v* 3/33 [9%] with oral antipsychotics; RR 0.73, 95% CI 0.13 to 4.16	No significant difference
				Adverse effects: movement disorders requiring anticholinergic drugs: RR 1.36, 95% CI 1.0 to 1.8 (absolute numbers not reported)	
[23]	2005	5	Fluspirilene decanoate *v* other depots	Relapse (3 RCTs): RR 0.55, 95% CI 0.1 to 2.3 (absolute numbers not reported)	No significant difference
				Withdrawal: 4 RCTs, 83 people: 3/44 [7%] with fluspirilene decanoate *v* 4/39 [10%] with other depots; RR 0.55, 95% CI 0.14 to 2.27	
				Adverse effects (general, unspecified): 3 RCTs, 83 people: 12/44 [27%] with fluspirilene decanoate *v* 18/39 [46%] with other depots; RR 0.69, 95% CI 0.12 to 4.00	
[24]	2004	1	Perphenazine enanthate *v* clopenthixol decanoate	Relapse (6–12 months; 1 RCT, 172 people): 37/85 [44%] with perphenazine enanthate *v* 29/87 [33%] with clopenthixol decanoate; RR 1.31, 95% CI 0.89 to 1.92	No significant difference
				Withdrawal: 37/85 [44%] with perphenazine enanthate *v* 29/87 [33%] with clopenthixol decanoate; RR 1.31, 95% CI 0.89 to 1.92	
				Adverse effects (additional anticholinergic drugs required): 82/85 [96%] with perphenazine enanthate *v* 75/87 [86%] with clopenthixol decanoate; RR 1.12, 95% CI 1.02 to 1.23	
[25]	1998	4	Zuclopenthixol decanoate *v* other depots	Relapse: 3 RCTs, 296 people; 33/153 [22%] with zuclopenthixol decanoate *v* 48/143 [34%] with other depots; RR 0.67, 95% CI 0.47 to 0.96; NNT 8, 95% CI 5 to 53	People taking zuclopenthixol had lower relapse rates over 12 weeks to 1 year

Ref	Search date	Number of RCTs	Comparisons	Results	Main conclusion
				Withdrawal (any reason): 4 RCTs, 332 people: 36/171 [21%] with zuclopenthixol decanoate *v* 49/161 [30%] with other depots; RR 0.70, 95% CI 0.50 to 1.00	
[16]	1999	31	Clozapine *v* first-generation antipsychotic drugs	Relapse: shorter term (up to 12 weeks; 19 RCTs, 1303 people): 51/639 [8%] with clozapine *v* 86/664 [13%] with first-generation; RR 0.62, 95% CI 0.45 to 0.84	Relapse rates up to 12 weeks were lower with clozapine
				long-term (over 26 weeks; 4 RCTs, 578 people): 22/290 [8%] with clozapine *v* 102/288 [35%] with first-generation; RR 0.22, 95% CI 0.14 to 0.34	
[17]	2003	3	Bromperidol *v* haloperidol or fluphenazine	Relapse (2 RCTs, 68 people): 9/33 [27%] with bromperidol *v* 2/34 [6%] with haloperidol or fluphenazine; RR 3.92, 95% CI 1.05 to 14.60	Relapse rates over 6–12 months were lower with haloperidol or fluphenazine
				Withdrawal: 3 RCTs, 97 people: 10/48 [21%] with bromperidol *v* 5/49 [10%] with haloperidol or fluphenazine; RR 1.92, 95% CI 0.80 to 4.60	
[21]	2002	23	Risperidone *v* other antipsychotic drugs (or placebo: 1 RCT)	Relapse (by 1 year; 1 RCT, 265 people): 26/179 [15%] with risperidone *v* 43/188 [23%] with other antipsychotic drugs: RR 0.64, 95% CI 0.41 to 0.99	Relapse rates over 1 year were lower with risperidone
				Withdrawal: 23 RCTs, 4364 people; 791/2820 [28%] with risperidone *v* 532/1544 [34%] with other antipsychotic drugs; RR 0.80, 95% CI 0.73 to 0.88	
[14]	2002	10	Second-generation antipsychotics *v* first-generation antipsychotics	Relapse (10 RCTs, 1710 people): 161/1096 [15%] with second-generation *v* 142/614 [23%] with first-generation: AR –0.08, 95% CI –0.12 to –0.04; NNT 13, 95% CI 8 to 25	Relapse rates after 52–130 weeks' follow-up were significantly lower with second-generation agents
				Withdrawal due to adverse effects (6 RCTs, 1537 people): 111/985 [11%] with second-generation *v* 85/552 [15%] with first-generation; AR –0.02, 95% CI –0.05 to +0.02; P = 0.40	
[14]	2002	2	Risperidone *v* first-generation antipsychotic	Relapse rate (2 RCTs, 428 people): 43/210 [20%] with risperidone *v* 68/218 [31%] with first-generation agent; AR –0.10, 95% CI –0.18 to –0.02	Relapse rates are significantly lower with risperidone
		1	Sertindole *v* first-generation antipsychotic	Relapse rate (1 RCT, 203 people): 2/94 [2%] with sertindole *v* 12/109 [11%] with first-generation agent; AR –0.09, 95% CI –0.15 to –0.02	Relapse rates are significantly lower with sertindole
		3	Clozapine *v* first-generation antipsychotic	Relapse rate (3 RCTs, 212 people): 24/136 [18%] with clozapine *v* 19/76 [25%] with first-generation agent; AR –0.08, 95% CI –0.19 to +0.04	No significant difference between clozapine and first-generation antipsychotics
		3	Olanzapine *v* first-generation antipsychotic	Relapse rate (3 RCTs, 807 people): 87/627 [14%] with olanzapine *v* 34/180 [19%] with first-generation agent; AR –0.05, 95% CI –0.11 to +0.01	No significant difference between olanzapine and first-generation antipsychotics
		1	Amisulpride *v* first-generation antipsychotic	Relapse rate (1 RCT, 60 people): 5/29 [17%] with amisulpride *v* 9/31 [29%] with first-generation agent; AR –0.12, 95% CI –0.33 to +0.09	No significant difference between amisulpride and first-generation antipsychotics

Ref, reference.

TABLE **GRADE evaluation of interventions for schizophrenia**

Important outcomes	Symptom improvement, relapse rates, adherence to treatment, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments to reduce relapse rates in people with schizophrenia?									
At least 16 (at least 1166) [11] [10] [12] [13]	Relapse rate	Continuing first-generation antipsychotic treatment *v* placebo or no treatment	4	0	–1	–1	0	Low	Consistency point deducted for statistical heterogeneity among studies. Directness point deducted for inclusion of people with schizophrenia-related disorders
6 (983) [14]	Relapse rate	Continuing second generation antipsychotic treatment *v* placebo	4	0	–1	–1	0	Low	Consistency point deducted for statistical heterogeneity among studies. Directness point deducted for inclusion of people with schizophrenia-related disorders
At least 57 (at least 5714) [13] [14] [15] [16] [17] [19] [20] [22] [24] [25]	Relapse rate	Different antipsychotic drugs compared with each other	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
At least 16 (at least 857) [32] [33] [34]	Relapse rate	Family interventions *v* usual care, single-session family intervention or psychoeducational interventions	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting of results and inclusion of quasi-RCTs. Directness points deducted for multiple interventions in control group and for wide range of interventions
At least 7 (at least 716) [34] [35]	Relapse rate	Psychoeducation *v* usual care	4	–1	0	–2	0	Low	Quality point deducted for incomplete reporting of statistical analysis. Directness points deducted for diverseness in comparators and for inclusion of people with schizophrenia-related disorders
At least 5 (at least 479) [36] [37]	Relapse rate	CBT plus standard care *v* standard care alone	4	0	–1	–2	0	Very low	Consistency point deducted for conflicting results. Directness point deducted for inclusion of people with schizophrenia-related disorders and for analysis based on small number of events in one group
2 (264) [38]	Relapse rate	Social-skills training *v* usual care	4	–2	0	0	+1	Moderate	Quality points deducted for incomplete reporting of results and unclear comparator. Effect-size point added for OR greater than 2
5 (219) [38] [39]	Relapse rate	Social-skills training *v* psychoeducational intervention	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (36) [40]	Relapse rate	Social-skills training *v* supportive group discussion	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for not carrying out between-group statistical assessment
Which interventions are effective in people with schizophrenia who are resistant to standard antipsychotic drugs?									
6 (1018) [19]	Symptom improvement	Clozapine *v* first-generation antipsychotic drugs	4	0	0	–2	0	Low	Directness points deducted for inclusion of partial responders and for unclear comparator
At least 4 (at least 315) [42]	Symptom improvement	Clozapine *v* olanzapine, risperidone, and zotepine	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of non-treatment-resistant people
3 (355) [19] [43]	Symptom improvement	Clozapine *v* olanzapine	4	0	0	0	0	High	

Important outcomes	Symptom improvement, relapse rates, adherence to treatment, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (84) [42]	Symptom improvement	Olanzapine *v* chlorpromazine	4	–1	0	–2	0	Very low	Quality point deducted for sparse data. Directness points deducted for inclusion of partial responders and for unclear duration of treatment-resistant illness
1 (306) [45]	Symptom improvement	Ziprasidone *v* chlorpromazine	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for unclear washout period
1 (300) [46]	Symptom improvement	Aripiprazole *v* perphenazine	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting. Directness point deducted for no statistical analysis between groups for all outcomes
Which interventions improve adherence to antipsychotic medication in people with schizophrenia?									
1 (36) [47]	Adherence to treatment	Behavioural therapy *v* usual care	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertain validity of outcome assessment (pill count)
4 (419) [35] [48]	Adherence to treatment	Psychoeducational interventions *v* usual treatment	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of data. Consistency point deducted for conflicting results. Directness point deducted for unclear measure of outcome
2 (75) [47] [49]	Adherence to treatment	Psychoeducational interventions*v* behavioural therapy	4	–2	–1	–2	0	Very low	Quality point deducted for sparse data and poor-follow up. Consistency point deducted for conflicting results. Directness point deducted for use inclusion of co-intervention (pill box) and uncertain validity of outcome assessment (pill count)
2 (465) [50] [51]	Adherence to treatment	Compliance therapy *v* non-specific therapy	4	0	0	–1	0	Moderate	Directness point deducted for unclear comparator
At least 7 (at least 369) [32] [33]	Adherence to treatment	Multiple-session family interventions *v* usual care, single-session family intervention or psychoeducational intervention	4	–2	0	–1	0	Very low	Quality point deducted for incomplete reporting of results and inclusion of quasi-randomised RCTs. Directness point deducted for inclusion of people with schizophrenia-related disorders

Type of evidence: 4 = RCT; 2 = Observational.
Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio