ClinicalEvidence

Schizophrenia

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ABSTRACT

INTRODUCTION: The lifetime prevalence of schizophrenia is approximately 0.7% and incidence rates vary between 7.7 and 43.0 per 100,000; about 75% of people have relapses and continued disability, and one 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: What are the effects of drug treatments for positive, negative, or cognitive symptoms of schizophrenia? What are the effects of drug treatments in people with schizophrenia who are resistant to standard antipsychotic drugs? What are the effects of interventions to improve adherence to antipsychotic medication in people with schizophrenia? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2010 (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 51 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: amisulpride, chlorpromazine, clozapine, depot haloperidol decanoate, haloperidol, olanzapine, pimozide, quetiapine, risperidone, sulpiride, ziprasidone, zotepine, aripiprazole, sertindole, paliperidone, flupentixol, depot flupentixol decanoate, zuclopenthixol, depot zuclopenthixol decanoate, behavioural therapy, clozapine, compliance therapy, first-generation antipsychotic drugs in treatment-resistant people, multiple-session family interventions, psychoeducational interventions, and second-generation antipsychotic drugs in treatment-resistant people.

QUESTIONS

INTERVENTIONS

TREATMENT OF POSITIVE, NEGATIVE, OR COGNITIVE SYMPTOMS

Trade off between benefits and harms

Unknown effectiveness

TREATMENTS IN PEOPLE RESISTANT TO STANDARD ANTIPSYCHOTICS

Trade off between benefits and harms

Unknown effectiveness

ADHERENCE TO ANTIPSYCHOTICS

Unknown effectiveness

To be covered in future updates

Cognitive remediation

Combinations of therapies for adherence

Key points

- The lifetime prevalence of schizophrenia is approximately 0.7% and incidence rates vary between 7.7 and 43.0 per 100,000; about 75% of people have relapses and continued disability, and one 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.

- Standard treatment of schizophrenia has been antipsychotic drugs, the first of which included chlorpromazine and haloperidol, but these so-called first-generation antipsychotics can all cause adverse effects such as extrapyramidal adverse effects, hyperprolactinaemia, and sedation. Attempts to address these adverse effects led to the development of second-generation antipsychotics.
- The second-generation antipsychotics amisulpride, clozapine, olanzapine, and risperidone may be more effective at reducing positive symptoms compared with first-generation antipsychotic drugs, but may cause similar adverse effects, plus additional metabolic effects such as weight gain.
- CAUTION: Clozapine has been associated with potentially fatal blood dyscrasias. Blood monitoring is essential, and it is recommended that its use be limited to people with treatment-resistant schizophrenia.
- Pimozide, quetiapine, aripiprazole, sulpiride, ziprasidone, and zotepine seem to be as effective as standard antipsychotic drugs at improving positive symptoms. Again, these drugs cause similar adverse effects to first-generation antipsychotics and other second-generation antipsychotics.
- CAUTION: Pimozide has been associated with sudden cardiac death at doses above 20 mg daily.
- We found very little evidence regarding depot injections of haloperidol decanoate, flupentixol decanoate, or zuclopenthixol decanoate; thus, we don't know if they are more effective than oral treatments at improving symptoms.
- In people who are resistant to standard antipsychotic drugs, clozapine may improve symptoms compared with first-generation antipsychotic agents, but this benefit must be balanced against the likelihood of adverse effects.

  We found limited evidence on other individual first- or second-generation antipsychotic drugs other than clozapine in people with treatment-resistant schizophrenia.

  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, or how clozapine compares with other second-generation antipsychotic agents, because of a lack of evidence.

- We don't know whether behavioural interventions, compliance therapy, psychoeducational interventions, or family interventions improve adherence to antipsychotic medication compared with usual care because of a paucity of good-quality evidence.
- It is clear that some included studies in this review have serious failings and that the evidence base for the efficacy of antipsychotic medication and other interventions is surprisingly weak. For example, although in many trials haloperidol has been used as the standard comparator, the clinical trial evidence for haloperidol is less impressive may be expected.
- By their very nature, systematic reviews and RCTs provide average indices of probable efficacy in groups of selected individuals. Although some RCTs limit inclusion criteria to a single category of diagnosis, many studies include individuals with different diagnoses such as schizoaffective disorder. In all RCTs, even in those recruiting people with a single DSM or ICD-10 diagnosis, there is considerable clinical heterogeneity.
- Genome-wide association studies of large samples with schizophrenia demonstrate that this clinical heterogeneity reflects, in turn, complex biological heterogeneity. For example, genome-wide association studies suggest that around 1000 genetic variants of low penetrance and other individually rare genetic variants of higher penetrance, along with epistasis and epigenetic mechanisms, are thought to be responsible, probably with the biological and psychological effects of environmental factors, for the resultant complex clinical phenotype. A more stratified approach to clinical trials would help to identify those subgroups that seem to be the best responders to a particular intervention.
- To date, however, there is little to suggest that stratification on the basis of clinical characteristics successfully helps to predict which drugs work best for which people. There is a pressing need for the development of biomarkers with clinical utility for mental health problems. Such measures could help to stratify clinical populations or provide better markers of efficacy in clinical trials, and would complement the current use of clinical outcome scales. Clinicians are also well aware that many people treated with antipsychotic medication develop significant adverse effects such as extrapyramidal symptoms or weight gain. Again, our ability to identify which people will develop which adverse effects is poorly developed, and might be assisted by using biomarkers to stratify populations.
- The results of this review tend to indicate that as far as antipsychotic medication goes, current drugs are of limited efficacy in some people, and that most drugs cause adverse effects in most people. Although this is a rather downbeat conclusion, it should not be too surprising, given clinical experience and our knowledge of the pharma-

cology of the available antipsychotic medication. All currently available antipsychotic medications have the same putative mechanism of action — namely, dopaminergic antagonism with varying degrees of antagonism at other receptor sites. More efficacious antipsychotic medication awaits a better understanding of the biological pathogenesis of these conditions so that rational treatments can be developed.

DEFINITION

Schizophrenia is a complex syndrome characterised by three major 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 the beneficial 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 two to three regimens of treatment with standard antipsychotic drugs for at least 6 weeks; an additional 30% to 40% of people improve but are residually symptomatic despite antipsychotic treatment. [3] Several pharmacological strategies have been advocated for this group of people. This review focuses on three key aspects of the management of schizophrenia: 1) What are the effects of drug treatments for positive, negative, or cognitive symptoms of schizophrenia? 2) What are the effects of interventions in people with schizophrenia who are resistant to standard antipsychotic drugs? and 3) What are the effects of interventions to improve adherence to antipsychotic medication in people with schizophrenia?

INCIDENCE/ PREVALENCE

The lifetime prevalence of schizophrenia is approximately 0.7% and incidence rates vary between 7.7 and 43.0 per 100,000. [4] The 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 (including genetic factors), obstetric complications, developmental difficulties, central nervous system infections in childhood, cannabis use, and acute life events. [6] 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. [7] 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. [8] Drug treatment is more successful in treating positive symptoms, but up to one third of people derive little benefit, and negative symptoms are difficult to treat. About half of people with schizophrenia do not adhere to treatment in the short term, and in the long term adherence is even lower. [9]

AIMS OF INTERVENTION

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

OUTCOMES

We have reported **symptom severity** (severity of positive and negative symptoms; global clinical improvement; global clinical impression [a composite measure of symptoms and everyday functioning]) for the first two questions, and **adverse effects** for all three questions. For the third question on interventions to improve treatment adherence, we have reported **adherence to 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 May 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to May 2010, Embase 1980 to May 2010, and The Cochrane Database of Systematic Reviews, May 2010 [online] (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. 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 of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >50% 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, although we realise that there are inherent difficulties with blinding in studies of antipsychotics. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews 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 relative risks (RRs) and odds ratios (ORs). Changes at this update: this review replaces and updates sections of two previous *Clinical Evidence* reviews, namely, Schizophrenia (acute) and Schizophrenia (maintenance treatment). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 166). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of drug treatments for positive, negative, or cognitive symptoms of schizophrenia?**

OPTION **AMISULPRIDE**

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Amisulpride may be more effective at reducing positive symptoms compared with first-generation antipsychotic drugs, but may cause similar adverse effects, plus additional metabolic effects such as weight gain.

Benefits and harms

Amisulpride versus placebo:

We found one systematic review (search date 1999, 4 RCTs, 514 people). [10] It should be noted that the included studies were in patients with primarily negative rather than positive symptoms.

Symptom severity

Compared with placebo Amisulpride may be more effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[10] Systematic review	514 people with negative symptoms 4 RCTs in this analysis At least 2 RCTs excluded patients with prominent positive symptoms At least 1 RCT included people with schizotypal personality disorder	**Scale for the Assessment of Negative Symptoms (SANS) score , 6 to 26 weeks** with amisulpride (50–300 mg) with placebo Absolute results reported graphically	Reported as significant	○○○	amisulpride
[10] Systematic review	514 people with negative symptoms 4 RCTs in this analysis At least 2 RCTs excluded patients with prominent positive symptoms.	**Scale for the Assessment of Positive Symptoms (SAPS) score , 6 to 26 weeks** with amisulpride (50–300 mg) with placebo Absolute results not reported	Significance not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	At least 1 RCT included people with schizotypal personality disorder	Study reports that the overall analysis shows that the improvement in SANS was accompanied by a small simultaneous improvement in SAPS			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[10] Systematic review	541 people with negative symptoms 4 RCTs in this analysis	**Extrapyramidal symptoms , 6 to 26 weeks** with amisulpride (50–300 mg) with placebo Absolute results not reported	Reported as not significant P value not reported The review reported a small decrease in all treatment groups without statistically significant differences between groups	⟷	Not significant

Amisulpride versus haloperidol:

We found one systematic review (search date 2006, 13 RCTs, 1017 people). [11] The review did not report any outcomes of interest for this *Clinical Evidence* review but did report treatment-related adverse effects.

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	783 people 8 RCTs in this analysis	**Extrapyramidal symptoms** with amisulpride with haloperidol Absolute results not reported	RR 0.58 95% CI 0.45 to 0.76	●○○	amisulpride
[11] Systematic review	373 people 2 RCTs in this analysis	**Mean weight gain (kg)** with amisulpride with haloperidol Absolute results not reported	Mean difference 0.9 kg 95% CI 0.2 kg to 1.6 kg	○○○	haloperidol
[11] Systematic review	490 people 4 RCTs in this analysis	**Risk of sedation** with amisulpride with haloperidol Absolute results not reported	RR 0.69 95% CI 0.15 to 3.13	⟷	Not significant

Amisulpride versus olanzapine:

We found one systematic review (search date 2007, 5 RCTs, 804 people) [12] and one subsequent RCT. [13]

Symptom severity

Compared with olanzapine We don't know whether amisulpride is more effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[12] Systematic review	701 people 4 RCTs in this analysis	**Mean difference in Positive and Negative Syndrome Scale (PANSS) positive symptom subscore** with amisulpride (100–1000 mg/day) with olanzapine (5–20 mg/day) Absolute results not reported	Mean difference +0.66 95% CI –0.56 to +1.88	⟷	Not significant
[12] Systematic review	701 people 4 RCTs in this analysis	**Mean difference in PANSS negative symptom subscore** with amisulpride (100–1000 mg/day) with olanzapine (5–20 mg/day) Absolute results not reported	Mean difference +0.21 95% CI –0.69 to +1.10	⟷	Not significant
[13] RCT	80 people Single-blind RCT; 40 people randomised to amisulpride and 40 to olanzapine 3 people lost to follow-up (1 on amisulpride, 2 on olanzapine)	**Scale for the Assessment of Positive Symptoms (SAPS) score at baseline , 4 to 12 weeks** with amisulpride (100–800 mg/day) with olanzapine (10–20 mg/day) Absolute results not reported	Significant improvement in both groups from baseline to 12 weeks (21.3, 95% CI 16.54 to 24.13 with amisulpride *v* 31.4, 95% CI 27.14 to 35.70 with olanzapine) The RCT reported that the scores between groups were not significantly different at baseline to study end; no further data reported	⟷	Not significant
[13] RCT	80 people Single-blind RCT, 40 people randomised to amisulpride and 40 to olanzapine 3 people lost to follow-up (1 on amisulpride, 2 on olanzapine)	**Scale for the Assessment of Negative Symptoms (SANS) score at baseline , 4 to 12 weeks** with amisulpride (100–800 mg/day) with olanzapine (10–20 mg/day) Absolute results not reported	Significant improvement in both groups from baseline to 12 weeks (25.7, 95% CI 22.22 to 29.21 with amisulpride *v* 26.3, 95% CI 23.6 to 28.97 with olanzapine) The RCT reported that the scores between groups were not significantly different at baseline to study end; no further data reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Systematic review	462 people 2 RCTs in this analysis	**At least 1 adverse effect** with amisulpride (100–1000 mg/day) with olanzapine (5–20 mg/day) Absolute results not reported	RR 1.03 95% CI 0.87 to 1.21	⟷	Not significant
[12] Systematic review	587 people 2 RCTs in this analysis	**Extrapyramidal symptoms** with amisulpride (100–1000 mg/day) with olanzapine (5–20 mg/day)	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
[12] Systematic review	672 people 3 RCTs in this analysis	**Number of people with weight gain** with amisulpride (100–1000 mg/day) with olanzapine (5–20 mg/day) Absolute results not reported Weight gain as adverse event or >7% total body weight	RR 0.55 95% CI 0.40 to 0.75	●○○	amisulpride
[12] Systematic review	672 people 3 RCTs in this analysis	**Weight change from baseline (kg)** with amisulpride (100–1000 mg/day) with olanzapine (5–20 mg/day) Absolute results not reported	Difference –2.11 kg 95% CI –2.94 kg to –1.29 kg	○○○	amisulpride
[12] Systematic review	303 people 2 RCTs in this analysis	**Mean difference in change from baseline in QTc (ms)** with amisulpride (100–1000 mg/day) with olanzapine (5–20 mg/day) Absolute results not reported	Mean difference +5.25 ms 95% CI –0.57 ms to +11.07 ms	⟷	Not significant
[13] RCT	80 people Single-blind RCT; 40 people randomised to amisulpride and 40 to olanzapine 3 people lost to follow-up (1 on amisulpride, 2 on olanzapine)	**Mean weight gain (kg) , 12 weeks** 3.5 kg with amisulpride (100–800 mg/day) 4.7 kg with olanzapine (10–20 mg/day)	P <0.001	○○○	amisulpride
[13] RCT	80 people Single-blind RCT; 40 people randomised to amisulpride and 40 to olanzapine 3 people lost to follow-up (1 on amisulpride, 2 on olanzapine)	**Proportion of people with 1 treatment-emergent adverse effect** 68% with amisulpride (100–800 mg/day) 48% with olanzapine (10–20 mg/day) Absolute numbers not reported Adverse effects included: tremor, akathisia, insomnia, increased salivation, >10% weight gain, increased appetite, sedation, increased blood glucose level	P = 0.113	⟷	Not significant

Amisulpride versus risperidone:

We found one systematic review (search date 2007, 4 RCTs, 622 people [12]) and one RCT. [14]

Symptom severity

Compared with risperidone We don't know whether amisulpride is more effective at improving positive and negative symptoms in people with schizophrenia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[12] Systematic review	586 people 3 RCTs in this analysis	**No clinically important change (as defined by original studies)** with amisulpride (100–1000 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	RR 0.89 95% CI 0.67 to 1.20	⟷	Not significant
[12] Systematic review	310 people Data from 1 RCT	**<50% reduction in Positive and Negative Syndrome Scale (PANSS) total score** with amisulpride (100–1000 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	RR 0.81 95% CI 0.65 to 1.00	⟷	Not significant
[12] Systematic review	48 people Data from 1 RCT	**20% reduction in PANSS total score , short term** with amisulpride (100–1000 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	RR 1.45 95% CI 0.59 to 3.54	⟷	Not significant
[12] Systematic review	310 people Data from 1 RCT	**<50% reduction in Brief Psychiatric Rating Scale (BPRS) score** with amisulpride (100–1000 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	RR 0.78 95% CI 0.62 to 0.98 NNT 8 95% CI 4 to 100	●○○	amisulpride
[12] Systematic review	228 people Data from 1 RCT	**<40% reduction in BPRS score , short term** with amisulpride (100–1000 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	RR 0.78 95% CI 0.56 to 1.09	⟷	Not significant
[12] Systematic review	519 people 3 RCTs in this analysis	**Mean difference in PANSS positive symptom subscore** with amisulpride (100–1000 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	Mean difference –0.03 95% CI –1.29 to +1.24	⟷	Not significant
[12] Systematic review	519 people 3 RCTs in this analysis	**Mean difference in PANSS negative symptom subscore** with amisulpride (100–1000 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	Mean difference –1.0 95% CI –2.11 to +0.11	⟷	Not significant
[14] RCT	38 older people Double-blind RCT; 25 people randomised to amisulpride and 13 to risperidone	**Reduction in PANSS score , 6 weeks** 28% with amisulpride (100–400 mg/day) 29% with risperidone (1–4 mg/day)	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The RCT included a mixed population of schizophrenia, schizophreniform, schizoaffective, delusional, and shared psychotic disorders but details not given	Absolute numbers not reported			
[14] RCT	38 older people Double-blind RCT; 25 people randomised to amisulpride and 13 to risperidone The RCT included a mixed population of schizophrenia, schizophreniform, schizoaffective, delusional, and shared psychotic disorders but details not given	**Proportion of people who responded to treatment** 10/25 (40%) with amisulpride (100–400 mg/day) 5/13 (38%) with risperidone (1–4 mg/day) Improvement of >20% in PANSS score constitutes "response" Per-protocol analysis on actual score	P value not reported		
[14] RCT	38 older people Double-blind RCT; 25 people randomised to amisulpride and 13 to risperidone The RCT included a mixed population of schizophrenia, schizophreniform, schizoaffective, delusional, and shared psychotic disorders but details not given	**BPRS score , 6 weeks** with amisulpride (100–400 mg/day) with risperidone (1–4 mg/day) Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[14] RCT	38 older people Double-blind RCT; 25 people randomised to amisulpride and 13 to risperidone The RCT included a mixed population of schizophrenia, schizophreniform, schizoaffective, delusional, and shared psychotic disorders but details not given	**Mini-Mental State Examination , 6 weeks** with amisulpride (100–400 mg/day) with risperidone (1–4 mg/day) Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Systematic review	622 people 4 RCTs in this analysis	**At least 1 adverse effect** with amisulpride (100–1000 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	RR 1.00 95% CI 0.91 to 1.11	⟷	Not significant
[12] Systematic review	538 people 2 RCTs in this analysis	**Extrapyramidal symptoms measured by Abnormal Involuntary Movement Scale** with amisulpride (100–1000 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	Mean difference +0.08 95% CI –0.55 to +0.72	⟷	Not significant
[12] Systematic review	538 people 2 RCTs in this analysis	**Extrapyramidal symptoms measured by Simpson-Angus Scale** with amisulpride (100–1000 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	Mean difference –0.03 95% CI –0.13 to +0.06	⟷	Not significant
[12] Systematic review	538 people 2 RCTs in this analysis	**Number of patients with significant weight gain** with amisulpride (100–1000 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	RR 0.57 95% CI 0.35 to 0.95	●○○	amisulpride
[12] Systematic review	538 people 2 RCTs in this analysis	**Weight change from baseline (kg)** with amisulpride (100–1000 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	Mean difference –0.99 kg 95% CI –1.61 kg to –0.37 kg	○○○	amisulpride
[14] RCT	38 older people Double-blind RCT; 25 people randomised to amisulpride and 13 to risperidone The RCT included a mixed population of schizophrenia, schizophreniform, schizoaffective, delusional, and shared psychotic disorders but details not given	**Extrapyramidal symptoms measured by Simpson-Angus Scale** with amisulpride (100–400 mg/day) with risperidone (1–4 mg/day) Absolute results not reported	No significant difference in change from baseline between groups P value not reported	⟷	Not significant
[14] RCT	38 older people Double-blind RCT; 25 people randomised to amisulpride and 13 to risperidone The RCT included a mixed population of schizophrenia,	**Extrapyramidal symptoms measured by Barnes Akathisia Scale** with amisulpride (100–400 mg/day) with risperidone (1–4 mg/day) Absolute results not reported	No significant difference in change from baseline between groups P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	schizophreniform, schizoaffective, delusional, and shared psychotic disorders but details not given				

Amisulpride versus ziprasidone:

We found one systematic review (search date 2007, 1 RCT, 123 people). [12]

Symptom severity

Compared with ziprasidone We don't know whether amisulpride is more effective at improving negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[12] Systematic review	123 people Data from 1 RCT	**<50% reduction in Positive and Negative Syndrome Scale (PANSS) negative symptom score** with amisulpride (100–1000 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	RR 0.95 95% CI 0.84 to 1.08	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Systematic review	123 people Data from 1 RCT	**At least 1 adverse effect** with amisulpride (100–1000 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	RR 0.90 95% CI 0.66 to 1.22	⟷	Not significant
[12] Systematic review	123 people Data from 1 RCT	**Extrapyramidal symptoms** with amisulpride (100–1000 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[12] Systematic review	123 people Data from 1 RCT	**Weight gain >7%** with amisulpride (100–1000 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	RR 2.10 95% CI 0.77 to 5.67	⟷	Not significant

Amisulpride versus first-generation antipsychotics:

We found one systematic review (search date 2006, 13 RCTs, 1017 people). [11]

Symptom severity

Compared with first-generation antipsychotics Amisulpride seems more effective at improving positive and negative symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[11] Systematic review	703 people 4 RCTs in this analysis	**Hedges' adjusted g effect size for positive symptoms (Positive and Negative Symptom Scale [PANSS])** with amisulpride with first-generation antipsychotic drugs Absolute results not reported First-generation antipsychotic drugs included haloperidol, chlorpromazine, perphenazine, fluphenazine, flupentixol, perazine, thioridazine, levomepromazine, clopenthixol, zuclopenthixol, mosapramine, tiothixene, clocapramine, trifluoperazine, periciazine	Hedges' adjusted g effect size –0.22 95% CI –0.37 to –0.06	○○○	amisulpride
[11] Systematic review	929 people 10 RCTs in this analysis	**Hedges' adjusted g effect size for negative symptoms (PANSS)** with amisulpride with first-generation antipsychotic drugs Absolute results not reported First-generation antipsychotic drugs included haloperidol, chlorpromazine, perphenazine, fluphenazine, flupentixol, perazine, thioridazine, levomepromazine, clopenthixol, zuclopenthixol, mosapramine, tiothixene, clocapramine, trifluoperazine, periciazine	Hedges' adjusted g effect size for negative symptoms –0.27 95% CI –0.40 to –0.14	○○○	amisulpride

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	30 people Data from 1 RCT	**Extrapyramidal symptoms** with amisulpride with low potency first-generation antipsychotics Absolute results not reported First-generation antipsychotics included chlorpromazine, perphenazine, fluphenazine, flupentixol, perazine, thioridazine, levomepromazine, clopenthixol, zuclopenthixol, mosapramine, tioth-	RR 1.00 95% CI 0.70 to 1.43	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		ixene, clocapramine, trifluoperazine, periciazine			
[11] Systematic review	30 people Data from 1 RCT	**Mean weight gain difference (kg)** with amisulpride with low-potency first-generation antipsychotics Absolute results not reported First-generation antipsychotics included chlorpromazine, perphenazine, fluphenazine, flupentixol, perazine, thioridazine, levomepromazine, clopenthixol, zuclopenthixol, mosapramine, tiothixene, clocapramine, trifluoperazine, periciazine	Mean difference +0.3 kg 95% CI –3.6 kg to +4.2 kg	⟷	Not significant

Further information on studies

[10] There was high withdrawal rate in the individual studies (12–68%). At least one study included patients that had disorders with diagnoses other than schizophrenia (e.g., schizotypal personality disorder). Patients with predominantly negative symptoms were included in the studies and low doses were given, with two trials excluding patients with prominent positive symptoms.

[11] The review did not include a comparison of amisulpride versus some first-generation drugs alone, but grouped first-generation antipsychotics together; thus, it is not possible to do individual comparisons. Some studies included patients that had disorders with diagnoses other than schizophrenia (e.g., schizophreniform disorder, schizoaffective disorder, psychotic state).

[12] RCTs included in the systematic review included patients with schizophrenia and other types of schizophrenia-like diagnoses. There was high overall withdrawal rate (35%). Six trials were sponsored by companies producing amisulpride; three were sponsored by companies marketing the comparator (sponsoring of 1 study unclear). There was a high risk of bias in at least one aspect of every study. One study (sponsored by a company manufacturing the comparator) used an unusually low dose of amisulpride.

[13] Missing values were dealt with in the RCT using last observation carried forward (LOCF), but the paper did not report how many missing values there were. Outcomes were compared between groups at baseline and at each follow-up point, even when there were differences at baseline. Change from baseline should have been compared between groups — if it had, there probably would have been a significant difference between the groups for SAPS score.

[14] The RCT had a very small sample size and a per-protocol analysis was carried out on most outcome measures, thereby ignoring the 9 patients that withdrew. The RCT also had very unbalanced group sizes, despite supposed randomisation. The study was sponsored and funded by Sanofi-Aventis, manufacturers of amisulpride.

Comment: Two systematic reviews [11] [12] were methodologically strong but the included studies were poor (as acknowledged by the authors). One systematic review included studies with unusually low doses of amisulpride and high rates of withdrawal and may not have a robust analysis. [10] The two RCTs [13] [14] were either poorly designed or poorly analysed (or both). Study lengths were very short, with the shortest being 4 weeks and the longest 26 weeks. Overall, the evidence suggests that, for some people, amisulpride may have advantages in terms of response over first-generation antipsychotics and in adverse effects over second-generation antipsychotic drugs, although the evidence is generally weak, and it is not clear from the studies reviewed which patient groups might benefit from amisulpride.

Clinical guide:
Amisulpride treatment shows some advantages over first-generation antipsychotics, although the evidence is poor. On the basis of clinical evidence and experience, most clinicians regard it to be

effective. When choosing between amisulpride and other antipsychotics, adverse-effect profiles should be taken into consideration.

OPTION CHLORPROMAZINE

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Chlorpromazine may be as effective as haloperidol, clozapine, and risperidone at reducing symptoms, and shows a similar adverse-effect profile of metabolic and extrapyramidal adverse effects.

Benefits and harms

Chlorpromazine versus placebo:

We found one systematic review (search date 2002, 50 RCTs, 5276 people). [15]

Symptom severity

Compared with placebo Chlorpromazine may be more effective at improving global improvement scores in people with schizophrenia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[15] Systematic review	49 people 2 RCTs in this analysis	**Mean difference in Brief Psychiatric Rating Scale (BPRS) score , 1 day to 3 years** with chlorpromazine (25–2000 mg/day) with placebo Absolute results not reported	Mean difference –4.82 95% CI –8.5 to +1.2	⟷	Not significant
[15] Systematic review	1131 people 13 RCTs in this analysis	**No global improvement , 1 day to 3 years** with chlorpromazine (25–2000 mg/day) with placebo Absolute results not reported	RR 0.76 95% CI 0.7 to 0.9	●○○	chlorpromazine

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] Systematic review	1242 people 18 RCTs in this analysis	**Sedation , 1 day to 3 years** with chlorpromazine (25–2000 mg/day) with placebo Absolute results not reported	RR 2.3 95% CI 1.7 to 3.1 NNH 6 95% CI 5 to 8	●●○	placebo
[15] Systematic review	165 people 5 RCTs in this analysis	**Weight gain >10 lb (4.5 kg) , 1 day to 3 years** with chlorpromazine (25–2000 mg/day) with placebo Absolute results not reported	RR 4.44 95% CI 2.1 to 9.3 NNH 3 95% CI 2 to 5	●●○	placebo
[15] Systematic review	1002 people 8 RCTs in this analysis	**Akathisia , 1 day to 3 years** with chlorpromazine (25–2000 mg/day)	RR 0.95 95% CI 0.5 to 1.9	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with placebo Absolute results not reported			
[15] Systematic review	780 people 4 RCTs in this analysis	**Acute dystonia , 1 day to 3 years** with chlorpromazine (25–2000 mg/day) with placebo Absolute results not reported	RR 3.1 95% CI 1.3 to 7.7 NNH 24 95% CI 15 to 57	●●○	placebo
[15] Systematic review	1265 people 12 RCTs in this analysis	**Parkinsonism , 1 day to 3 years** with chlorpromazine (25–2000 mg/day) with placebo Absolute results not reported	RR 2.6 95% CI 1.2 to 5.4 NNH 10 95% CI 8 to 16	●●○	placebo
[15] Systematic review	799 people 6 RCTs in this analysis	**Photosensitive reaction , 1 day to 3 years** with chlorpromazine (25–2000 mg/day) with placebo Absolute results not reported	RR 5.19 95% CI 3 to 10 NNH 7 95% CI 6 to 10	●●●	placebo
[15] Systematic review	1232 people 15 RCTs in this analysis	**Hypotension and dizziness , 1 day to 3 years** with chlorpromazine (25–2000 mg/day) with placebo Absolute results not reported	RR 1.9 95% CI 1.4 to 27 NNH 12 95% CI 8 to 22	●○○	placebo
[15] Systematic review	756 people 5 RCTs in this analysis	**Dry mouth , 1 day to 3 years** with chlorpromazine (25–2000 mg/day) with placebo Absolute results not reported	RR 4 95% CI 1.6 to 10 NNH 18 95% CI 13 to 37	●●○	placebo
[15] Systematic review	657 people Data from 1 RCT It is unclear whether these data are from 1 or 2 RCTs	**Eye opacities , 1 day to 3 years** with chlorpromazine (25–2000 mg/day) with placebo Absolute results not reported	RR 3.09 95% CI 1.9 to 5.1 NNH 7 95% CI 5 to 10	●●○	placebo
[15] Systematic review	955 people 9 RCTs in this analysis	**Constipation , 1 day to 3 years** with chlorpromazine (25–2000 mg/day) with placebo Absolute results not reported	RR 1.68 95% CI 0.9 to 2.9	↔	Not significant
[15] Systematic review	712 people 3 RCTs in this analysis	**Urinary retention , 1 day to 3 years** with chlorpromazine (25–2000 mg/day) with placebo Absolute results not reported	RR 1.49 95% CI 0.5 to 4.3	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[15] Systematic review	910 people 6 RCTs in this analysis	**Blurred vision , 1 day to 3 years** with chlorpromazine (25–2000 mg/day) with placebo Absolute results not reported	RR 1.10 95% CI 0.5 to 2.9	⟷	Not significant

Chlorpromazine versus clozapine:

We found one systematic review (search date 2006, 1 RCT, 164 people). [16]

Symptom severity

Compared with clozapine We don't know whether chlorpromazine is more effective at improving positive and negative symptoms in people who are antipsychotic naive at 12 to 52 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[16] Systematic review	164 people with first-episode psychosis, who are antipsychotic naive Data from 1 RCT	**Mean difference in change from baseline in Scale for the Assessment of Negative Symptoms (SANS) total score , 12 weeks** with chlorpromazine (600 mg/day) with clozapine (400 mg/day) Absolute results not reported	P = 0.01	○○○	clozapine
[16] Systematic review	164 people with first-episode psychosis, who are antipsychotic naive Data from 1 RCT	**Mean difference in change from baseline in SANS total score , 52 weeks** with chlorpromazine (600 mg/day) with clozapine (400 mg/day) Absolute results not reported	P = 0.40	⟷	Not significant
[16] Systematic review	164 people with first-episode psychosis, who are antipsychotic naive Data from 1 RCT	**Mean difference in change from baseline in Clinical Global Impression scale Severity (CGI-S) score , 12 weeks** with chlorpromazine (600 mg/day) with clozapine (400 mg/day) Absolute results not reported	P = 0.13	⟷	Not significant
[16] Systematic review	164 people with first-episode psychosis, who are antipsychotic naive Data from 1 RCT	**Mean difference in change from baseline in CGI-S score , 52 weeks** with chlorpromazine (600 mg/day) with clozapine (400 mg/day) Absolute results not reported	P = 0.36	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[16] Systematic review	164 people with first-episode psychosis, who are antipsychotic naive Data from 1 RCT	**Difference in Simpson-Angus Extrapyramidal Symptom Scale (SAESS) total score , 12 weeks** with chlorpromazine (600 mg/day) with clozapine (400 mg/day) Absolute results not reported	P <0.01	○○○	clozapine
[16] Systematic review	164 people with first-episode psychosis, who are antipsychotic naive Data from 1 RCT	**Difference in SAESS total score , 52 weeks** with chlorpromazine (600 mg/day) with clozapine (400 mg/day) Absolute results not reported	P = 0.40	⟷	Not significant
[16] Systematic review	164 people with first-episode psychosis, who are antipsychotic naive Data from 1 RCT	**Parkinsonism score , 12 weeks** with chlorpromazine (600 mg/day) with clozapine (400 mg/day) Absolute results not reported	P <0.01	○○○	clozapine
[16] Systematic review	164 people with first-episode psychosis, who are antipsychotic naive Data from 1 RCT	**Parkinsonism score , 52 weeks** with chlorpromazine (600 mg/day) with clozapine (400 mg/day) Absolute results not reported	P = 0.32	⟷	Not significant
[16] Systematic review	164 people with first-episode psychosis, who are antipsychotic naive Data from 1 RCT	**Mean weight gain (kg)** 6.5 kg with chlorpromazine (600 mg/day) 9.9 kg with clozapine (400 mg/day)	P = 0.30	⟷	Not significant

Chlorpromazine versus haloperidol:

We found one systematic review (search date 2007, 14 RCTs, 794 people). [17]

Symptom severity

Compared with haloperidol We don't know whether chlorpromazine is more effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[17] Systematic review	241 people 5 RCTs in this analysis	**No clinically significant improvement** with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported	RR 0.91 95% CI 0.73 to 1.13	⟷	Not significant
[17]	37 people Data from 1 RCT	**Mean difference for mean Clinical Global Impression scale (CGI) Severity score**	Mean difference –0.2 95% CI –0.98 to +0.58	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Systematic review		with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported			
[17] Systematic review	37 people Data from 1 RCT	**Mean Brief Psychiatric Rating Scale (BPRS) total score** with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported	Mean difference –2.70 95% CI –7.28 to +1.88	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] Systematic review	38 people 2 RCTs in this analysis	**Anticholinergic events** with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[17] Systematic review	28 people Data from 1 RCT	**At least 1 adverse effect** with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported	RR 0.92 95% CI 0.65 to 1.30	⟷	Not significant
[17] Systematic review	29 people Data from 1 RCT	**Hypertension** with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported	RR 6.07 95% CI 0.32 to 116.33	⟷	Not significant
[17] Systematic review	66 people 2 RCTs in this analysis	**Hypotension** with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported	RR 0.22 95% CI 0.04 to 1.24	⟷	Not significant
[17] Systematic review	86 people 3 RCTs in this analysis	**Sedation** with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported	RR 0.35 95% CI 0.02 to 5.73	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[17] Systematic review	37 people Data from 1 RCT	**Galactorrhoea** with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported	RR 1.88 95% CI 0.76 to 4.68	⟷	Not significant
[17] Systematic review	48 people 2 RCTs in this analysis	**Weight gain** with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported	RR 0.11 95% CI 0.01 to 1.89	⟷	Not significant
[17] Systematic review	287 people Data from 1 RCT	**Weight loss** with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported	RR 3 95% CI 0.73 to 12.39	⟷	Not significant
[17] Systematic review	103 people 3 RCTs in this analysis	**At least 1 extrapyramidal adverse effect** with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported	RR 1.96 95% CI 0.93 to 4.10	⟷	Not significant
[17] Systematic review	48 people 2 RCTs in this analysis	**Skin photosensitivity** with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported	RR 0.17 95% CI 0.02 to 1.3	⟷	Not significant
[17] Systematic review	38 people Data from 1 RCT	**Rash** with oral chlorpromazine (50–1800 mg/day) with oral haloperidol (2–100 mg/day) Absolute results not reported	RR 3 95% CI 0.13 to 69.31	⟷	Not significant

Chlorpromazine versus risperidone:

We found one systematic review (search date 2007, 6 RCTs, 256 people). [18]

Symptom severity

Compared with risperidone We don't know whether chlorpromazine is more effective at improving Brief Psychiatric Rating Scale scores in children at 8 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[18] Systematic review	60 children (age 7–16 years) Data from 1 RCT The blinding of this RCT was unclear	**No improvement in Brief Psychiatric Rating Scale (BPRS) score , 8 weeks** with chlorpromazine (400 mg/day) with risperidone (0.5–5 mg/day) Absolute results not reported	RR 1.2 95% CI 0.41 to 3.51	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] Systematic review	60 children (aged 7–16 years) Data from 1 RCT The blinding of this RCT was unclear	**Anticholinergic effects** with chlorpromazine (400 mg/day) with risperidone (0.5–5 mg/day) Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

Further information on studies

[16] The trial included in this systematic review compared clozapine versus chlorpromazine in antipsychotic-naive patients with first-episode schizophrenia. This is an unlikely comparison as clozapine is only licensed for treatment-resistant schizophrenia. The trial analysis used last observation carried forward (LOCF) to adjust for loss to follow-up, which is not a particularly robust method.

[15] [17] [18] The methodology for these reviews was good but most included studies are reported as having a moderate risk of bias, because of inadequate reporting of randomisation and blinding procedures. Some RCTs included in the reviews may be open label [15] [18] and report inadequate description of loss to follow-up.

Comment: The evidence suggests that patients have better global improvement with chlorpromazine than with placebo, but there was no difference between groups in Brief Psychiatric Rating Scale (BPRS) score. There is no evidence of any difference in benefit between chlorpromazine and clozapine, haloperidol, or risperidone. Chlorpromazine is strongly associated with several adverse effects compared with placebo but is broadly similar to clozapine, haloperidol, and risperidone; however, it may be associated with worse extrapyramidal symptoms than clozapine in the short term.

Clinical guide:
Decades of experience of using chlorpromazine for schizophrenia have led to consensus that it is effective in many patients for treatment of positive symptoms. It is, however, associated with several well recognised adverse effects.

OPTION CLOZAPINE

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Clozapine has a similar efficacy profile to other second-generation antipsychotics and some superiority over first-generation antipsychotics. Clozapine is associated with a higher risk of blood abnormalities, hypersalivation, sedation, and weight gain than first-generation antipsychotics and a higher risk of seizures and hypersalivation

than other second-generation antipsychotics. However, clozapine has a lower risk of extrapyramidal symptoms and prolactin problems than other antipsychotics. Clozapine is licensed to treat treatment-resistant schizophrenia.

Benefits and harms

Clozapine versus chlorpromazine:

See treatment option on chlorpromazine, p 14 .

Clozapine versus haloperidol:

We found two systematic reviews (search date 2009, 52 RCTs, 4746 people; [19] and search date 2006, 23 RCTs, 1997 people [11]). The second review did not report on any outcomes of interest for this *Clinical Evidence* review for this comparison, but did report treatment-related adverse effects, which are reported below. [11]

Symptom severity

Compared with haloperidol Clozapine may be more effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[19] Systematic review	235 people Data from 1 RCT	**Mean difference in Positive and Negative Syndrome Scale (PANSS) negative symptom score , long term** with clozapine (100–900 mg/day) with haloperidol (5–30 mg) Absolute results not reported	Mean difference –0.90 95% CI –6.63 to +4.83	↔	Not significant
[19] Systematic review	235 people Data from 1 RCT	**Mean difference in PANSS positive symptoms endpoint score , long term** with clozapine (100–900 mg/day) with haloperidol (5–30 mg) Absolute results not reported	Mean difference –2.20 95% CI –3.27 to –1.13	○○○	clozapine
[19] Systematic review	82 people Data from 1 RCT	**Cognitive functioning: impairment (Syndrome kurz test [SKT]) , short term** with clozapine (mean 350 mg/day) with haloperidol (mean 16 mg/day) Absolute results not reported	RR 0.56 95% CI 0.34 to 0.92	●○○	clozapine

No data from the following reference on this outcome. [11]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	162 people 3 RCTs in this analysis	**Extrapyramidal symptoms** with clozapine with haloperidol	RR 0.17 95% CI 0.03 to 0.88	●●●	clozapine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
[11] Systematic review	170 people 3 RCTs in this analysis	**Mean difference in weight gain (kg)** with clozapine with haloperidol Absolute results not reported	Mean difference 3.4 kg 95% CI 2.0 kg to 4.9 kg	○○○	haloperidol
[11] Systematic review	655 people 6 RCTs in this analysis	**Sedation** with clozapine with haloperidol Absolute results not reported	RR 1.50 95% CI 1.01 to 2.23	●○○	haloperidol

No data from the following reference on this outcome. [19]

Clozapine versus quetiapine:

We found one systematic review (search date 2007, 5 RCTs, 306 people). [20]

Symptom severity

Compared with quetiapine We don't know whether clozapine is more effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[20] Systematic review	142 people 2 RCTs in this analysis	**Mean difference in Positive and Negative Syndrome Scale (PANSS) positive subscore** with clozapine with quetiapine Absolute results not reported	–0.70 95% CI –2.07 to +0.68	⟷	Not significant
[20] Systematic review	72 people Data from 1 RCT	**No clinically important change in negative symptoms , short term** with clozapine (initial dose 50 mg/day, after 10 days 400–600 mg) with quetiapine (initial dose 100 mg/day, after 10 days 400–700 mg) Absolute results not reported No clinically important change: <50% reduction in Scale for the Assessment of Negative Symptoms (SANS) total score	RR 0.94 95% CI 0.78 to 1.13	⟷	Not significant
[20] Systematic review	142 people 2 RCTs in this analysis	**Mean difference in PANSS negative subscore , end of study** with clozapine (mean dose 292.4 mg/day) with quetiapine (mean dose 369 mg/day) Absolute results not reported	Mean difference –2.23 95% CI –3.48 to –0.99	○○○	quetiapine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20] Systematic review	67 people Data from 1 RCT	**Mean difference in SANS negative symptom score , short term** with clozapine (100–550 mg/day, mean 256 mg/day) with quetiapine (150–650 mg/day, mean 362 mg/day) Absolute results not reported	Mean difference –1.64 95% CI –8.17 to +4.89	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[20] Systematic review	72 people Data from 1 RCT	**Cardiac effects: ECG abnormalities** with clozapine (initial dose 50 mg/day, after 10 days 400–600 mg) with quetiapine (initial dose 100 mg/day, after 10 days 400–700 mg) Absolute results not reported	RR 0.13 95% CI 0.02 to 0.95	●●●	quetiapine
[20] Systematic review	63 people Data from 1 RCT	**At least 1 adverse effect** with clozapine (mean dose 270.5 mg/day) with quetiapine (mean dose 478.5 mg/day) Absolute results not reported	RR 0.42 95% CI 0.26 to 0.66	●●○	
[20] Systematic review	135 people 2 RCTs in this analysis	**Sedation** with clozapine with quetiapine Absolute results not reported	RR 0.22 95% CI 0.11 to 0.47	●●○	quetiapine
[20] Systematic review	135 people 2 RCTs in this analysis	**Akathisia** with clozapine with quetiapine Absolute results not reported	RR 0.40 95% CI 0.08 to 1.99	⟷	Not significant
[20] Systematic review	63 people Data from 1 RCT	**Rigor** with clozapine (mean dose 270.5 mg/day) with quetiapine (mean dose 478.5 mg/day) Absolute results not reported	RR 1.94 95% CI 0.18 to 20.30	⟷	Not significant
[20] Systematic review	135 people 2 RCTs in this analysis	**Tremor** with clozapine with quetiapine Absolute results not reported	RR 0.99 95% CI 0.29 to 3.34	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20] Systematic review	135 people 2 RCTs in this analysis	**Weight gain** with clozapine with quetiapine Absolute results not reported	RR 0.53 95% CI 0.25 to 1.11	⟷	Not significant
[20] Systematic review	27 people Data from 1 RCT	**Weight, change from baseline (kg)** with clozapine (mean 207.1 mg/day) with quetiapine (mean 535.7 mg/day) Absolute results not reported	Mean difference –2.11 kg 95% CI –4.30 kg to +0.08 kg	⟷	Not significant

Clozapine versus olanzapine:

We found two systematic reviews (search date 2007, 12 RCTs, 1763 people; [21] and search date 2000, 1 RCT, 180 people [22]).

Symptom severity

Compared with olanzapine We don't know whether clozapine is more effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[21] Systematic review	89 people 2 RCTs in this analysis	**Mean difference in Positive and Negative Syndrome Scale (PANSS) positive symptom score , short term** with clozapine (200–800 mg/day) with olanzapine (10–35 mg/day) Absolute results not reported	Mean difference +0.63 95% CI –1.00 to +2.27	⟷	Not significant
[21] Systematic review	503 people 4 RCTs in this analysis	**Mean difference in PANSS positive symptoms endpoint score , medium term** with clozapine (100–800 mg/day) with olanzapine (5–40 mg/day) Absolute results not reported	Mean difference –0.54 95% CI –1.87 to +0.78	⟷	Not significant
[21] Systematic review	284 people 2 RCTs in this analysis	**Mean difference in Brief Psychiatric Rating Scale (BPRS) positive symptoms endpoint score , medium term** with clozapine (100–600 mg/day) with olanzapine (5–25 mg/day) Absolute results not reported	Mean difference –0.30 95% CI –1.51 to +0.91	⟷	Not significant
[21] Systematic review	25 people Data from 1 RCT	**Mean difference in Scale for the Assessment of Positive Symptoms (SAPS) positive symptoms total endpoint score** with clozapine (150–500 mg/day) with olanzapine (5–25 mg/day) Absolute results not reported	Mean difference +9.0 95% CI –4.06 to +22.06	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] Systematic review	89 people 2 RCTs in this analysis	**Mean difference in PANSS negative symptoms endpoint score , short term** with clozapine (200–800 mg/day) with olanzapine (10–35 mg/day) Absolute results not reported	Mean difference –1.32 95% CI –3.05 to +0.42	⟷	Not significant
[21] Systematic review	503 people 4 RCTs in this analysis	**Mean difference in PANSS negative symptom endpoint score , medium term** with clozapine (100–800 mg/day) with olanzapine (5–40 mg/day) Absolute results not reported	Mean difference –0.52 95% CI –1.72 to +0.68	⟷	Not significant
[21] Systematic review	284 people 2 RCTs in this analysis	**Mean difference in BPRS negative symptoms endpoint score , medium term** with clozapine (100–600 mg/day) with olanzapine (5–25 mg/day) Absolute results not reported	Mean difference –0.15 95% CI –0.89 to +0.60	⟷	Not significant
[21] Systematic review	64 people 2 RCTs in this analysis	**Mean difference in Scale for the Assessment of Negative Symptoms (SANS) negative symptoms total endpoint score** with clozapine (50–700 mg/day) with olanzapine (5–30 mg/day) Absolute results not reported	Mean difference +4.81 95% CI –4.71 to +14.33	⟷	Not significant
[21] Systematic review	79 people Data from 1 RCT	**No clinically important change in cognitive functioning , medium term** with clozapine (200–800 mg/day) with olanzapine (10–40 mg/day) Absolute results not reported	RR 0.61 95% CI 0.43 to 0.87	●○○	olanzapine
[21] Systematic review	50 people Data from 1 RCT	**Mean difference in global neurocognitive endpoint score , medium term** with clozapine (200–800 mg/day) with olanzapine (10–40 mg/day) Absolute results not reported	Mean difference +0.29 95% CI –0.08 to +0.66	⟷	Not significant

No data from the following reference on this outcome. [22]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] Systematic review	422 people 7 RCTs in this analysis	**At least 1 adverse effect** with clozapine (25–700 mg/day) with olanzapine (5–50 mg/day) Absolute results not reported	RR 0.72 95% CI 0.53 to 0.97	●○○	olanzapine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] Systematic review	1445 people 7 RCTs in this analysis	**Sedation** with clozapine (25–900 mg/day) with olanzapine (5–50 mg/day) Absolute results not reported	RR 0.61 95% CI 0.39 to 0.95	●○○	olanzapine
[21] Systematic review	1097 people 4 RCTs in this analysis	**Seizures** with clozapine (150–900 mg/day) with olanzapine (5–50 mg/day) Absolute results not reported	RR 0.15 95% CI 0.04 to 0.58	●●●	olanzapine
[21] Systematic review	1320 people 4 RCTs in this analysis	**Akathisia** with clozapine (100–900 mg/day) with olanzapine (5–50 mg/day) Absolute results not reported	RR 1.37 95% CI 0.71 to 2.63	⟷	Not significant
[21] Systematic review	327 people 2 RCTs in this analysis	**Dyskinesia** with clozapine (100–600 mg/day) with olanzapine (5–25 mg/day) Absolute results not reported	RR 2.29 95% CI 0.81 to 6.45	⟷	Not significant
[21] Systematic review	327 people 2 RCTs in this analysis	**Parkinsonism** with clozapine (100–600 mg/day) with olanzapine (5–25 mg/day) Absolute results not reported	RR 0.78 95% CI 0.30 to 2.00	⟷	Not significant
[21] Systematic review	980 people Data from 1 RCT	**Rigor** with clozapine (200–900 mg/day) with olanzapine (5–20 mg/day) Absolute results not reported	RR 6.0 95% CI 0.73 to 49.65	⟷	Not significant
[21] Systematic review	561 people 6 RCTs in this analysis	**Use of antiparkinsonian medication** with clozapine (25–900 mg/day) with olanzapine (2.5–50 mg/day) Absolute results not reported	RR 1.14 95% CI 0.60 to 2.19	⟷	Not significant
[21] Systematic review	1264 people 4 RCTs in this analysis	**Significant low white blood cell count** with clozapine (150–900 mg/day) with olanzapine (5–40 mg/day) Absolute results not reported	RR 0.18 95% CI 0.08 to 0.41	●●●	olanzapine
[21] Systematic review	120 people Data from 1 RCT	**Mean difference in change from baseline in prolactin (ng/mL)** with clozapine (200–600 mg/day) with olanzapine (15–25 mg/day) Absolute results not reported	Mean difference 0.57 ng/mL 95% CI 0.09 ng/mL to 1.05 ng/mL	○○○	clozapine
[21] Systematic review	47 people 2 RCTs in this analysis	**Mean difference in change from baseline in prolactin (ng/mL), men only** with clozapine (50–800 mg/day) with olanzapine (10–40 mg/day) Absolute results not reported	Mean difference +8.65 ng/mL 95% CI –3.26 ng/mL to +20.55 ng/mL	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] Systematic review	1600 people 7 RCTs in this analysis	**Weight gain** with clozapine (25–900 mg/day) with olanzapine (5–40 mg/day) Absolute results not reported	RR 1.13 95% CI 0.70 to 1.81	⟷	Not significant
[21] Systematic review	581 people 7 RCTs in this analysis	**Mean difference in change from baseline in weight (kg)** with clozapine (25–900 mg/day) with olanzapine (2.5–50 mg/day) Absolute results not reported	Mean difference +0.04 kg 95% CI –0.97 kg to +1.06 kg	⟷	Not significant
[21] Systematic review	980 people Data from 1 RCT	**Death — suicide attempt** with clozapine (200–900 mg/day) with olanzapine (5–20 mg/day) Absolute results not reported	RR 1.78 95% CI 1.22 to 2.62	●○○	clozapine
[21] Systematic review	993 people 2 RCTs in this analysis	**Death — suicide** with clozapine (200–900 mg/day) with olanzapine (5–50 mg/day) Absolute results not reported	RR 0.6 95% CI 0.14 to 2.50	⟷	Not significant
[22] Systematic review	180 people Data from 1 RCT	**Extrapyramidal symptoms** with clozapine (290–600 mg/day) with olanzapine (22 mg/day) Absolute results not reported	RR 0.44 95% CI 0.14 to 1.39	⟷	Not significant
[22] Systematic review	Number of people unclear	**Nausea** with clozapine (290–600 mg/day) with olanzapine (22 mg/day) Absolute results not reported	RR 0.10 95% CI 0.01 to 0.77	●●●	olanzapine

Clozapine versus risperidone:

We found two systematic reviews (search date 2007, 4 RCTs, 541 people; [23] and search date 2005, 1 RCT, 50 people [24]).

Symptom severity

Compared with risperidone We don't know whether clozapine is more effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[23] Systematic review	451 people 4 RCTs in this analysis	**Weighted mean difference in Positive and Negative Syndrome Scale (PANSS) positive symptom subscore** with clozapine with risperidone Absolute results not reported	Mean difference –0.7 95% CI –2.4 to +1.0	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[23] Systematic review	451 people 4 RCTs in this analysis	**Weighted mean difference in PANSS negative symptom subscore** with clozapine with risperidone Absolute results not reported	Mean difference –0.4 95% CI –1.8 to +1.0	⟷	Not significant
[24] Systematic review	50 treatment-resistant people Data from 1 RCT	**Change in global neurocognitive score from baseline** 0.15 with clozapine (mean daily dose 498 mg) 0.42 with risperidone (mean daily dose 11.3 mg)	P >0.05	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [23] [24]

Clozapine versus ziprasidone:

We found one systematic review (search date 2007, 1 RCT, 146 people). [25]

Symptom severity

Compared with ziprasidone We don't know whether clozapine is more effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[25] Systematic review	146 people Data from 1 RCT	**Mean difference in Positive and Negative Syndrome Scale (PANSS) total score , medium term** with clozapine (250–600 mg/day, mean 345.7 mg/day) with ziprasidone (80–160 mg/day, mean 130.4 mg/day) Absolute results not reported	Mean difference –0.5 95% CI –7.72 to +6.72	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [25]

Clozapine versus zotepine:

We found one systematic review (search date 2010, 3 RCTs, 289 people). [26]

Symptom severity

Compared with zotepine We don't know whether clozapine is more effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[26] Systematic review	57 people Data from 1 RCT	**Mean difference in Brief Psychiatric Rating Scale (BPRS) total score , short term** with clozapine (mean 387 mg/day) with zotepine (mean 377 mg/day) Absolute results not reported	Mean difference 6.0 95% CI 2.17 to 9.83	○○○	clozapine
[26] Systematic review	57 people Data from 1 RCT	**Mean difference in BPRS total score at endpoint , short term** with clozapine (400 mg/day) with zotepine (225 mg/day) Absolute results not reported	Mean difference +2.20 95% CI –7.77 to +12.17	⟷	Not significant
[26] Systematic review	57 people Data from 1 RCT	**No improvement in cognitive functioning (SKT)** with clozapine (400 mg/day) with zotepine (225 mg/day) Absolute results not reported	RR 0.57 95% CI 0.21 to 1.52	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[26] Systematic review	57 people Data from 1 RCT	**Mean difference in endpoint extrapyramidal symptom score** with clozapine (400 mg/day) with zotepine (225 mg/day) Absolute results not reported	Mean difference +2.1 95% CI –0.25 to +4.45	⟷	Not significant
[26] Systematic review	116 people 2 RCTs in this analysis	**Use of antiparkinsonian medication** with clozapine (mean 387–400 mg) with zotepine (mean 225–377 mg/day) Absolute results not reported	RR 20.96 95% CI 2.89 to 151.90	●●●	clozapine
[26] Systematic review	59 people Data from 1 RCT	**Mean difference in change from baseline in prolactin (ng/mL)** with clozapine (mean 387 mg/day) with zotepine (mean 377 mg/day) Absolute results not reported	Mean difference 33.4 ng/mL 95% CI 14.87 ng/mL to 51.93 ng/mL	○○○	clozapine

Clozapine versus newer atypical antipsychotics (risperidone, zotepine, olanzapine, remoxipride, pooled):

We found one systematic review (search date 2000, 8 RCTs [1 single-blinded, 6 double-blinded, 1 unknown], 795 people). [22]

Symptom severity

Compared with newer atypical antipsychotics We don't know whether clozapine is more effective at improving symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[22] Systematic review	351 people Number of studies in analysis not clear	**<20% decrease in Brief Psychiatric Rating Scale (BPRS)/Positive and Negative Syndrome Scale (PANSS) scores** with clozapine (mean 290–600 mg/day) with risperidone (mean 4–8 mg/day)/zotepine (225 mg/day)/olanzapine (mean 22 mg/day)/remoxipride (mean 375–400 mg/day) Absolute results not reported	RR 0.93 95% CI 0.75 to 1.16	⟷	Not significant
[22] Systematic review	135 people Number of studies in analysis not clear	**No improvement in memory** with clozapine (mean 290–600 mg/day) with risperidone (mean 4–8 mg/day)/zotepine (225 mg/day)/olanzapine (mean 22 mg/day)/remoxipride (mean 375–400 mg/day Absolute results not reported	RR 0.70 95% CI 0.40 to 1.22	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[22] Systematic review	86 people	**Fatigue** with clozapine (mean 290–600 mg/day) with risperidone (mean 4–8 mg/day)/zotepine (225 mg/day)/olanzapine (mean 22 mg/day)/remoxipride (mean 375–400 mg/day) Absolute results not reported	RR 0.55 95% CI 0.31 to 0.96 NNT 4 95% CI 2 to 31	●○○	newer antipsychotics
[22] Systematic review	180 people	**Hypersalivation** with clozapine (mean 290–600 mg/day) with risperidone (mean 4–8 mg/day)/zotepine (225 mg/day)/olanzapine (mean 22 mg/day)/remoxipride (mean 375–400 mg/day) Absolute results not reported	RR 0.08 95% CI 0.02 to 0.31 NNT 4 95% CI 3 to 6	●●●	newer antipsychotics

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] Systematic review	266 people	**Orthostatic dizziness** with clozapine (mean 290–600 mg/day) with risperidone (mean 4–8 mg/day)/zotepine (225 mg/day)/olanzapine (mean 22 mg/day)/remoxipride (mean 375–400 mg/day) Absolute results not reported	RR 0.35 95% CI 0.15 to 0.85 NNT 12 95% CI 7 to 59	●○○	newer antipsy-chotics
[22] Systematic review	105 people	**Sedation/drowsiness** with clozapine (mean 290–600 mg/day) with risperidone (mean 4–8 mg/day)/zotepine (225 mg/day)/olanzapine (mean 22 mg/day)/remoxipride (mean 375–400 mg/day) Absolute results not reported	RR 0.63 95% CI 0.36 to 1.09	⟷	Not significant
[22] Systematic review	86 people	**Weight gain** with clozapine (mean 290–600 mg/day) with risperidone (mean 4–8 mg/day)/zotepine (225 mg/day)/olanzapine (mean 22 mg/day)/remoxipride (mean 375–400 mg/day) Absolute results not reported	RR 0.62 95% CI 0.32 to 1.22	⟷	Not significant
[22] Systematic review	558 people	**White blood cell problems** with clozapine (mean 290–600 mg/day) with risperidone (mean 4–8 mg/day)/zotepine (225 mg/day)/olanzapine (mean 22 mg/day)/remoxipride (mean 375–400 mg/day) Absolute results not reported	RR 0.76 95% CI 0.27 to 2.18	⟷	Not significant
[22] Systematic review	305 people	**Extrapyramidal symptoms** with clozapine (mean 290–600 mg/day) with risperidone (mean 4–8 mg/day)/zotepine (225 mg/day)/olanzapine (mean 22 mg/day)/remoxipride (mean 375–400 mg/day) Absolute results not reported	RR 3.55 95% CI 1.79 to 7.06 NNH 6 95% CI 4 to 9	●●○	clozapine

Clozapine versus typical/first-generation antipsychotics:

We found two systematic reviews (search date 2009, 52 RCTs, 4746 people; [27] and search date 2006, 23 RCTs, 1997 people [11]).

Symptom severity

Compared with first-generation antipsychotic drugs Clozapine seems more effective at improving positive and negative symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[27] Systematic review	215 people 5 RCTs in this analysis	**Mean difference in Scale for the Assessment of Negative Symptoms (SANS) score , short term** with clozapine (25–900 mg/day) with haloperidol (10–30 mg/day), chlorpromazine (50–1800 mg/day) Absolute results not reported	Mean difference –7.12 95% CI –8.78 to –5.46	○○○	clozapine
[27] Systematic review	235 people Data from 1 RCT	**Mean difference in Positive and Negative Syndrome Scale (PANSS) negative symptom score , long term** with clozapine (100–900 mg/day) with haloperidol (5–30 mg/day) Absolute results not reported	Mean difference –0.90 95% CI –6.63 to +4.83	⟷	Not significant
[27] Systematic review	60 people Data from 1 RCT	**Mean difference in Scale for the Assessment of Positive Symptoms (SAPS) endpoint score , short term** with clozapine (300 mg/day) with chlorpromazine (500 mg/day) Absolute results not reported	Mean difference +4.39 95% CI –12.15 to +20.93	⟷	Not significant
[27] Systematic review	235 people Data from 1 RCT	**Mean difference in PANSS positive symptoms endpoint score , long term** with clozapine (100–900 mg/day) with haloperidol (5–30 mg) Absolute results not reported	Mean difference –2.20 95% CI –3.27 to –1.13	○○○	clozapine
[27] Systematic review	82 people Data from 1 RCT	**Cognitive functioning: impairment (SKT) , short term** with clozapine (mean 350 mg/day) with haloperidol (mean 16 mg/day) Absolute results not reported	RR 0.56 95% CI 0.34 to 0.92	●○○	clozapine
[11] Systematic review	1080 people 10 RCTs in this analysis	**Hedges' adjusted g effect size for positive symptoms (PANSS)** with clozapine with first-generation antipsychotics Absolute results not reported	Effect size –0.36 95% CI –0.56 to –0.16	○○○	clozapine
[11] Systematic review	1603 people 17 RCTs in this analysis	**Hedges' adjusted g effect size for negative symptoms (PANSS)** with clozapine with first-generation antipsychotics Absolute results not reported	Effect size –0.27 95% CI –0.42 to –0.13	○○○	clozapine

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[27] Systematic review	1243 people 12 RCTs in this analysis Included 1 trial in children	**Death** with clozapine (variety of doses from 12.5 mg to 1600 mg) with haloperidol, chlorpromazine, and fluphenazine (various doses) Absolute results not reported 1600 mg clozapine is above UK licensed dose	RR 0.56 95% CI 0.14 to 2.27	⟷	Not significant
[27] Systematic review	1031 people 13 RCTs in this analysis	**Abnormal blood results** with clozapine (6.25–1600 mg/day) with haloperidol (0.25–30 mg/day), chlorpromazine (25–1800 mg/day) Absolute results not reported	RR 7.09 95% CI 1.96 to 25.62	●●●	first-generation antipsychotics
[27] Systematic review	4632 people 2 RCTs in this analysis	**Blood problems** with clozapine with haloperidol Absolute results not reported	RR 1.35 95% CI 0.66 to 2.79	⟷	Not significant
[27] Systematic review	62 people Data from 1 RCT	**Abnormal erythrocyte sedimentation rate** with clozapine (225–500 mg/day) with chlorpromazine (400–700 mg/day) Absolute results not reported	RR 10.78 95% CI 2.78 to 41.85	●●●	first-generation antipsychotics
[27] Systematic review	122 people 2 RCTs in this analysis	**White blood cell count increase** with clozapine (25–600 mg/day) with chlorpromazine (400–700 mg/day), loxapine (34–340 mg/day) Absolute results not reported	RR 13.02 95% CI 2.59 to 65.51	●●●	clozapine
[27] Systematic review	1527 people 16 RCTs in this analysis	**Drowsiness** with clozapine (6.25–1600 mg/day) with haloperidol (0.25–30 mg/day), chlorpromazine (25–1800 mg/day) Absolute results not reported	RR 1.23 95% CI 1.13 to 1.34	●○○	first-generation antipsychotics
[27] Systematic review	1479 people 17 RCTs in this analysis	**Hypersalivation** with clozapine (6.25–1600 mg/day) with haloperidol (0.25–30 mg/day), chlorpromazine (25–1800 mg/day), loxapine (34–340 mg/day) Absolute results not reported	RR 2.25 95% CI 1.96 to 2.58	●●○	first-generation antipsychotics

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[27] Systematic review	859 people 9 RCTs in this analysis	**Too little salivation** with clozapine (25–1000 mg/day) with haloperidol (2.25–30 mg/day), chlorpromazine (25–1800 mg/day), loxapine (34–340 mg/day), perphenazine (8–60 mg/day) Absolute results not reported	RR 0.38 95% CI 0.28 to 0.52	●○○	clozapine
[27] Systematic review	590 people 5 RCTs in this analysis	**Weight gain** with clozapine (6.25–900 mg/day) with haloperidol (0.25–30 mg/day), chlorpromazine (25–1800 mg/day) Absolute results not reported	RR 1.28 95% CI 1.07 to 1.53	●○○	first-generation antipsychotics
[27] Systematic review	1495 people 19 RCTs in this analysis	**Movement disorder** with clozapine (6.25–1600 mg/day) with haloperidol (0.25–30 mg/day), chlorpromazine (25–1800 mg/day), loxapine (34–340 mg/day) Absolute results not reported	RR 0.57 95% CI 0.50 to 0.65	●○○	clozapine
[27] Systematic review	1157 people 9 RCTs in this analysis	**Fits** with clozapine (6.25–1000 mg/day) with haloperidol (0.25–30 mg/day), chlorpromazine (25–1800 mg/day) Absolute results not reported	RR 1.51 95% CI 0.82 to 2.78	↔	Not significant
[27] Systematic review	1147 people 9 RCTs in this analysis	**High temperature** with clozapine (12.5–1000 mg/day) with haloperidol (2.25–30 mg/day), chlorpromazine (25–1800 mg/day) Absolute results not reported	RR 1.57 95% CI 1.25 to 1.98	●○○	first-generation antipsychotics
[11] Systematic review	775 people 11 RCTs in this analysis	**Extrapyramidal symptoms** with clozapine with low-potency first-generation antipsychotic drugs Absolute results not reported	RR 0.66 95% CI 0.48 to 0.91	●○○	clozapine
[11] Systematic review	232 people 3 RCTs in this analysis	**Mean difference in weight gain (kg)** with clozapine with low-potency first-generation antipsychotic drugs Absolute results not reported	Mean difference +0.3 kg 95% CI –1.6 kg to +2.2 kg	↔	Not significant
[11] Systematic review	928 people 9 RCTs in this analysis	**Sedation** with clozapine with low-potency first-generation antipsychotics Absolute results not reported	RR 1.32 95% CI 1.10 to 1.59	●○○	first-generation antipsychotics

Further information on studies

[16] The trial included in this systematic review compares clozapine with chlorpromazine in antipsychotic-naive patients with first-episode schizophrenia. This is an unlikely comparison as clozapine is only licensed for treatment-resistant schizophrenia. The trial analysis used last observation carried forward (LOCF) to adjust for loss to follow-up, which is not a particularly robust method.

[19] The blinding for most of the included studies was unclear. Eight trials included only populations with treatment-resistant schizophrenia, although some non-standard definitions of treatment-resistant schizophrenia were used. Some studies used comparatively low doses of the first-generation antipsychotic. Several trials did not report the doses used, while others used comparison drugs at doses above the maximum UK licensed dose. One study was in children and adolescents. The review authors considered the risk of bias to be high.

[20] Three of five reported studies are considered at high risk of bias by the authors of the systematic review, while the other two had unclear risk of bias for some aspects. All studies were short term. There is no mention of whether patients met the definition of treatment-resistant schizophrenia.

[21] The studies in this review had high rates of attrition in general. Most of the included studies were considered at high risk of bias. One study was in children and adolescents with schizophrenia and schizoaffective disorder. The dose of clozapine was relatively low with only two studies having a mean dose of >500 mg/day, while some studies used doses of olanzapine up to 50 mg (maximum licensed dose 20 mg).

[22] RCTs in the review included mainly treatment-resistant patients. Randomisation, blinding, and withdrawal rates were generally not well reported so studies are at risk of bias. Studies that did report withdrawal used LOCF. All studies but one were short term. Two studies used remoxipride, which has been withdrawn, as a comparator. The pooled data do not report the number of RCTs for each outcome.

[23] The authors of the systematic review noted that low or very low doses of clozapine were used in most studies. The review did not report on adverse effects.

[24] Adverse effects were reported in a different paper, considered in various systematic reviews. The method of random allocation was not stated. The study was medium term (14 weeks) and was primarily funded by the National Institute of Mental Health with supplemental funding from the manufacturer of olanzapine. The risperidone dose was relatively high compared with the clozapine dose.

[25] High rate of withdrawal. No adverse events recorded. Study considered at high risk of bias.

[26] The RCTs included in the review were small, short term, and considered at high risk of bias by the systematic review authors, due in particular to selective reporting and inadequate reporting and treatment of missing data, and because they were of limited methodological quality. All patients in one RCT had previously been on clozapine for at least 5 months. Two of the three studies used doses above the maximum UK licensed dose.

Comment: Overall, the evidence suggests that there are no consistent differences in efficacy between clozapine and any of the second-generation antipsychotics in a general population of patients with schizophrenia. There is some evidence of the superiority of clozapine over first-generation antipsychotics. There is strong evidence that patients on clozapine are more likely to have abnormal blood values than those on first-generation antipsychotics. There is moderate evidence that clozapine induces more weight gain, hypersalivation, sedation, and white blood cell problems, but fewer extrapyramidal symptoms than first-generation antipsychotics. There is some evidence that compared with newer atypical/second-generation antipsychotics, clozapine induces more hypersalivation but possibly fewer problems with prolactin and short-term extrapyramidal symptoms. There is strong evidence that clozapine is associated with more seizures than olanzapine, but there is no evidence of a difference in long-term extrapyramidal symptoms. In general, the evidence base is weak, with most reported studies being small, at high risk of bias, and short term.

Clinical guide:
While clozapine and the other second-generation antipsychotics have not been shown in RCTs to consistently differ in efficacy, there is a consensus that clozapine may benefit a subgroup of patients. Because of the risk of potentially fatal blood dyscrasias, patients should only be offered clozapine if they are deemed to have treatment-resistant schizophrenia. See clozapine versus first-generation antipsychotic drugs, p 133 . Patients taking clozapine should always be registered with a clozapine blood monitoring service, and undergo regular blood tests.

OPTION DEPOT HALOPERIDOL DECANOATE

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- We found insufficient evidence to conclude whether depot haloperidol decanoate is effective for positive, negative, or cognitive symptoms.

Benefits and harms

Depot haloperidol decanoate versus standard antipsychotic drugs:

We found one systematic review (search date 1998), which identified one small RCT (22 people) comparing depot haloperidol versus oral haloperidol. [28]

Symptom severity

Compared with oral haloperidol We don't know whether depot haloperidol is more effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[28] Systematic review	22 people Data from 1 RCT	**Proportion of people with "no improvement" in clinical impression , 4 months** 8/11 (73%) with depot haloperidol 9/11 (82%) with oral haloperidol	RR 0.61 95% CI 0.09 to 4.28 P = 0.62 The RCT may have been too small to detect a clinically important difference	⟷	Not significant
[28] Systematic review	22 people Data from 1 RCT	**Mean difference in Brief Psychiatric Rating Scale (BPRS) , 4 months** with depot haloperidol with oral haloperidol Absolute results not reported	WMD +3.20 95% CI –2.19 to +8.59 P = 0.24 The RCT may have been too small to detect a clinically important difference	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[28] Systematic review	22 people Data from 1 RCT	**Proportion of people who needed anticholinergic medication** 3/11 (27%) with depot haloperidol 1/11 (9%) with oral haloperidol	RR 3.21 95% CI 0.39 to 26.67 P = 0.28 This RCT is likely to have been too small to detect a clinically important difference	⟷	Not significant

Depot haloperidol decanoate versus placebo:

We found one systematic review (search date 1998), which identified one small RCT (36 people) comparing depot haloperidol versus oral placebo. [28]

Symptom severity

Compared with placebo Depot haloperidol seems more effective at improving mental state at 4 months in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[28] Systematic review	32 people Data from 1 RCT	**Mental state: no discernible effect , 4 months** 0/16 (0%) with depot haloperidol 13/16 (81%) with placebo	OR 0.04 95% CI 0.01 to 0.15 P <0.00001	●●●	depot haloperidol

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[28] Systematic review	32 people Data from 1 RCT	**Anticholinergic effects , 4 months** 1/16 (6%) with depot haloperidol 6/16 (37%) with placebo	OR 0.17 95% CI 0.03 to 0.89 P = 0.035	●●●	depot haloperidol
[28] Systematic review	32 people Data from 1 RCT	**Tremor** 6/16 (37%) with depot haloperidol 6/16 (37%) with placebo	OR 1.00 95% 0.24 to 4.09 P = 1.0	⟷	Not significant

Further information on studies

Comment: Depot haloperidol is likely to be effective at improving mental state but there is insufficient evidence to conclude whether depot haloperidol is effective for positive, negative, or cognitive symptoms.

Clinical guide:
Depot haloperidol decanoate has been used for decades in the treatment of schizophrenia, despite the absence of strong evidence from RCTs.

OPTION HALOPERIDOL

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Haloperidol may be effective for positive, negative, and cognitive symptoms and comparable to other antipsychotics, although evidence is variable and weak. Haloperidol shows a similar adverse-effect profile to other first-generation antipsychotics and is associated with less weight gain but more extrapyramidal symptoms than second-generation antipsychotics.

Benefits and harms

Haloperidol versus chlorpromazine:
See treatment option on chlorpromazine, p 14 .

Haloperidol versus amisulpride:
See treatment option on amisulpride, p 4 .

Haloperidol versus clozapine:

See treatment option on clozapine, p 20 .

Haloperidol versus placebo:

We found one systematic review (search date 2006, 21 RCTs, 1519 people). [29]

Symptom severity

Compared with placebo Haloperidol may be more effective at improving mental state scores in people with schizophrenia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[29] Systematic review	24 people Data from 1 RCT	**Mental state: no clinical improvement (<20% reduction in Brief Psychiatric Rating Scale [BPRS] score) , 0 to 6 weeks** with haloperidol (4–10 mg/day) with placebo Absolute results not reported	RR 0.76 95% CI 0.54 to 1.08	⟷	Not significant
[29] Systematic review	72 people 2 RCTs in this analysis	**Mental state: average endpoint BPRS score , 6 weeks** with haloperidol (5–75 mg/day) with placebo Absolute results not reported	Mean difference –11.89 95% CI –17.04 to –6.74	○○○	haloperidol

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[29] Systematic review	109 people 3 RCTs in this analysis	**Acute dystonia** with haloperidol (4–75 mg/day) with placebo Absolute results not reported	RR 8.52 95% CI 1.66 to 43.85	●●●	placebo
[29] Systematic review	333 people 4 RCTs in this analysis	**Non-acute akathisia** with haloperidol (0.75–20 mg/day) with placebo Absolute results not reported	RR 2.57 95% CI 1.39 to 4.75	●●○	placebo
[29] Systematic review	246 people 3 RCTs in this analysis	**Non-acute needing antiparkinsonian medication** with haloperidol (6–75 mg/day) with placebo Absolute results not reported	RR 2.69 95% CI 1.53 to 4.72	●●○	placebo
[29] Systematic review	163 people 4 RCTs in this analysis	**Non-acute parkinsonism (including extrapyramidal symptoms)**	RR 11.65 95% CI 2.88 to 47.11	●●●	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with haloperidol (1–75 mg/day) with placebo Absolute results not reported			
[29] Systematic review	99 people 3 RCTs in this analysis	**Non-acute rigidity** with haloperidol (0.75–75 mg/day) with placebo Absolute results not reported	RR 4.30 95% CI 0.94 to 19.74	⟷	Not significant
[29] Systematic review	323 people 4 RCTs in this analysis	**Non-acute tremor** with haloperidol (0.75–200 mg/day) with placebo Absolute results not reported	RR 2.49 95% CI 0.59 to 10.49	⟷	Not significant
[29] Systematic review	33 people Data from 1 RCT	**Chronic dyskinesia and tardive dyskinesia** with haloperidol (maximum dose 200 mg/day) with placebo Absolute results not reported	RR 2.83 95% CI 0.12 to 64.89	⟷	Not significant
[29] Systematic review	364 people 3 RCTs in this analysis	**Sleepiness** with haloperidol (1–200 mg/day) with placebo Absolute results not reported	RR 3.43 95% CI 1.53 to 7.73	●●○	placebo
[29] Systematic review	207 people Data from 1 RCT	**Weight gain** with haloperidol (10 mg/day) with placebo Absolute results not reported	RR 10.10 95% CI 1.32 to 77.46	●●●	placebo

Haloperidol versus risperidone:

We found 4 systematic reviews (search date 2006, 5 RCTs, 1124 people; [16] search date 2006, 34 RCTs, 4173 people; [11] search date 2005, 1 RCT, 397 people; [30] and search date 2005, 1 RCT, 51 people [24]) and one subsequent RCT. [31]

Symptom severity

Compared with risperidone Haloperidol may be less effective at improving positive and negative symptoms in people with schizophrenia; however, results were inconsistent (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[16] Systematic review	183 people Data from 1 RCT	**Proportion of people clinically improved , short term** with haloperidol (range 2–8 mg/day, mean daily dose 5.6 mg/day) with risperidone (range 2–8 mg/day, mean daily dose 6.1 mg/day)	Difference 7% P = 0.19	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported Clinical improvement defined as 50% or greater reduction in Positive and Negative Syndrome Scale (PANSS) total score			
[16] Systematic review	555 people Data from 1 RCT	**Proportion of people with clinical improvement , short term** with haloperidol (range 1–4 mg/day, mean modal dose 2.9 mg/day) with risperidone (range 1–4 mg/day, mean modal dose 3.3 mg/day) Absolute results not reported Clinical improvement defined as 20% or greater reduction in PANSS total score	Difference 2.6 P = 0.48	⟷	Not significant
[16] Systematic review	555 people Data from 1 RCT	**Mean improvement in PANSS total score at endpoint , long term** with haloperidol (range 1–4 mg/day, mean modal dose 2.9 mg/day) with risperidone (range 1–4 mg/day, mean modal dose 3.3 mg/day) Absolute results not reported	Mean difference 0.4 P = 0.49	⟷	Not significant
[31] RCT	289 inpatients with first-episode schizophrenia	**Estimated difference in improvement (units unclear), Scale for the Assessment of Negative Symptoms (SANS) total "composite" score , 8 weeks** with haloperidol (mean daily dose 3.7 mg/day) with risperidone (mean daily dose 3.8 mg/day) Absolute results not reported	Difference –0.238 P = 0.552	⟷	Not significant
[31] RCT	289 inpatients with first-episode schizophrenia	**Estimated difference in improvement (units unclear), PANSS negative score , 8 weeks** with haloperidol (mean daily dose 3.7 mg/day) with risperidone (mean daily dose 3.8 mg/day) Absolute results not reported	Difference –0.031 P = 0.770	⟷	Not significant
[31] RCT	289 inpatients with first-episode schizophrenia	**Estimated difference in improvement (units unclear), PANSS positive score , 8 weeks** with haloperidol (mean daily dose 3.7 mg/day) with risperidone (mean daily dose 3.8 mg/day) Absolute results not reported	Difference 0.059 P = 0.510	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[30] Systematic review	397 people Data from 1 RCT	**Difference in change from baseline in PANSS negative score** with haloperidol (mean modal dose 11.7 mg/day) with risperidone (mean modal dose 4.9 mg/day) Absolute results not reported	P = 0.003	○○○	risperidone
[30] Systematic review	397 people Data from 1 RCT	**Difference in change from baseline in PANSS positive score** with haloperidol (mean modal dose 11.7 mg/day) with risperidone (mean modal dose 4.9 mg/day) Absolute results not reported	P = 0.004	○○○	risperidone
[24] Systematic review	51 treatment-resistant inpatients Data from 1 RCT	**Change from baseline in global neurocognitive score** –0.04 with haloperidol (mean daily dose 26.8 mg) +0.42 with risperidone (mean daily dose 11.3 mg)	P <0.006	○○○	risperidone

No data from the following reference on this outcome. [11]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[16] Systematic review	183 people Data from 1 RCT	**Difference in percentage of people clinically improved , short term** with haloperidol (range 2–8 mg/day, mean daily dose 5.6 mg/day) with risperidone (range 2–8 mg/day, mean daily dose 6.1 mg/day) Absolute results not reported Clinical improvement defined as 50% or greater reduction in Positive and Negative Syndrome Scale total score	Difference 12% P <0.05	○○○	risperidone
[16] Systematic review	183 people Data from 1 RCT	**Difference in percentage of people withdrawing because of adverse events** with haloperidol (range 2–8 mg/day, mean daily dose 5.6 mg/day) with risperidone (range 2–8 mg/day, mean daily dose 6.1 mg/day) Absolute results not reported	Difference 18% P = 0.02	○○○	risperidone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[16] Systematic review	183 people Data from 1 RCT	**Difference in percentage of patients requiring antiparkinsonian medication** with haloperidol (range 2–8 mg/day, mean daily dose 5.6 mg/day) with risperidone (range 2–8 mg/day, mean daily dose 6.1 mg/day) Absolute results not reported	Difference 25% P <0.001	○○○	risperidone
[16] Systematic review	183 people Data from 1 RCT	**Difference in percentage of patients with non-extrapyramidal adverse events , short term** with haloperidol (range 2–8 mg/day, mean daily dose 5.6 mg/day) with risperidone (range 2–8 mg/day, mean daily dose 6.1 mg/day) Absolute results not reported	Difference 3% P value not reported		
[16] Systematic review	555 people Data from 1 RCT	**Difference in mean increase in body weight , short term** with haloperidol (range 1–4 mg/day, mean modal dose 2.9 mg/day) with risperidone (range 1–4 mg/day, mean modal dose 3.3 mg/day) Absolute results not reported	Difference 1.6 kg P = 0.03	○○○	haloperidol
[16] Systematic review	555 people Data from 1 RCT	**Difference in percentage of patients withdrawing because of adverse events , long term** with haloperidol (range 1–4 mg/day, mean modal dose 2.9 mg/day) with risperidone (range 1–4 mg/day, mean modal dose 3.3 mg/day) Absolute results not reported	Difference 0.7% P = 0.71	⟷	Not significant
[16] Systematic review	555 people Data from 1 RCT	**Difference in percentage of patients with persistent dyskinesia , long term** with haloperidol (range 1–4 mg/day, mean modal dose 2.9 mg/day) with risperidone (range 1–4 mg/day, mean modal dose 3.3 mg/day) Absolute results not reported	Difference 1.5% P = 0.28	⟷	Not significant
[31] RCT	289 inpatients with first-episode schizophrenia	**Prevalence of movement disorder adverse effects (Simpson-Angus Scale total score >0) , 8 weeks** with haloperidol (mean daily dose 3.7 mg/day) with risperidone (mean daily dose 3.8 mg/day) Absolute results not reported	OR 1.32 P = 0.036	●○○	risperidone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[31] RCT	289 inpatients with first-episode schizophrenia	**Prevalence of movement disorder adverse effects (Abnormal Involuntary Movement Scale total score >0) , 8 weeks** with haloperidol (mean daily dose 3.7 mg/day) with risperidone (mean daily dose 3.8 mg/day) Absolute results not reported	OR 1.42 P = 0.004	●○○	risperidone
[31] RCT	289 inpatients with first-episode schizophrenia	**Prevalence of movement disorder adverse effects (Hillside Akathisia Scale total score >0) , 8 weeks** with haloperidol (mean daily dose 3.7 mg/day) with risperidone (mean daily dose 3.8 mg/day) Absolute results not reported	OR 1.28 P = 0.103	⟷	Not significant
[11] Systematic review	2783 people 21 RCTs in this analysis	**Extrapyramidal symptoms** with haloperidol with risperidone Absolute results not reported	RR 0.61 95% CI 0.52 to 0.72	●○○	risperidone
[11] Systematic review	1336 people 9 RCTs in this analysis	**Mean difference in weight gain (kg)** with haloperidol with risperidone Absolute results not reported	Mean difference 1.7 kg 95% CI 0.9 kg to 2.4 kg	○○○	haloperidol
[11] Systematic review	2914 people 15 RCTs in this analysis	**Sedation** with haloperidol with risperidone Absolute results not reported	RR 0.86 95% CI 0.70 to 1.05	⟷	Not significant
[30] Systematic review	397 people Data from 1 RCT	**Change from baseline in Extrapyramidal Symptom Rating Scale total score** +0.3 with haloperidol (11.7 mg/day) –0.1 with risperidone (4.9 mg/day)	P = 0.02	○○○	risperidone
[30] Systematic review	397 people Data from 1 RCT	**Change from baseline in parkinsonism subscale** +0.5 with haloperidol (11.7 mg/day) –0.7 with risperidone (4.9 mg/day)	P = 0.03	○○○	risperidone
[30] Systematic review	397 people Data from 1 RCT	**Change from baseline in global impression score for parkinsonism** +0.1 with haloperidol (11.7 mg/day) –0.3 with risperidone (4.9 mg/day)	P = 0.0002	○○○	risperidone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[30] Systematic review	397 people Data from 1 RCT	**Change from baseline in global impression score for dyskinesia** +0.1 with haloperidol (11.7 mg/day) –0.1 with risperidone (4.9 mg/day)	P = 0.03	○○○	risperidone
[30] Systematic review	397 people Data from 1 RCT	**Change from baseline in weight gain (kg)** 0.73 kg with haloperidol (11.7 mg/day) 2.3 kg with risperidone (4.9 mg/day)	P <0.001	○○○	haloperidol

No data from the following reference on this outcome. [24]

Haloperidol versus aripiprazole:

We found one systematic review (search date 2006, 5 RCTs, 2049 people). [11] The review did not include any outcomes of interest for this *Clinical Evidence* review for this comparison, but did include treatment-related adverse effects, which are reported below.

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	1794 people 4 RCTs in this analysis	**Extrapyramidal symptoms** with haloperidol with aripiprazole Absolute results reported graphically	RR 0.45 95% CI 0.32 to 0.64	●●●	aripiprazole
[11] Systematic review	1589 people 2 RCTs in this analysis	**Mean difference in weight gain (kg)** with haloperidol with aripiprazole Absolute results not reported	Mean difference +0.6 kg 95% CI –0.1 kg to +1.2 kg	⟷	Not significant
[11] Systematic review	1602 people 2 RCTs in this analysis	**Sedation** with haloperidol with aripiprazole Absolute results not reported	RR 0.65 95% CI 0.45 to 0.95	●○○	aripiprazole

Haloperidol versus olanzapine:

We found two systematic reviews (search date 2006, 28 RCTs, 4966 people; [11] and search date 2006, 5 RCTs, 1124 people [16]) and three subsequent RCTs. [32] [33] [34]

Symptom severity

Compared with olanzapine Haloperidol may be less effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[16] Systematic review	83 people Data from 1 RCT	**Mean improvement in total Positive and Negative Syndrome Scale (PANSS) scores at endpoint , short term** with haloperidol (mean modal dose 10.8 mg/day) with olanzapine (mean modal dose 11.6 mg/day) Absolute results not reported	Mean difference 11.2 P = 0.02	○○○	olanzapine
[16] Systematic review	83 people Data from 1 RCT	**Difference in percentage of people with clinical response , short term** with haloperidol (mean modal dose 10.8 mg/day) with olanzapine (mean modal dose 11.6 mg/day) Absolute results not reported Clinical response defined as 40% or greater improvement in Brief Psychiatric Rating Scale (BPRS) total score from baseline	Mean difference 38% P = 0.003	○○○	olanzapine
[16] Systematic review	83 people Data from 1 RCT	**Difference in percentage of people with 20% or greater reduction in BPRS total score , short term** with haloperidol (mean modal dose 10.8 mg/day) with olanzapine (mean modal dose 11.6 mg/day) Absolute results not reported	Mean difference 23.9% P = 0.03	○○○	olanzapine
[16] Systematic review	263 people Data from 1 RCT	**Mean improvement in total PANSS scores , short term** 75.56 to 59.33 with haloperidol (mean modal dose 4.4 mg/day) 75.9 to 55.85 with olanzapine (mean modal dose 9.1 mg/day)	P = 0.58	⟷	Not significant
[16] Systematic review	263 people Data from 1 RCT	**Difference in percentage of people achieving response , short term** with haloperidol (mean modal dose 4.4 mg/day) with olanzapine (mean modal dose 9.1 mg/day) Absolute results not reported Response defined as no rating of >3 on items P1, P2, P3, P5, P6 on the PANSS and Clinical Global Impression scale (CGI) Severity score 3 or lower	Mean difference 7.3% P value not reported		
[32] RCT	27 people	**Difference in mean PANSS total score , 0 to 56 days** 72.38 to 56.10 with haloperidol (average daily dose 9.32 mg)	P >0.05	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		76.14 to 62.00 with olanzapine (average daily dose 12 mg)			
[33] RCT	35 people	**Change from baseline in PANSS positive score , end-point** 13.05 to 14.16 with haloperidol (doses 15–20 mg/day) 14.13 to 12.06 with olanzapine (doses 15–20 mg/day)	P = 0.884	⟷	Not significant
[33] RCT	35 people	**Change from baseline in PANSS negative score , end-point** 26.16 to 22.58 with haloperidol (doses 15–20 mg/day) 26.88 to 18.25 with olanzapine (doses 15–20 mg/day)	P = 0.031	○○○	olanzapine
[34] RCT	276 people	**Change from baseline in PANSS positive score , 8 weeks** –8.9 with haloperidol (doses 5–20 mg/day) –9.7 with olanzapine (doses 5–20 mg/day)	P = 0.325	⟷	Not significant
[34] RCT	276 people	**Change from baseline in PANSS positive score , 24 weeks** –10.2 with haloperidol (doses 5–20 mg/day) –11.5 with olanzapine (doses 5–20 mg/day)	P = 0.128	⟷	Not significant
[34] RCT	276 people	**Change from baseline in PANSS negative score , 8 weeks** –7.1 with haloperidol (doses 5–20 mg/day) –8.1 with olanzapine (doses 5–20 mg/day)	P = 0.218	⟷	Not significant
[34] RCT	276 people	**Change from baseline in PANSS negative score , 24 weeks** –8.6 with haloperidol (doses 5–20 mg/day) –11.0 with olanzapine (doses 5–20 mg/day)	P = 0.007	○○○	olanzapine

No data from the following reference on this outcome. [11]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	3670 people 12 RCTs in this analysis	**Extrapyramidal symptoms** with haloperidol with olanzapine Absolute results not reported	RR 0.39 95% CI 0.30 to 0.51	●●○	olanzapine
[11] Systematic review	2952 people 9 RCTs in this analysis	**Mean difference in weight gain (kg)** with haloperidol with olanzapine Absolute results not reported	Mean difference 3.3 kg 95% CI 2.2 kg to 4.4 kg	○○○	haloperidol
[11] Systematic review	2762 people 6 RCTs in this analysis	**Sedation** with haloperidol with olanzapine Absolute results not reported	RR 0.95 95% CI 0.82 to 1.10	↔	Not significant
[16] Systematic review	83 people Data from 1 RCT	**Difference in percentage of patients withdrawing because of adverse events , short term** with haloperidol (mean modal dose 10.8 mg/day) with olanzapine (mean modal dose 11.6 mg/day) Absolute results not reported	Difference 15% P value not reported		
[16] Systematic review	83 people Data from 1 RCT	**Extrapyramidal symptoms, mean change from baseline to endpoint in Simpson-Angus Scale (SAS) total score , short term** +4.5 with haloperidol (mean modal dose 10.8 mg/day) –0.5 with olanzapine (mean modal dose 11.6 mg/day)	P <0.001	○○○	olanzapine
[16] Systematic review	83 people Data from 1 RCT	**Akathisia, mean change from baseline to endpoint on Barnes Akathisia Scale (BAS) , short term** +0.5 with haloperidol (mean modal dose 10.8 mg/day) –0.1 with olanzapine (mean modal dose 11.6 mg/day)	P = 0.005	○○○	olanzapine
[16] Systematic review	83 people Data from 1 RCT	**Difference in percentage of people receiving anticholinergic medications , short term** with haloperidol (mean modal dose 10.8 mg/day) with olanzapine (mean modal dose 11.6 mg/day) Absolute results not reported	Difference 28.1% P = 0.008	○○○	olanzapine
[16] Systematic review	83 people Data from 1 RCT	**Mean increase in body weight (kg) , short term** 0.5 kg with haloperidol (mean modal dose 10.8 mg/day) 4.1 kg with olanzapine (mean modal dose 11.6 mg/day)	P <0.001	○○○	haloperidol

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[16] Systematic review	83 people Data from 1 RCT	**Prolactin at endpoint , short term** with haloperidol (mean modal dose 10.8 mg/day) with olanzapine (mean modal dose 11.6 mg/day) Absolute results not reported	4.5 times higher in haloperidol group P <0.001	○○○	olanzapine
[16] Systematic review	263 people Data from 1 RCT	**Difference in percentage of people withdrawing because of adverse events** 7% with haloperidol (mean modal dose 4.4 mg/day) 3% with olanzapine (mean modal dose 9.1 mg/day) Absolute numbers not reported	P value not reported		
[16] Systematic review	263 people Data from 1 RCT	**Difference in incidence of treatment-emergent parkinson-ism , short term** 54.8% with haloperidol (mean modal dose 4.4 mg/day) 26.1% with olanzapine (mean modal dose 9.1 mg/day) Absolute numbers not reported Change in incidence defined as change in SAS from 3 or less at baseline to >3 post-baseline	P <0.001	○○○	olanzapine
[16] Systematic review	263 people Data from 1 RCT	**Difference in incidence of treatment-emergent akathisia , short term** 51.2% with haloperidol (mean modal dose 4.4 mg/day) 11.9% with olanzapine (mean modal dose 9.1 mg/day) Absolute numbers not reported Change defined as change in BAS from <2 at baseline to 2 or greater post-baseline	P <0.001	○○○	olanzapine
[16] Systematic review	263 people Data from 1 RCT	**Mean increase in prolactin , short term** 6.9 ng/mL with haloperidol (mean modal dose 4.4 mg/day) 1.2 ng/mL with olanzapine (mean modal dose 9.1 mg/day)	P <0.0001	○○○	olanzapine
[16] Systematic review	263 people Data from 1 RCT	**Proportion of people with a >7% increase in body weight , short term** 23% with haloperidol (mean modal dose 4.4 mg/day) 62% with olanzapine (mean modal dose 9.1 mg/day) Absolute numbers not reported	P <0.001	○○○	haloperidol
[16] Systematic review	263 people Data from 1 RCT	**Percentage of people withdraw-ing because of adverse events , long term** 16% with haloperidol (mean modal dose 4.4 mg/day)	P <0.03	○○○	olanzapine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		7% with olanzapine (mean modal dose 9.1 mg/day) Absolute numbers not reported			
[16] Systematic review	263 people Data from 1 RCT	**Symptoms of parkinsonism (SAS) , long term** 4.57 with haloperidol (mean modal dose 4.4 mg/day) 2.28 with olanzapine (mean modal dose 9.1 mg/day)	P <0.001	○○○	olanzapine
[16] Systematic review	263 people Data from 1 RCT	**Symptoms of akathisia (BAS) , long term** 2.83 with haloperidol (mean modal dose 4.4 mg/day) 0.98 with olanzapine (mean modal dose 9.1 mg/day)	P <0.0001	○○○	olanzapine
[16] Systematic review	263 people Data from 1 RCT	**Percentage of people receiving anticholinergic medications , long term** 47% with haloperidol (mean modal dose 4.4 mg/day) 20% with olanzapine (mean modal dose 9.1 mg/day) Absolute results not reported	P <0.0001	○○○	olanzapine
[16] Systematic review	263 people Data from 1 RCT	**Percentage of people with a >7% increase in weight gain , long term** 42% with haloperidol (mean modal dose 4.4 mg/day) 72% with olanzapine (mean modal dose 9.1 mg/day) Absolute numbers not reported	P <0.0001	○○○	olanzapine
[16] Systematic review	263 people Data from 1 RCT	**Percentage of people with at least one abnormal prolactin level** 67% with haloperidol (mean modal dose 4.4 mg/day) 50% with olanzapine (mean modal dose 9.1 mg/day) Absolute numbers not reported	P <0.0004	○○○	olanzapine
[32] RCT	27 people	**Difference in mean Extrapyramidal Symptom Rating Scale (ESRS) parkinsonism , days 0 to 56** 5.69 to 6.80 with haloperidol (average daily dose 9.32 mg) 6.93 to 7.79 with olanzapine (average daily dose 12 mg)	P >0.05	⟷	Not significant
[33] RCT	35 people	**Extrapyramidal symptoms, change from baseline in SAS total score , endpoint** 0.95 to 0.89 with haloperidol (doses 15–20 mg/day) 1.63 to 1.00 with olanzapine (doses 15–20 mg/day)	P = 0.523	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[33] RCT	35 people	**Extrapyramidal symptoms, change from baseline in Abnormal Involuntary Movement Scale (AIMS) total score , endpoint** 0.74 to 0.53 with haloperidol (doses 15–20 mg/day) 1.63 to 1.00 with olanzapine (doses 15–20 mg/day)	P = 0.894	↔	Not significant
[33] RCT	35 people	**Change from baseline in weight (lb) , endpoint** 197.05 lb to 194.08 lb with haloperidol (doses 15–20 mg/day) 194.91 lb to 203.28 lb with olanzapine (doses 15–20 mg/day)	P = 0.012	○○○	haloperidol
[33] RCT	35 people	**Change from baseline in glucose (mg/dL) , endpoint** 84.44 mg/dL to 83.22 mg/dL with haloperidol (doses 15–20 mg/day) 100.73 mg/dL to 94.00 mg/dL with olanzapine (doses 15–20 mg/day)	P = 0.031	○○○	olanzapine
[34] RCT	276 people	**Any adverse effect** 58% with haloperidol (doses 5–20 mg/day) 42% with olanzapine (doses 5–20 mg/day) Absolute numbers not reported	P = 0.011	○○○	olanzapine
[34] RCT	276 people	**Akathisia, change from baseline in BAS total score , 8 weeks** +0.7 with haloperidol (doses 5–20 mg/day) –0.2 with olanzapine (doses 5–20 mg/day)	P = 0.001	○○○	olanzapine
[34] RCT	276 people	**Akathisia, change from baseline in BAS total score , 24 weeks** +0.5 with haloperidol (doses 5–20 mg/day) –0.2 with olanzapine (doses 5–20 mg/day)	P = 0.003	○○○	olanzapine
[34] RCT	276 people	**Extrapyramidal symptoms, change from baseline in SAS total score , 8 weeks** +1.0 with haloperidol (doses 5–20 mg/day) –0.9 with olanzapine (doses 5–20 mg/day)	P <0.001	○○○	olanzapine
[34] RCT	276 people	**Extrapyramidal symptoms, change from baseline in SAS total score , 24 weeks** +0.4 with haloperidol (doses 5–20 mg/day)	P <0.001	○○○	olanzapine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		–1.0 with olanzapine (doses 5–20 mg/day)			
[34] RCT	276 people	**Extrapyramidal symptoms: change from baseline in AIMS total score , 8 weeks** –0.1 with haloperidol (doses 5–20 mg/day) –0.8 with olanzapine (doses 5–20 mg/day)	P = 0.053	⟷	Not significant
[34] RCT	276 people	**Extrapyramidal symptoms: change from baseline in AIMS total score , 24 weeks** –0.3 with haloperidol (doses 5–20 mg/day) –0.9 with olanzapine (doses 5–20 mg/day)	P = 0.096	⟷	Not significant
[34] RCT	276 people	**Weight gain (in excess of 7% of baseline weight)** 12% with haloperidol (doses 5–20 mg/day) 26% with olanzapine (doses 5–20 mg/day) Absolute numbers not reported	P = 0.012	○○○	haloperidol
[34] RCT	276 people	**Dystonia** 5% with haloperidol (doses 5–20 mg/day) 0% with olanzapine (doses 5–20 mg/day) Absolute numbers not reported	P = 0.01	○○○	olanzapine
[34] RCT	276 people	**Tremor** 14% with haloperidol (doses 5–20 mg/day) 6% with olanzapine (doses 5–20 mg/day) Absolute numbers not reported	P = 0.014	○○○	olanzapine

Haloperidol versus quetiapine:

We found one systematic review (search date 2006, 11 RCTs, 2412 people). [11] The review did not include any outcomes of interest for this *Clinical Evidence* review for this comparison, but did assess treatment-related adverse effects, which are reported below.

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	945 people 3 RCTs in this analysis	**Mean difference in weight gain (kg)** with haloperidol with quetiapine	Mean difference 1.4 kg 95% CI 0.7 kg to 2.1 kg	○○○	haloperidol

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
[11] Systematic review	970 people 4 RCTs in this analysis	**Sedation** with haloperidol with quetiapine Absolute results not reported	RR 2.07 95% CI 1.01 to 4.27	○○○	haloperidol
[11] Systematic review	1167 people 5 RCTs in this analysis	**Extrapyramidal symptoms** with haloperidol with quetiapine Absolute results not reported	RR 0.43 95% CI 0.25 to 0.74	●●○	quetiapine

Haloperidol versus sertindole:

We found two systematic reviews (search date 2006, 4 RCTs, 1344 people; [11] and search date 2005, 1 RCT, 282 people). [30]

Symptom severity

Compared with sertindole We don't know whether haloperidol is more effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[11] Systematic review	1145 people 3 RCTs in this analysis	**Hedges' adjusted g effect size for positive symptoms (Positive and Negative Syndrome Scale [PANSS])** with haloperidol with sertindole Absolute results not reported	Effect size +0.17 95% CI –0.03 to +0.36	⟷	Not significant
[11] Systematic review	1198 people 4 RCTs in this analysis	**Hedges' adjusted g effect size for negative symptoms (PANSS)** with haloperidol with sertindole Absolute results not reported	Effect size –0.11 95% CI –0.22 to +0.01	⟷	Not significant
[30] Systematic review	282 people Data from 1 RCT	**Mean change from baseline in total PANSS score , 1 year** –1.4 with haloperidol (10 mg/day) –5.8 with sertindole (24 mg/day)	P value not reported		
[30] Systematic review	282 people Data from 1 RCT	**Mean change from baseline in total Scale for the Assessment of Negative Symptoms score , 2 months** –0.1 with haloperidol (10 mg/day) –3.9 with sertindole (24 mg/day)	P less-than or equal to 0.05	○○○	sertindole

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	1472 people 4 RCTs in this analysis	**Extrapyramidal symptoms** with haloperidol with sertindole Absolute results not reported	RR 0.36 95% CI 0.29 to 0.45	●●○	sertindole
[11] Systematic review	779 people 2 RCTs in this analysis	**Mean difference in weight gain (kg)** with haloperidol with sertindole Absolute results not reported	Mean difference 3.3 kg 95% CI 0.2 kg to 6.4 kg	●○○	sertindole
[11] Systematic review	1127 people 3 RCTs in this analysis	**Sedation** with haloperidol with sertindole Absolute results not reported	RR 0.77 95% CI 0.44 to 1.34	↔	Not significant
[30] Systematic review	282 people Data from 1 RCT	**Incidence of extrapyramidal adverse events** 46% with haloperidol (10 mg/day) 29% with sertindole (24 mg/day) Absolute results not reported	P less-than or equal to 0.05	○○○	sertindole
[30] Systematic review	282 people Data from 1 RCT	**Mean weight gain (kg)** –0.73 kg with haloperidol (10 mg/day) +4.6 kg with sertindole (24 mg/day) Absolute results not reported	P less-than or equal to 0.05	○○○	haloperidol

Haloperidol versus ziprasidone:

We found one systematic review (search date 2006, 5 RCTs, 980 people). [11] The review did not include any outcomes of interest for this *Clinical Evidence* review for this comparison, but did include treatment-related adverse effects, which are reported below.

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	501 people 3 RCTs in this analysis	**Extrapyramidal symptoms** with haloperidol with ziprasidone Absolute results not reported	RR 0.50 95% CI 0.26 to 0.96	●○○	ziprasidone
[11] Systematic review	301 people Data from 1 RCT	**Mean difference in weight gain (kg)** with haloperidol with ziprasidone Absolute results not reported	Mean difference +0.1 kg 95% CI –1.2 kg to +1.3 kg	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[11] Systematic review	301 people Data from 1 RCT	**Sedation** with haloperidol with ziprasidone Absolute results not reported	RR 1.59 95% CI 0.82 to 3.08	⟷	Not significant

Haloperidol versus zotepine:

We found one systematic review (search date 2006, 5 RCTs, 980 people). [11] The review did not include any outcomes of interest for this *Clinical Evidence* review for this comparison, but did include treatment-related adverse effects, which are reported below.

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	398 people 4 RCTs in this analysis	**Extrapyramidal symptoms** with haloperidol with zotepine Absolute results not reported	RR 0.59 95% CI 0.44 to 0.79	●○○	zotepine
[11] Systematic review	321 people 3 RCTs in this analysis	**Mean difference in weight gain (kg)** with haloperidol with zotepine Absolute results not reported	Mean difference 2.7 kg 95% CI 1.7 kg to 3.7 kg	○○○	haloperidol
[11] Systematic review	221 people 3 RCTs in this analysis	**Sedation** with haloperidol with zotepine Absolute results not reported	RR 1.86 95% CI 1.04 to 3.33	●○○	haloperidol

Further information on studies

[11] Most studies were short term. Bias may have been induced in individual studies by selective reporting.

[16] Very high withdrawal in the long-term study included in this review.

[24] Adverse effects were reported in a different paper, considered in various systematic reviews. The method of random allocation method was not stated. The study was medium term (14 weeks) and was primarily funded by the National Institute of Mental Health with supplemental funding from the manufacturer of olanzapine. The haloperidol and risperidone doses were relatively high.

[29] All studies included were short to medium term. There was approximately 50% withdrawal across the studies. Most studies had a very small sample size.

[30] The systematic review did not assess the quality of the included studies.

[31] A reasonably well conducted study, but units of differences between groups were not given for symptoms. They may be raw scores or SDs.

[32] A very small study. Several patients were excluded because of missing data; last observation carried forward (LOCF) was used for the analysis of the other patients.

[33] Follow-up rates in this RCT were relatively good, but LOCF was used for those that withdrew.

[34] Follow-up rates in this RCT were reasonable, but LOCF was used for those that withdrew.

Comment: Although there is some evidence of efficacy of haloperidol for positive, negative, and cognitive symptoms and comparability with other drugs, it is mainly based on trials with poor methodology and small sample sizes. There was no evidence of a difference between haloperidol and chlorpromazine. A review of two very small studies showed superiority of haloperidol over placebo in clinical improvement but no evidence of a difference for short-term Brief Psychiatric Rating Scale. Comparisons with second-generation antipsychotics showed mixed results, with haloperidol being worse on some measures in some studies, while others showed no difference.

There is evidence that haloperidol causes weight gain, extrapyramidal symptoms, and sedation. There was no evidence of any difference in adverse effects between haloperidol and chlorpromazine. Haloperidol consistently caused less weight gain than second-generation antipsychotics, apart from aripiprazole; but haloperidol was generally associated with more extrapyramidal symptoms/movement disorders, although the rate of extrapyramidal symptoms with haloperidol was similar to that with olanzapine in some studies. Levels of sedation were comparable with other antipsychotics. Haloperidol may cause greater changes in prolactin and glucose concentrations than olanzapine, although studies were few and small.

In general the evidence base is weak, particularly for efficacy, with most reported studies being small and at moderate to high risk of bias. The placebo and chlorpromazine trials used high doses of haloperidol, which would be outside current product licensing.

Clinical guide:
Decades of experience of using haloperidol for schizophrenia support a clinical consensus that it is effective, but the actual evidence base for efficacy is weaker than one might expect. Haloperidol is particularly associated with extrapyramidal symptoms, which may limit its use. When choosing between haloperidol and second-generation antipsychotics, the adverse-effect profiles of the agents should be taken into consideration. Regular ECG monitoring is now recommended for patients taking haloperidol.

OPTION OLANZAPINE

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Olanzapine shows superior effectiveness over first-generation antipsychotics for treatment of positive and negative symptoms and a similar efficacy profile to other second-generation antipsychotics. Olanzapine is associated with greater weight gain and adverse metabolic effects than most other antipsychotics and is generally similar to other second-generation antipsychotics in terms of prolactin increase, somnolence, extrapyramidal symptoms, seizures, and cardiac effects.

Benefits and harms

Olanzapine versus placebo:

We found one systematic review (search date 2004, 4 RCTs, 773 people) [35] and one subsequent RCT. [36]

Symptom severity

Compared with placebo Olanzapine may be more effective at improving positive symptoms at 6 weeks, but may be no more effective at improving negative symptoms at 6 weeks or 6 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[35] Systematic review	94 people Data from 1 RCT	**Mean difference in negative symptoms (Scale for the Assessment of Negative Symptoms [SANS]) , 6 months** with olanzapine with placebo	Mean difference –0.5 95% CI –2.87 to +1.87	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
[35] Systematic review	98 people Data from 1 RCT	**Mean difference in negative symptoms (Positive and Negative Syndrome Scale [PANSS]) , 6 weeks** with olanzapine with placebo Absolute results not reported	Mean difference –1.39 95% CI –4.42 to +1.64	⟷	Not significant
[35] Systematic review	98 people Data from 1 RCT	**Mean difference in positive symptoms (PANSS) , 6 weeks** with olanzapine with placebo Absolute results not reported	Mean difference –4.0 95% CI –7.10 to –0.90	○○○	olanzapine
[36] RCT	107 adolescents 2:1 randomisation	**Mean change from baseline in positive symptoms (PANSS) , 6 weeks** –6.6 with olanzapine (mean daily dose 11.1 mg/day) –2.7 with placebo	P = 0.002	○○○	olanzapine
[36] RCT	107 adolescents 2:1 randomisation	**Mean change from baseline in negative symptoms (PANSS) , 6 weeks** –3.8 with olanzapine (mean daily dose 11.1mg/day) –1.8 with placebo	P = 0.081	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[35] Systematic review	266 people Data from 1 RCT	**Dry mouth , 6 weeks** with olanzapine with placebo Absolute results not reported	RR 1.60 95% CI 0.47 to 5.41	⟷	Not significant
[35] Systematic review	266 people Data from 1 RCT	**Dizziness** with olanzapine with placebo Absolute results not reported	RR 3.95 95% CI 0.96 to 16.31	⟷	Not significant
[35] Systematic review	248 people 2 RCTs in this analysis	**Needing anticholinergic medication , 6 weeks** with olanzapine with placebo Absolute results not reported	RR 0.90 95% CI 0.29 to 2.79	⟷	Not significant
[35] Systematic review	266 people Data from 1 RCT	**Akathisia , 6 weeks** with olanzapine with placebo Absolute results not reported	RR 4.12 95% CI 0.55 to 31.11	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[35] Systematic review	266 people Data from 1 RCT	**Tremor , 6 weeks** with olanzapine with placebo Absolute results not reported	RR 2.40 95% CI 0.30 to 19.19	⟷	Not significant
[35] Systematic review	227 people 2 RCTs in this analysis	**Mean difference in weight (units not given) , 6 to 8 weeks** with olanzapine with placebo Absolute results not reported	Mean difference +3.58 95% CI –1.18 to +8.34	⟷	Not significant
[35] Systematic review	104 people Data from 1 RCT	**Mean difference in weight (units not given) , 3 to 12 months** with olanzapine with placebo Absolute results not reported	Mean difference –0.52 95% CI –6.14 to +5.10	⟷	Not significant
[36] RCT	107 adolescents 2:1 randomisation	**Mean change from baseline in prolactin (micrograms/L) , 6 weeks** +8.8 micrograms/L with olanzapine (mean daily dose 11.1 mg/day) –3.3 micrograms/L with placebo	P = 0.002	○○○	placebo
[36] RCT	107 adolescents 2:1 randomisation	**Mean change from baseline in weight (kg) , 6 weeks** 4.3 kg with olanzapine (mean daily dose 11.1 mg/day) 0.1 kg with placebo	P <0.001	○○○	placebo
[36] RCT	107 adolescents 2:1 randomisation	**Somnolence** 24% with olanzapine (mean daily dose 11.1 mg/day) 3% with placebo Absolute numbers not reported	P = 0.006	○○○	placebo
[36] RCT	107 adolescents 2:1 randomisation	**Sedation** 15% with olanzapine (mean daily dose 11.1 mg/day) 6% with placebo Absolute numbers not reported	P = 0.214	⟷	Not significant
[36] RCT	107 adolescents 2:1 randomisation	**Mean change from baseline in extrapyramidal symptoms (Simpson-Angus Scale (SAS); Barnes Akathisia Scale (BAS); Involuntary Movement Scale (IMS) non-global total [questions 1–7]) , 6 weeks** with olanzapine (mean daily dose 11.1 mg/day) with placebo Absolute results not reported	SAS P = 0.260 BAS P = 0.747 IMS P = 0.897	⟷	Not significant
[36] RCT	107 adolescents 2:1 randomisation	**Treatment with anticholinergic medication** 4% with olanzapine (mean daily dose 11.1 mg/day)	P = 0.661	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		6% with placebo Absolute numbers not reported			

Olanzapine versus amisulpride:

See treatment option on amisulpride, p 4 .

Olanzapine versus aripiprazole:

We found one systematic review (search date 2007, 2 RCTs, 794 people). [21]

Symptom severity

Compared with aripiprazole Olanzapine seems more effective at improving positive and negative symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[21] Systematic review	794 people 2 RCTs in this analysis	**Mean difference in average endpoint Positive and Negative Syndrome Scale total score** with olanzapine (10–20 mg/day) with aripiprazole (15–30 mg/day) Absolute results not reported	Mean difference –4.96 95% CI –8.06 to –1.85	○○○	olanzapine

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] Systematic review	317 people Data from 1 RCT	**QTc prolongation** with olanzapine (10–20 mg/day, mean dose 16.5 mg/day) with aripiprazole (15–30 mg/day, mean dose 25.1 mg/day) Absolute results not reported	RR 2.91 95% CI 0.60 to 14.18	⟷	Not significant
[21] Systematic review	317 people Data from 1 RCT	**QTc abnormalities: mean difference in change from baseline (ms)** with olanzapine (10–20 mg/day, mean dose 16.5 mg/day) with aripiprazole (15–30 mg/day, mean dose 25.1 mg/day) Absolute results not reported	Mean difference +3.70 ms 95% CI –2.11 ms to +9.51 ms	⟷	Not significant
[21] Systematic review	317 people Data from 1 RCT	**Sedation** with olanzapine (10–20 mg/day, mean dose 16.5 mg/day) with aripiprazole (15–30 mg/day, mean dose 25.1 mg/day)	RR 2.99 95% CI 1.62 to 5.51	●●○	aripiprazole

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
[21] Systematic review	317 people Data from 1 RCT	**Akathisia** with olanzapine (10–20 mg/day, mean dose 16.5 mg/day) with aripiprazole (15–30 mg/day, mean dose 25.1 mg/day) Absolute results not reported	RR 0.54 95% CI 0.18 to 1.57	↔	Not significant
[21] Systematic review	317 people Data from 1 RCT	**Extrapyramidal symptoms** with olanzapine (10–20 mg/day, mean dose 16.5 mg/day) with aripiprazole (15–30 mg/day, mean dose 25.1 mg/day) Absolute results not reported	RR 0.93 95% CI 0.56 to 1.54	↔	Not significant
[21] Systematic review	317 people Data from 1 RCT	**Parkinsonism** with olanzapine (10–20 mg/day, mean dose 16.5 mg/day) with aripiprazole (15–30 mg/day, mean dose 25.1 mg/day) Absolute results not reported	RR 1.08 95% CI 0.58 to 2.01	↔	Not significant
[21] Systematic review	317 people Data from 1 RCT	**Abnormally high prolactin value** with olanzapine (10–20 mg/day, mean dose 16.5 mg/day) with aripiprazole (15–30 mg/day, mean dose 25.1 mg/day) Absolute results not reported	RR 3.74 95% CI 1.68 to 8.33	●●○	aripiprazole
[21] Systematic review	223 people Data from 1 RCT	**Significant cholesterol increase** with olanzapine (10–20 mg/day) with aripiprazole (15–30 mg/day) Absolute results not reported	RR 3.15 95% CI 1.84 to 5.39	●●○	aripiprazole
[21] Systematic review	223 people Data from 1 RCT	**Mean difference in change from baseline in cholesterol (mg/dL)** with olanzapine (10–20 mg/day) with aripiprazole (15–30 mg/day) Absolute results not reported	Mean difference 17.43 mg/dL 95% CI 7.65 mg/dL to 27.21 mg/dL	●●●	aripiprazole
[21] Systematic review	317 people Data from 1 RCT	**Weight gain of 7% or more of total body weight** with olanzapine (10–20 mg/day, mean dose 16.5 mg/day) with aripiprazole (15–30 mg/day, mean dose 25.1 mg/day) Absolute results not reported	RR 2.68 95% CI 1.71 to 4.19	●●○	aripiprazole
[21] Systematic review	90 people Data from 1 RCT	**Mean difference in change from baseline in weight (kg)** with olanzapine (10–20 mg/day) with aripiprazole (15–30 mg/day) Absolute results not reported	Mean difference 5.60 kg 95% CI 2.15 kg to 9.05 kg	●●●	aripiprazole

Olanzapine versus clozapine:

See option on clozapine, p 20 .

Olanzapine versus haloperidol:

See option on haloperidol, p 37 .

Olanzapine versus paliperidone:

We found one systematic review (search date 2008, 3 RCTs, 1327 people). [37]

Symptom severity

Compared with paliperidone Olanzapine seems to be as effective at improving positive and negative symptoms in people with schizophrenia at 6 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[37] Systematic review	327 people Data from 1 RCT 3-armed trial	**No clinically important change , 6 weeks** with olanzapine (10 mg/day) with paliperidone (6 mg/day) with paliperidone (12 mg/day) Absolute results not reported Clinically important change defined as <30% reduction from baseline in Positive and Negative Syndrome Scale (PANSS)	RR 0.90 95% CI 0.73 to 1.13	⟷	Not significant
[37] Systematic review	715 people 3 RCTs in this analysis	**Mean difference in average change score for PANSS , 6 weeks** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	Mean difference +2.42 95% CI –0.52 to +5.35	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[37] Systematic review	216 people Data from 1 RCT	**Mean difference in average change in QTc LD (ms) from baseline (6 mg)** with olanzapine (10 mg/day) with paliperidone (6 mg/day) Absolute results not reported	Mean difference 1.50 ms 95% CI 1.12 ms to 1.88 ms	○○○	olanzapine
[37] Systematic review	216 people Data from 1 RCT	**Mean difference in average change in QTc LD (ms) from baseline (12 mg)** with olanzapine (10 mg/day)	Mean difference –3.20 ms 95% CI –3.59 ms to –2.81 ms	○○○	paliperidone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with paliperidone (12 mg/day) Absolute results not reported			
[37] Systematic review	687 people 3 RCTs in this analysis	**Mean difference in average change in cholesterol (mmol/L)** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	Mean difference –0.31 mmol/L 95% CI –0.44 mmol/L to –0.19 mmol/L	○○○	paliperidone
[37] Systematic review	687 people 3 RCTs in this analysis	**Mean difference in average change in triglycerides (mmol/L)** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	Mean difference –0.32 mmol/L 95% CI –0.46 mmol/L to –0.17 mmol/L	○○○	paliperidone
[37] Systematic review	1317 people 3 RCTs in this analysis	**Sleepiness** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	RR 0.49 95% CI 0.37 to 0.65	●●○	paliperidone
[37] Systematic review	433 people 3 RCTs in this analysis	**Mean difference in average change in prolactin (ng/mL), men** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	Mean difference 26.81 ng/mL 95% CI 22.94 ng/mL to 30.68 ng/mL	○○○	olanzapine
[37] Systematic review	253 people 3 RCTs in this analysis	**Mean difference in average change in prolactin (ng/mL), women** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	Mean difference 81.63 ng/mL 95% CI 68.31 ng/mL to 94.94 ng/mL	○○○	olanzapine
[37] Systematic review	660 people 3 RCTs in this analysis	**Mean difference in average change in weight (kg)** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	Mean difference –0.88 kg 95% CI –1.38 kg to –0.37 kg	○○○	paliperidone
[37] Systematic review	1327 people 3 RCTs in this analysis	**Extrapyramidal symptoms** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	RR 2.99 95% CI 1.44 to 6.18	●●○	olanzapine
[37] Systematic review	1327 people 3 RCTs in this analysis	**Hyperkinesia** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	RR 3.14 95% CI 1.53 to 6.42	○○○	olanzapine
[37] Systematic review	836 people 2 RCTs in this analysis	**Hypertonia** with olanzapine (10 mg/day) with paliperidone (6–12 mg/day) Absolute results not reported	RR 9.28 95% CI 1.26 to 68.51	●●●	olanzapine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[37] Systematic review	502 people Data from 1 RCT	**Akathisia: absent** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	RR 0.90 95% CI 0.82 to 0.98	●○○	paliperidone
[37] Systematic review	502 people Data from 1 RCT	**Akathisia: questionable** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	RR 1.19 95% CI 0.64 to 2.18	⟷	Not significant
[37] Systematic review	502 people Data from 1 RCT	**Akathisia: mild** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	RR 1.02 95% CI 0.38 to 2.74	⟷	Not significant
[37] Systematic review	502 people Data from 1 RCT	**Akathisia: moderate** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	RR 3.06 95% CI 0.17 to 56.52	⟷	Not significant
[37] Systematic review	502 people Data from 1 RCT	**Akathisia: marked** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	RR 0.00 95% CI 0.00 to 0.00	⟷	Not significant
[37] Systematic review	1327 people 3 RCTs in this analysis	**Pain: headache** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	RR 1.45 95% CI 1.03 to 2.04	●○○	olanzapine
[37] Systematic review	1327 people 3 RCTs in this analysis	**Suicide attempt** with olanzapine (10 mg/day) with paliperidone (3–15 mg/day) Absolute results not reported	RR 0.69 95% CI 0.21 to 2.30	⟷	Not significant

Olanzapine versus quetiapine:

We found one systematic review (search date 2007, 13 RCTs, 1818 people). [21]

Symptom severity

Compared with quetiapine Olanzapine seems more effective at improving positive and negative symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[21] Systematic review	30 people Data from 1 RCT	**Positive symptoms: <20% reduction in Scale for the Assessment of Positive Symptoms (SAPS) total score** with olanzapine (mean dose 23 mg/day)	RR 0.07 95% CI 0.00 to 1.07	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with quetiapine (mean dose 826.67 mg/day) Absolute results not reported			
[21] Systematic review	115 people 3 RCTs in this analysis	**Mean difference in average endpoint Positive and Negative Syndrome Scale (PANSS) positive subscore , short term** with olanzapine (2.5–20 mg/day) with quetiapine (50–800 mg/day) Absolute results not reported	Mean difference –1.05 95% CI –2.85 to +0.75	⟷	Not significant
[21] Systematic review	483 people 3 RCTs in this analysis	**Mean difference in average endpoint PANSS positive subscore , medium term** with olanzapine (7.5–30 mg/day) with quetiapine (200–800 mg/day) Absolute results not reported	Mean difference –2.21 95% CI –3.52 to –0.90	●●○	olanzapine
[21] Systematic review	81 people Data from 1 RCT	**Mean difference in average endpoint PANSS positive subscore , long term** with olanzapine (2.5–20 mg/day) with quetiapine (100–800 mg/day) Absolute results not reported	Mean difference –1.80 95% CI –3.21 to –0.39	○○○	olanzapine
[21] Systematic review	30 people Data from 1 RCT	**Positive symptoms: percent change in SAPS total score** with olanzapine (mean dose 23 mg/day) with quetiapine (mean dose 826.67 mg/day) Absolute results not reported	Mean difference –40.84% 95% CI –57.71% to –23.97%	○○○	olanzapine
[21] Systematic review	30 people Data from 1 RCT	**Negative symptoms: <20% reduction in Scale for the Assessment of Negative Symptoms (SANS) total score** with olanzapine (mean dose 23 mg/day) with quetiapine (mean dose 826.67 mg/day) Absolute results not reported	RR 0.67 95% CI 0.23 to 1.89	⟷	Not significant
[21] Systematic review	115 people 3 RCTs in this analysis	**Mean difference in average endpoint PANSS negative subscore , short term** with olanzapine (2.5–20 mg/day) with quetiapine (50–800 mg/day) Absolute results not reported	Mean difference –0.01 95% CI –1.73 to +1.72	⟷	Not significant
[21] Systematic review	483 people 3 RCTs in this analysis	**Mean difference in average endpoint PANSS negative subscore , medium term** with olanzapine (7.5–30 mg/day) with quetiapine (200–800 mg/day) Absolute results not reported	Mean difference –0.40 95% CI –1.47 to +0.67	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] Systematic review	483 people Data from 1 RCT	**Mean difference in average endpoint PANSS negative subscore , long term** with olanzapine (2.5–20 mg/day) with quetiapine (100–800 mg/day) Absolute results not reported	Mean difference –0.70 95% CI –2.13 to +0.73	⟷	Not significant
[21] Systematic review	335 people Data from 1 RCT	**Mean difference in average endpoint SANS subscore , medium term** with olanzapine (10–20 mg/day) with quetiapine (300–700 mg/day) Absolute results not reported	Mean difference –3.70 95% CI –7.88 to +0.48	⟷	Not significant
[21] Systematic review	30 people Data from 1 RCT	**Negative symptoms: percent change in SANS total score** with olanzapine (mean dose 23 mg/day) with quetiapine (mean dose 826.67 mg/day) Absolute results not reported	RR –2.46 95% CI –36.82 to +31.90	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] Systematic review	1269 people 5 RCTs in this analysis	**At least 1 adverse effect** with olanzapine (2.5–30 mg/day) with quetiapine (100–800 mg/day) Absolute results not reported	RR 1.04 95% CI 0.95 to 1.13	⟷	Not significant
[21] Systematic review	940 people 2 RCTs in this analysis	**Suicide attempt** with olanzapine (2.5–30 mg) with quetiapine (100–800 mg/day) Absolute results not reported	RR 2.86 95% CI 0.44 to 18.71	⟷	Not significant
[21] Systematic review	940 people 2 RCTs in this analysis	**Suicide** with olanzapine (2.5–30 mg/day) with quetiapine (100–800 mg/day) Absolute results not reported	RR 0.20 95% CI 0.01 to 4.16	⟷	Not significant
[21] Systematic review	673 people Data from 1 RCT	**QTc prolongation** with olanzapine (7.5–30 mg/day) with quetiapine (200–800 mg/day) Absolute results not reported	RR 0.08 95% CI 0.00 to 1.36	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] Systematic review	643 people 3 RCTs in this analysis	**QTc abnormalities: mean difference** with olanzapine (7.5–30 mg/day) with quetiapine (50–800 mg/day) Absolute results not reported	Mean difference –4.81 95% CI –9.28 to +0.34	⟷	Not significant
[21] Systematic review	1615 people 6 RCTs in this analysis	**Sedation** with olanzapine (5–20 mg/day, mean dose 16 mg/day) with quetiapine (200–800 mg/day, mean dose 637.2 mg/day) Absolute results not reported	RR 1.01 95% CI 0.88 to 1.15	⟷	Not significant
[21] Systematic review	40 people Data from 1 RCT	**Seizures** with olanzapine (5–20 mg/day, mean dose 16 mg/day) with quetiapine (200–800 mg/day, mean dose 637.2 mg/day) Absolute results not reported	RR 0.30 95% CI 0.01 to 7.02	⟷	Not significant
[21] Systematic review	1277 people 5 RCTs in this analysis	**Akathisia** with olanzapine (2.5–30 mg/day) with quetiapine (50–800 mg/day) Absolute results not reported	RR 1.03 95% CI 0.71 to 1.47	⟷	Not significant
[21] Systematic review	267 people Data from 1 RCT	**Akinesia** with olanzapine (2.5–20 mg/day, mean dose 11.7 mg/day) with quetiapine (100–800 mg/day, mean dose 506 mg/day) Absolute results not reported	RR 0.98 95% CI 0.64 to 1.49	⟷	Not significant
[21] Systematic review	42 people Data from 1 RCT	**Dystonia** with olanzapine (10–20 mg/day, mean dose 19.5 mg) with quetiapine (50–700 mg/day, mean dose 677.3 mg/day) Absolute results not reported	RR 0.22 95% CI 0.01 to 4.30	⟷	Not significant
[21] Systematic review	245 people 2 RCTs in this analysis	**Extrapyramidal symptoms** with olanzapine (7.5–30 mg/day) with quetiapine (100–800 mg/day) Absolute results not reported	RR 0.62 95% CI 0.27 to 1.39	⟷	Not significant
[21] Systematic review	40 people Data from 1 RCT	**Parkinsonism** with olanzapine (5–20 mg/day, mean dose 16 mg/day) with quetiapine (200–800 mg/day, mean dose 637.2 mg/day) Absolute results not reported	RR 1.51 95% CI 0.42 to 5.48	⟷	Not significant
[21] Systematic review	42 people Data from 1 RCT	**Tremor** with olanzapine (10–20 mg/day, mean dose 19.5 mg/day) with quetiapine (50–700 mg/day, mean dose 677.3 mg/day) Absolute results not reported	RR 2.57 95% CI 0.77 to 8.60	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] Systematic review	1090 people 3 RCTs in this analysis	**Use of antiparkinsonism medication** with olanzapine with quetiapine Absolute results not reported	RR 2.05 95% CI 1.26 to 3.32	●●○	quetiapine
[21] Systematic review	50 people Data from 1 RCT	**Akathisia: mean difference on Barnes Akathisia Scale** with olanzapine (10–20 mg/day, mean dose 14.6 mg/day) with quetiapine (400–800 mg/day, mean dose 602.4 mg/day) Absolute results not reported	Mean difference +0.10 95% CI –0.38 to +0.58	⟷	Not significant
[21] Systematic review	50 people Data from 1 RCT	**Extrapyramidal symptoms: mean difference on Extrapyramidal Symptom Rating Scale** with olanzapine (10–20 mg/day, mean dose 15.82 mg/day) with quetiapine (400–800 mg/day, mean dose 586.86 mg/day) Absolute results not reported	Mean difference 0.00 95% CI –2.68 to +2.68	⟷	Not significant
[21] Systematic review	50 people Data from 1 RCT	**Extrapyramidal symptoms: mean difference on Simpson-Angus Scale** with olanzapine (10–20 mg/day, mean dose 14.6 mg/day) with quetiapine (400–800 mg/day, mean dose 602.4 mg/day) Absolute results not reported	Mean difference –0.60 95% CI –2.58 to +1.38	⟷	Not significant
[21] Systematic review	42 people Data from 1 RCT	**Abnormally high prolactin value** with olanzapine (10–20 mg/day, mean dose 19.5 mg/day) with quetiapine (50–700 mg/day, mean dose 677.3 mg/day) Absolute results not reported	RR 9.86 95% CI 0.56 to 172.33	⟷	Not significant
[21] Systematic review	1021 people 5 RCTs in this analysis	**Mean difference in change from baseline in prolactin (ng/mL)** with olanzapine (2.5–30 mg/day) with quetiapine (50–800 mg/day) Absolute results not reported	Mean difference 5.89 ng/mL 95% CI 0.16 ng/mL to 11.62 ng/mL	○○○	quetiapine
[21] Systematic review	1177 people 4 RCTs in this analysis	**Sexual dysfunction** with olanzapine (2.5–30 mg/day) with quetiapine (100–800 mg/day) Absolute results not reported	RR 1.25 95% CI 1.01 to 1.55	●○○	quetiapine
[21] Systematic review	986 people 4 RCTs in this analysis	**Mean difference in change from baseline in glucose (mg/dL)** with olanzapine (2.5–30 mg/day) with quetiapine (100–800 mg/day) Absolute results not reported	Mean difference 9.32 mg/dL 95% CI 0.82 mg/dL to 17.82 mg/dL	○○○	quetiapine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] Systematic review	1667 people 6 RCTs in this analysis	**Weight gain** with olanzapine (2.5–30 mg/day) with quetiapine (50–800 mg/day) Absolute results not reported	RR 1.47 95% CI 1.09 to 1.98	●○○	quetiapine
[21] Systematic review	1173 people 5 RCTs in this analysis	**Mean difference in weight gain (kg)** with olanzapine with quetiapine Absolute results not reported	Mean difference 2.68 kg 95% CI 1.10 kg to 4.26 kg	○○○	quetiapine

Olanzapine versus risperidone:

We found two systematic reviews (search date 2007, 23 RCTs, 4982 people; [21] and search date 2004, 16 RCTs, 4110 people [38]).

Symptom severity

Compared with risperidone We don't know whether olanzapine is more effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[21] Systematic review	377 people Data from 1 RCT	**<50% reduction in Positive and Negative Syndrome Scale (PANSS) positive subscore , short term** with olanzapine (5–20 mg/day, mean dose 13.1 mg/day) with risperidone (2–6 mg/day, mean dose 4.7 mg/day) Absolute results not reported	RR 1.02 95% CI 0.96 to 1.07	⟷	Not significant
[21] Systematic review	661 people 5 RCTs in this analysis	**Mean difference in average endpoint PANSS positive sub-score , short term** with olanzapine with risperidone Absolute results not reported	Mean difference +0.48 95% CI –0.57 to +1.53	⟷	Not significant
[21] Systematic review	231 people 3 RCTs in this analysis	**Mean difference in average endpoint PANSS positive sub-score , medium term** with olanzapine (7.5–40 mg/day) with risperidone (1.5–16 mg/day) Absolute results not reported	Mean difference –1.58 95% CI –3.20 to +0.03	⟷	Not significant
[21] Systematic review	810 people 5 RCTs in this analysis	**Mean difference in average endpoint PANSS positive sub-score , long term** with olanzapine (2.5–20 mg/day) with risperidone (0.5–12 mg/day) Absolute results not reported	Mean difference –0.68 95% CI –1.40 to +0.04	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] Systematic review	661 people 5 RCTs in this analysis	**Mean difference in average endpoint PANSS negative subscore , short term** with olanzapine with risperidone Absolute results not reported	Mean difference –0.19 95% CI –1.22 to +0.85	⟷	Not significant
[21] Systematic review	231 people 3 RCTs in this analysis	**Mean difference in average endpoint PANSS negative subscore , medium term** with olanzapine (7.5–40 mg/day) with risperidone (1.5–16 mg/day) Absolute results not reported	Mean difference 0.00 95% CI –1.59 to +1.58	⟷	Not significant
[21] Systematic review	810 people 5 RCTs in this analysis	**Mean difference in average endpoint PANSS negative subscore , long term** with olanzapine (2.5–20 mg/day) with risperidone (0.5–12 mg/day) Absolute results not reported	Mean difference –0.81 95% CI –1.54 to –0.07	○○○	olanzapine
[21] Systematic review	308 people Data from 1 RCT	**Mean difference in average endpoint Scale for the Assessment of Negative Symptoms (SANS) total subscore , long term** with olanzapine (10–20 mg/day, mean dose 17.2 mg/day) with risperidone (4–12 mg/day, mean dose 7.2 mg/day) Absolute results not reported	Mean difference –1.40 95% CI –2.43 to –0.37	○○○	olanzapine
[21] Systematic review	80 people Data from 1 RCT	**<0.5 SD improvement in global neurocognitive score , medium term** with olanzapine (10–40 mg/day, mean dose 30.4 mg/day) with risperidone (4–16 mg/day, mean dose 11.6 mg/day) Absolute results not reported	RR 0.77 95% CI 0.52 to 1.14	⟷	Not significant
[21] Systematic review	52 people Data from 1 RCT	**Mean difference in average endpoint global neurocognitive score , medium term** with olanzapine (10–40 mg/day) with risperidone (4–16 mg/day) Absolute results not reported	Mean difference –0.04 95% CI –0.39 to +0.31	⟷	Not significant
[21] Systematic review	163 people Data from 1 RCT	**Mean difference in average endpoint neurocognitive composite score , long term** with olanzapine (5–20 mg/day) with risperidone (2–10 mg/day) Absolute results not reported	Mean difference –0.01 95% CI –0.13 to +0.11	⟷	Not significant
[38] Systematic review	612 people 3 RCTs in this analysis	**No clinically important response on Clinical Global Impression scale (CGI) score** 200/307 (65%) with olanzapine 208/305 (68%) with risperidone	RR 1.07 95% CI 0.90 to 1.27	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		No clinically important response on CGI score not further defined			
[38] Systematic review	394 people 2 RCTs in this analysis	**Mean average CGI score , long term** with olanzapine with risperidone Absolute results not reported	WMD +0.08 95% CI –0.15 to +0.32	⟷	Not significant
[38] Systematic review	339 people Data from 1 RCT	**No response** 70/172 (41%) with olanzapine 63/167 (38%) with risperidone No response was defined as up to <20% decrease in PANSS scores	RR 0.93 95% CI 0.71 to 1.21	⟷	Not significant
[38] Systematic review	339 people Data from 1 RCT	**No response** 84/172 (49%) with olanzapine 95/167 (57%) with risperidone No response was defined as up to <30% decrease in PANSS	RR 1.16 95% CI 0.95 to 1.43	⟷	Not significant
[38] Systematic review	339 people Data from 1 RCT	**No response** 111/172 (65%) with olanzapine 123/167 (74%) with risperidone No response was defined as up to <40% decrease in PANSS	RR 1.14 95% CI 0.99 to 1.30	⟷	Not significant
[38] Systematic review	339 people Data from 1 RCT	**No response** 136/172 (79%) with olanzapine 147/167 (88%) with risperidone Response defined as <50% decrease in PANSS score	RR 1.11 95% CI 1.01 to 1.22	●○○	olanzapine
[38] Systematic review	80 people Data from 1 RCT	**Mean total PANSS score , short term** with olanzapine with risperidone Absolute results not reported Mean total endpoint score on PANSS (higher score is worse)	WMD +0.70 95% CI –7.01 to +8.41	⟷	Not significant
[38] Systematic review	80 people Data from 1 RCT	**Mean total PANSS score , medium term** with olanzapine with risperidone Absolute results not reported Mean total endpoint score on PANSS (higher score is worse)	WMD +4.50 95% CI –4.70 to +13.70	⟷	Not significant
[38] Systematic review	435 people 3 RCTs in this analysis	**Mean total PANSS score , long term** with olanzapine with risperidone Absolute results not reported Mean total endpoint score on PANSS (higher score is worse)	WMD 5.80 95% CI 0.30 to 11.31	○○○	olanzapine

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] Systematic review	2576 people 11 RCTs in this analysis	**At least 1 adverse effect** with olanzapine (2.5–30 mg/day) with risperidone (0.5–12 mg/day) Absolute results not reported	RR 1.05 95% CI 0.97 to 1.13	⟷	Not significant
[21] Systematic review	1742 people 5 RCTs in this analysis	**Suicide attempt** with olanzapine (2.5–30 mg/day) with risperidone (0.5–12 mg/day) Absolute results not reported	RR 0.87 95% CI 0.28 to 2.67	⟷	Not significant
[21] Systematic review	430 people 4 RCTs in this analysis	**Suicide** with olanzapine (2.5–30 mg/day) with risperidone (0.5–8 mg/day) Absolute results not reported	RR 0.32 95% CI 0.01 to 7.79	⟷	Not significant
[21] Systematic review	415 people 2 RCTs in this analysis	**ECG abnormalities** with olanzapine (5–20 mg/day) with risperidone (4–2 mg/day) Absolute results not reported	RR 2.39 95% CI 0.43 to 13.14	⟷	Not significant
[21] Systematic review	853 people 2 RCTs in this analysis	**QTc prolongation** with olanzapine (5–30 mg/day) with risperidone (1–6 mg/day) Absolute results not reported	RR 0.37 95% CI 0.02 to 8.30	⟷	Not significant
[21] Systematic review	1518 people 6 RCTs in this analysis	**QTc abnormalities: mean difference in change from baseline (ms)** with olanzapine (2.5–30 mg/day) with risperidone (0.5–12 mg/day) Absolute results not reported	Mean difference –0.96 ms 95% CI –4.67 ms to +2.74 ms	⟷	Not significant
[21] Systematic review	2576 people 11 RCTs in this analysis	**Sedation** with olanzapine (2.5–30 mg/day) with risperidone (0.5–12 mg/day) Absolute results not reported	RR 1.07 95% CI 0.96 to 1.19	⟷	Not significant
[21] Systematic review	671 people 4 RCTs in this analysis	**Seizures** with olanzapine (5–40 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	RR 3.82 95% CI 0.43 to 34.35	⟷	Not significant
[21] Systematic review	1988 people 8 RCTs in this analysis	**Akathisia** with olanzapine (2.5–30 mg/day) with risperidone (0.5–12 mg/day) Absolute results not reported	RR 0.77 95% CI 0.60 to 0.98	●○○	olanzapine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] Systematic review	681 people 3 RCTs in this analysis	**Akinesia** with olanzapine (2.5–20 mg/day) with risperidone (0.5–12 mg/day) Absolute results not reported	RR 0.83 95% CI 0.56 to 1.23	⟷	Not significant
[21] Systematic review	580 people 3 RCTs in this analysis	**Dyskinesia** with olanzapine (5–20 mg/day) with risperidone (1–12 mg/day) Absolute results not reported	RR 0.98 95% CI 0.34 to 2.80	⟷	Not significant
[21] Systematic review	591 people 3 RCTs in this analysis	**Dystonia** with olanzapine (5–20 mg/day) with risperidone (1–12 mg/day) Absolute results not reported	RR 0.56 95% CI 0.11 to 2.73	⟷	Not significant
[21] Systematic review	1104 people 4 RCTs in this analysis	**Extrapyramidal symptoms** with olanzapine (5–30 mg/day) with risperidone (1–12 mg/day) Absolute results not reported	RR 0.75 95% CI 0.47 to 1.21	⟷	Not significant
[21] Systematic review	776 people 4 RCTs in this analysis	**Parkinsonism** with olanzapine (2.5–20 mg/day) with risperidone (1–12 mg/day) Absolute results not reported	RR 0.61 95% CI 0.40 to 0.92	●○○	olanzapine
[21] Systematic review	141 people 2 RCTs in this analysis	**Rigor** with olanzapine (5–20 mg/day) with risperidone (4–8 mg/day) Absolute results not reported	RR 2.44 95% CI 0.37 to 16.14	⟷	Not significant
[21] Systematic review	973 people 5 RCTs in this analysis	**Tremor** with olanzapine (5–20 mg/day) with risperidone (1–12 mg/day) Absolute results not reported	RR 1.15 95% CI 0.64 to 2.08	⟷	Not significant
[21] Systematic review	2599 people 11 RCTs in this analysis	**Use of antiparkinsonism medication** with olanzapine with risperidone Absolute results not reported	RR 0.78 95% CI 0.65 to 0.95	●○○	olanzapine
[21] Systematic review	302 people Data from 1 RCT	**Mean difference in Abnormal Involuntary Movement Scale** with olanzapine (5–20 mg/day) with risperidone (2–10 mg/day) Absolute results not reported	Mean difference –0.03 95% CI –0.78 to +0.72	⟷	Not significant
[21] Systematic review	353 people Data from 1 RCT	**Mean difference in Barnes Akathisia Scale** with olanzapine (5–20 mg/day) with risperidone (2–10 mg/day) Absolute results not reported	Mean difference –0.72 95% CI –1.81 to +0.36	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] Systematic review	359 people Data from 1 RCT	**Mean difference in Extrapyramidal Symptom Rating Scale (ESRS) subscore for akathisia** with olanzapine (5–20 mg/day) with risperidone (2–6 mg/day) Absolute results not reported	Mean difference 0.00 95% CI –0.27 to +0.27	⟷	Not significant
[21] Systematic review	572 people 3 RCTs in this analysis	**Mean difference in ESRS subscore for dyskinesia** with olanzapine (5–20 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	Mean difference +0.08 95% CI –0.60 to +0.76	⟷	Not significant
[21] Systematic review	42 people Data from 1 RCT	**Mean difference in ESRS subscore for dystonia** with olanzapine (5–20 mg/day, mean dose 11 mg/day) with risperidone (4–10 mg/day, mean dose 6 mg/day) Absolute results not reported	Mean difference +0.09 95% CI –0.73 to +0.91	⟷	Not significant
[21] Systematic review	682 people 4 RCTs in this analysis	**Mean difference in ESRS total score** with olanzapine (5–40 mg/day) with risperidone (1–16 mg/day) Absolute results not reported	Mean difference –0.30 95% CI –0.94 to +0.35	⟷	Not significant
[21] Systematic review	522 people 3 RCTs in this analysis	**Mean difference in Simpson-Angus Scale** with olanzapine with risperidone Absolute results not reported	Mean difference –0.62 95% CI –1.33 to +0.08	⟷	Not significant
[21] Systematic review	572 people 3 RCTs in this analysis	**Mean difference in ESRS subscore for parkinsonism** with olanzapine (5–20 mg/day) with risperidone (1–10 mg/day) Absolute results not reported	Mean difference –0.24 95% CI –1.57 to +1.09	⟷	Not significant
[21] Systematic review	531 people 2 RCTs in this analysis	**Abnormal ejaculation** with olanzapine (5–20 mg/day) with risperidone (2–12 mg/day) Absolute results not reported	RR 0.23 95% CI 0.08 to 0.67	●●○	olanzapine
[21] Systematic review	477 people 3 RCTs in this analysis	**Abnormally high prolactin value** with olanzapine (5–20 mg/day) with risperidone (1–12 mg/day) Absolute results not reported	RR 0.33 95% CI 0.11 to 1.01	⟷	Not significant
[21] Systematic review	565 people 7 RCTs in this analysis	**Amenorrhoea** with olanzapine (2.5–30 mg/day) with risperidone (0.5–12 mg/day) Absolute results not reported	RR 0.67 95% CI 0.45 to 0.98	●○○	olanzapine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] Systematic review	1291 people 6 RCTs in this analysis	**Mean difference in change from baseline in prolactin (ng/mL)** with olanzapine (2.5–30 mg/kg) with risperidone (0.5–10 mg/kg) Absolute results not reported	Mean difference –22.84 ng/mL 95% CI –27.98 ng/mL to –17.69 ng/mL	○○○	olanzapine
[21] Systematic review	266 people Data from 1 RCT	**Significant cholesterol increase** with olanzapine (2.5–20 mg/day) with risperidone (0.5–4 mg/day) Absolute results not reported	RR 1.28 95% CI 0.72 to 2.26	↔	Not significant
[21] Systematic review	1392 people 7 RCTs in this analysis	**Mean difference in change from baseline in cholesterol (mg/dL)** with olanzapine (2.5–40 mg/day) with risperidone (0.5–16 mg/day) Absolute results not reported	Mean difference 10.36 mg/dL 95% CI 6.28 ng/dL to 14.43 ng/dL	○○○	risperidone
[21] Systematic review	670 people 3 RCTs in this analysis	**Abnormally high fasting glucose value** with olanzapine (2.5–20 mg/day) with risperidone (0.5–12 mg/day) Absolute results not reported	RR 1.99 95% CI 0.87 to 4.60	↔	Not significant
[21] Systematic review	1201 people 7 RCTs in this analysis	**Mean difference in change from baseline in glucose (mg/dL)** with olanzapine (2.5–40 mg/day) with risperidone (0.5–16 mg/day) Absolute results not reported	Mean difference 7.58 mg/dL 95% CI 3.93 mg/dL to 11.23 mg/dL	○○○	risperidone
[21] Systematic review	2594 people 10 RCTs in this analysis	**Weight gain** with olanzapine (2.5–40 mg/day) with risperidone (0.5–16 mg/day) Absolute results not reported	RR 1.81 95% CI 1.39 to 2.35	●○○	risperidone
[21] Systematic review	2116 people 12 RCTs in this analysis	**Mean difference in change from baseline in weight (kg)** with olanzapine with risperidone Absolute results not reported	Mean difference 2.61 kg 95% CI 1.48 kg to 3.74 kg	●●○	risperidone
[38] Systematic review	893 people 3 RCTs in this analysis	**Extrapyramidal adverse effects** 83/449 (18%) with olanzapine 105/444 (24%) with risperidone	RR 1.18 95% CI 0.75 to 1.88	↔	Not significant
[38] Systematic review	300 people 2 RCTs in this analysis	**Withdrawal because of adverse effects , short term** 7/153 (5%) with olanzapine 6/147 (4%) with risperidone	RR 0.89 95% CI 0.30 to 2.60	↔	Not significant
[38] Systematic review	1361 people 4 RCTs in this analysis	**Withdrawal because of adverse effects** 96/682 (14%) with olanzapine 78/679 (12%) with risperidone	RR 0.98 95% CI 0.53 to 1.80	↔	Not significant

Olanzapine versus ziprasidone:

We found one systematic review (search date 2007, 6 RCTs, 1985 people). [21]

Symptom severity

Compared with ziprasidone Olanzapine seems more effective at improving positive and cognitive symptoms, but we don't know whether olanzapine is more effective at improving negative symptoms (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[21] Systematic review	730 people 2 RCTs in this analysis	**Mean difference in average Positive and Negative Syndrome Scale (PANSS) positive score at endpoint** with olanzapine (7.5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	Mean difference –3.11 95% CI –4.30 to –1.93	○○○	olanzapine
[21] Systematic review	790 people 2 RCTs in this analysis	**Mean difference in average PANSS negative score at endpoint** with olanzapine (7.5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	Mean difference –0.68 95% CI –3.81 to +2.45	⟷	Not significant
[21] Systematic review	529 people Data from 1 RCT	**Mean difference in average PANSS cognitive score at endpoint** with olanzapine (10–20 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	Mean difference –2.40 95% CI –3.63 to –1.17	○○○	olanzapine

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] Systematic review	1583 people 4 RCTs in this analysis	**At least 1 adverse effect** with olanzapine (5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.95 95% CI 0.85 to 1.07	⟷	Not significant
[21] Systematic review	521 people Data from 1 RCT	**Suicide attempt** with olanzapine (7.5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 1.10 95% CI 0.10 to 12.06	⟷	Not significant
[21] Systematic review	245 people Data from 1 RCT	**Suicide** with olanzapine (7.5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.25 95% CI 0.01 to 5.22	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] Systematic review	1184 people 3 RCTs in this analysis	**QTc prolongation** with olanzapine (5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.63 95% CI 0.04 to 9.93	⟷	Not significant
[21] Systematic review	1372 people 4 RCTs in this analysis	**QTc abnormalities: mean difference in change from baseline (ms)** with olanzapine (5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	Mean difference –2.19 ms 95% CI –4.96 ms to +0.58 ms	⟷	Not significant
[21] Systematic review	766 people 2 RCTs in this analysis	**Sedation** with olanzapine (7.5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 1.56 95% CI 0.96 to 2.55	⟷	Not significant
[21] Systematic review	766 people 2 RCTs in this analysis	**Akathisia** with olanzapine (7.5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.71 95% CI 0.40 to 1.28	⟷	Not significant
[21] Systematic review	548 people Data from 1 RCT	**Dystonia** with olanzapine (10–20 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	RR 0.08 95% CI 0.00 to 1.33	⟷	Not significant
[21] Systematic review	793 people 2 RCTs in this analysis	**Extrapyramidal symptoms** with olanzapine (7.5–30 mg) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.53 95% CI 0.21 to 1.31	⟷	Not significant
[21] Systematic review	1732 people 4 RCTs in this analysis	**Use of antiparkinsonism medication** with olanzapine (5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.70 95% CI 0.50 to 0.97	●○○	olanzapine
[21] Systematic review	925 people 2 RCTs in this analysis	**Extrapyramidal symptoms: mean difference in Abnormal Involuntary Movement Scale** with olanzapine (10–20 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	Mean difference –0.16 95% CI –0.46 to +0.15	⟷	Not significant
[21] Systematic review	924 people 2 RCTs in this analysis	**Extrapyramidal symptoms: mean difference in Barnes Akathisia Scale** with olanzapine (10–20 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	Mean difference –0.07 95% CI –0.17 to +0.04	⟷	Not significant
[21] Systematic review	269 people Data from 1 RCT	**Extrapyramidal symptoms: mean difference in Extrapyramidal Symptom Rating Scale total score** with olanzapine (5–15 mg/day)	Mean difference –0.40 95% CI –1.53 to +0.73	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with ziprasidone (80–160 mg/day) Absolute results not reported			
[21] Systematic review	922 people 2 RCTs in this analysis	**Extrapyramidal symptoms: mean difference in Simpson-Angus Scale** with olanzapine (10–20 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	Mean difference –0.34 95% CI –0.81 to +0.13	⟷	Not significant
[21] Systematic review	394 people Data from 1 RCT	**Abnormally high prolactin** with olanzapine (10–20 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	RR 1.12 95% CI 0.74 to 1.71	⟷	Not significant
[21] Systematic review	766 people 2 RCTs in this analysis	**Sexual dysfunction** with olanzapine (7.5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 1.33 95% CI 0.99 to 1.79	⟷	Not significant
[21] Systematic review	1079 people 3 RCTs in this analysis	**Mean difference in change from baseline in prolactin (ng/mL)** with olanzapine (7.5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	Mean difference –0.20 ng/mL 95% CI –3.72 ng/mL to +3.33 ng/mL	⟷	Not significant
[21] Systematic review	1502 people 2 RCTs in this analysis	**Mean difference in change from baseline in cholesterol (mg/dL)** with olanzapine (7.5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	Mean difference 15.83 mg/dL 95% CI 5.95 mg/dL to 25.72 mg/dL	○○○	ziprasidone
[21] Systematic review	1402 people 4 RCTs in this analysis	**Mean difference in change from baseline in glucose (mg/dL)** with olanzapine (7.5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	Mean difference 8.25 mg/dL 95% CI 2.77 mg/dL to 13.72 mg/dL	○○○	ziprasidone
[21] Systematic review	1708 people Data from 1 RCT	**Weight gain** with olanzapine (7.5–30 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 4.90 95% CI 3.38 to 7.12	●●○	ziprasidone
[21] Systematic review	1659 people 5 RCTs in this analysis	**Mean difference in change from baseline in weight (kg)** with olanzapine with ziprasidone Absolute results not reported	Mean difference 3.82 kg 95% CI 2.96 kg to 4.69 kg	○○○	ziprasidone

Olanzapine versus first-generation antipsychotics:

We found one systematic review (search date 2006, 28 RCTs, 4966 people). [11]

Symptom severity

Compared with first-generation antipsychotics Olanzapine seems more effective at improving positive and negative symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[11] Systematic review	4189 people 24 RCTs in this analysis	**Hedges' adjusted g for mean difference in positive symptoms** with olanzapine with first-generation antipsychotics Absolute results not reported	Mean difference –0.15 95% CI –0.21 to –0.09	○○○	olanzapine
[11] Systematic review	4187 people 24 RCTs in this analysis	**Hedges' adjusted g for mean difference in negative symptoms** with olanzapine with first-generation antipsychotics Absolute results not reported	Mean difference –0.32 95% CI –0.47 to –0.16	○○○	olanzapine

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	152 people 2 RCTs in this analysis	**Extrapyramidal symptoms** with olanzapine with low-potency first-generation antipsychotics Absolute results not reported	RR 0.53 95% CI 0.32 to 0.89	●○○	olanzapine
[11] Systematic review	84 people Data from 1 RCT	**Sedation** with olanzapine with low-potency first-generation antipsychotics Absolute results not reported	RR 0.68 95% CI 0.41 to 1.12	⟷	Not significant

Further information on studies

[11] The review did not include a comparison of olanzapine versus some first-generation drugs alone, but grouped first-generation antipsychotics together; thus, it is not possible to do individual comparisons. Some studies included patients that had disorders with diagnoses other than schizophrenia (e.g., schizophreniform disorder, schizoaffective disorder, psychotic state).

[21] The overall withdrawal was 49.2% and most studies used the last observation carried forward (LOCF) method to account for this. The authors considered most studies to be at a high risk of bias.

[21] [38] There is some overlap between these reviews in terms of the included studies.

[35] The authors of the systematic review reported a very high rate of withdrawal and a high risk of bias in all placebo-controlled studies. One trial in the second-generation antipsychotic comparison used sonepiprazole

as the comparator. One trial in the first-generation antipsychotic comparison used fluphenazine as the comparator and another used perphenazine. Most studies had a high rate of withdrawal and used LOCF. Two studies (one in the first-generation antipsychotic comparison and one very large one in the second-generation antipsychotic comparison) were not blinded.

[36] The RCT had a high rate of withdrawal, particularly in the placebo group (57% with placebo *v* 32% with olanzapine), with most withdrawal because of lack of efficacy. LOCF was used for dealing with missing data. The study was sponsored by the makers of olanzapine. It claimed to be double-blind, but no further details were given, and the dosing regimen was set at the discretion of the investigator. The RCT included a washout period of 2 to 14 days before the study so that patients were free of all psychotropic medications for at least 2 days before randomisation. This study is considered at high risk of bias.

[37] All studies were considered at high risk of selective reporting and other bias. All studies were funded by the company that makes paliperidone.

Comment: For positive symptoms, there is strong evidence of superiority of olanzapine over first-generation antipsychotics (as a group), evidence of superiority of olanzapine over placebo, quetiapine (medium and long term), and ziprasidone, and no evidence of any difference between olanzapine and haloperidol (although some studies were small), risperidone, amisulpride, or clozapine.

For negative symptoms, there is again strong evidence of superiority of olanzapine over first-generation antipsychotics, while there is some evidence of superiority of olanzapine over haloperidol in the medium term and over risperidone in the long term. There is no evidence of a difference versus placebo, quetiapine, ziprasidone, amisulpride, or clozapine (although some studies were small). There is no evidence of a difference between olanzapine and clozapine in neurocognitive score (small study).

There is consistent evidence that olanzapine is associated with weight gain and adverse metabolic effects to a greater extent than placebo, haloperidol, and most other second-generation antipsychotics. Olanzapine may also be associated with prolactin increase and somnolence. Olanzapine may be associated with more suicide attempts than clozapine, but less sedation and fewer seizures and white blood cell problems; and with fewer extrapyramidal symptoms. Some studies showed that olanzapine was associated with less drowsiness and vomiting than first-generation antipsychotics, while others showed no difference between groups in sedation. Extrapyramidal symptoms, seizures, and cardiac effects are similar for olanzapine and most other second-generation antipsychotics, although olanzapine may cause fewer extrapyramidal symptoms, hyperkinesias, and hypertonia than paliperidone. There is evidence that olanzapine is worse for increased prolactin than quetiapine, aripiprazole, and clozapine, but better than haloperidol, risperidone, and paliperidone, while for parkinsonism olanzapine may be worse than quetiapine and better than haloperidol, risperidone, and ziprasidone.

Clinical guide:
There is evidence of efficacy of olanzapine in treating both positive and negative symptoms compared with first-generation antipsychotics. Olanzapine and the other second-generation antipsychotics have not been shown consistently in RCTs to differ in efficacy, although they do differ with regards to their adverse-effect profiles. Olanzapine seems particularly associated with metabolic adverse effects, which may limit its use.

OPTION PIMOZIDE

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Pimozide is equally effective as standard antipsychotic drugs. However, there is a consensus that pimozide treatment should be restricted because of reports of sudden cardiac death. During pimozide treatment, a baseline and regular ECGs are recommended, and other drugs that may prolong QT interval should be avoided.

Benefits and harms

Pimozide versus standard antipsychotic drugs:

We found one systematic review (search date 1999), which compared pimozide (mean dose 7.5 mg/day, range 1–75 mg/day) versus standard antipsychotic drugs, including chlorpromazine, haloperidol, fluphenazine, and carpipramine. [39]

Symptom severity

Compared with standard antipsychotic drugs Pimozide is as effective at improving global clinical impression scores at 1 to 6 months (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[39] Systematic review	100 people 3 RCTs in this analysis	**Improvement or worsening of global clinical impression , 1 to 3 months** 18/50 (36%) with pimozide 22/50 (44%) with standard antipsychotic drugs	RR 0.82 95% CI 0.52 to 1.29	⟷	Not significant
[39] Systematic review	206 people 6 RCTs in this analysis	**Improvement or worsening of global clinical impression , 4 to 6 months** 57/104 (55%) with pimozide 55/102 (54%) with standard antipsychotic drugs	RR 1.01 95% CI 0.80 to 1.28	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[39] Systematic review	232 people Data from 1 RCT	**Sedation , 1 to 3 months** 53/117 (45%) with pimozide 68/115 (59%) with standard antipsychotic drugs	RR 0.77 95% CI 0.61 to 0.98 NNT 7 95% CI 4 to 61	●○○	pimozide
[39] Systematic review	192 people Data from 1 RCT	**Tremor , 1 to 3 months** 43/97 (44%) with pimozide 27/95 (28%) with standard antipsychotic drugs	RR 1.57 95% CI 1.07 to 2.29 NNH 6 95% CI 3 to 44	●○○	standard antipsychotic drugs
[39] Systematic review	56 people Data from 1 RCT	**ECG changes** 2/28 (7%) with pimozide 3/28 (11%) with standard antipsychotic drugs	RR 0.67 95% CI 0.10 to 3.70 The RCT may have been too small to detect a clinically important difference	⟷	Not significant

Further information on studies

[39] Sudden death has been reported in several people taking pimozide at doses >20 mg daily, but we found no evidence from RCTs that pimozide is more likely to cause sudden death than other antipsychotic drugs. The manufacturer recommends periodic ECG monitoring in all people taking >16 mg daily pimozide, and avoidance of other drugs known to prolong the QT interval on an ECG or cause electrolyte disturbances (other antipsychotic drugs, antihistamines, antidepressants, and diuretics).

Comment: **Clinical guide:**
A limited number of RCTs have shown that pimozide does not differ in efficacy from other antipsychotics. There is consensus that pimozide treatment should be restricted because of reports of sudden cardiac death. During pimozide treatment, baseline and regular ECGs are recommended, and other drugs that may prolong QT interval should be avoided.

OPTION QUETIAPINE

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Quetiapine shows a similar level of effectiveness to other antipsychotics for treatment of negative symptoms, although it seems less effective than first-generation antipsychotics and some other second-generation antipsychotics for positive symptoms. Quetiapine is associated with greater weight gain and fewer prolactin problems and extrapyramidal symptoms than most other antipsychotics.

Benefits and harms

Quetiapine versus placebo:

We found two RCTs. [40] [41]

Symptom severity

Compared with placebo Quetiapine seems no more effective at improving positive and negative symptoms at 2 weeks. However, at 6 weeks, 400 mg immediate-release quetiapine and 600 mg and 800 mg extended-release quetiapine seem more effective at improving both positive and negative symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[41] RCT **3-armed trial**	239 people The remaining arm assessed paliperidone	**Mean difference in change from baseline in Positive and Negative Syndrome Scale (PANSS) positive score , 14 days** with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg/day) with placebo Absolute results not reported	Mean difference –0.7 P >0.05	⟷	Not significant
[41] RCT **3-armed trial**	239 people The remaining arm assessed paliperidone	**Mean difference in change from baseline in PANSS negative score , 14 days** with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg/day) with placebo Absolute results not reported	Mean difference –1.0 P >0.05	⟷	Not significant
[40] RCT **5-armed trial**	573 people The remaining arms assessed quetiapine extended-release (XR) 600 mg and 800 mg, and quetiapine immediate-release (IR) 400 mg	**Mean difference in change from baseline in PANSS positive score , 6 weeks** with quetiapine XR 400 mg with placebo Absolute results not reported	Mean difference –1.8 95% CI –3.5 to –0.0	⟷	Not significant
[40] RCT **5-armed trial**	573 people The remaining arms assessed quetiapine XR 400 mg and	**Mean difference in change from baseline in PANSS positive score , 6 weeks** with quetiapine XR 600 mg with placebo	Mean difference –4.2 95% CI –5.9 to –2.4	○○○	quetiapine XR 600 mg

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	800 mg, and quetiapine IR 400 mg	Absolute results not reported			
[40] RCT **5-armed trial**	573 people The remaining arms assessed quetiapine XR 400 mg and 600 mg, and quetiapine IR 400 mg	**Mean difference in change from baseline in PANSS positive score , 6 weeks** with quetiapine XR 800 mg with placebo Absolute results not reported	Mean difference –3.6 95% CI –5.3 to –1.9	○○○	quetiapine XR 800 mg
[40] RCT **5-armed trial**	573 people The remaining arms assessed quetiapine XR 400 mg, 600 mg, and 800 mg	**Mean difference in change from baseline in PANSS positive score , 6 weeks** with quetiapine IR 400 mg with placebo Absolute results not reported	Mean difference –3.0 95% CI –4.7 to –1.3	○○○	quetiapine IR 400 mg
[40] RCT **5-armed trial**	573 people The remaining arms assessed quetiapine XR 600 mg and 800 mg, and quetiapine IR 400 mg	**Mean difference in change from baseline in PANSS negative score , 6 weeks** with quetiapine XR 400 mg with placebo Absolute results not reported	Mean difference –1.3 95% CI –2.8 to +0.2	⟷	Not significant
[40] RCT **5-armed trial**	573 people The remaining arms assessed quetiapine XR 400 mg and 800 mg, and quetiapine IR 400 mg	**Mean difference in change from baseline in PANSS negative score , 6 weeks** with quetiapine XR 600 mg with placebo Absolute results not reported	Mean difference –2.1 95% CI –3.6 to –0.6	○○○	quetiapine XR 600 mg
[40] RCT **5-armed trial**	573 people The remaining arms assessed quetiapine XR 400 mg and 600 mg, and quetiapine IR 400 mg	**Mean difference in change from baseline in PANSS negative score , 6 weeks** with quetiapine XR 800 mg with placebo Absolute results not reported	Mean difference –3.1 95% CI –4.6 to –1.6	○○○	quetiapine XR 800 mg
[40] RCT **5-armed trial**	573 people The remaining arms assessed quetiapine XR 400 mg, 600 mg, and 800 mg	**Mean difference in change from baseline in PANSS negative score , 6 weeks** with quetiapine IR 400 mg with placebo Absolute results not reported	Mean difference –1.4 95% CI –2.8 to +0.1	○○○	quetiapine IR 400 mg

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[41] RCT **3-armed trial**	239 people The remaining arm assessed paliperidone	**Change from baseline in least squares mean of Simpson-Angus Scale** –0.5 with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg/day)	P >0.05	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		–0.1 with placebo			
[41] RCT **3-armed trial**	239 people The remaining arm assessed paliperidone	**Use of antiparkinsonism medication** 37% with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg) 22% with placebo Absolute numbers not reported	P >0.05	⟷	Not significant
[41] RCT **3-armed trial**	239 people The remaining arm assessed paliperidone	**Change from baseline in least squares mean of prolactin value, men** –5.8 with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg) –6.5 with placebo	P >0.05	⟷	Not significant
[41] RCT **3-armed trial**	239 people The remaining arm assessed paliperidone	**Change from baseline in least squares mean of prolactin value, women** –16.1 with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg) –24.5 with placebo	P >0.05	⟷	Not significant
[41] RCT **3-armed trial**	239 people The remaining arm assessed paliperidone	**Change from baseline in least squares mean of weight (kg)** 0.8 with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg) 0.2 with placebo	P <0.05	○○○	placebo

No data from the following reference on this outcome. [40]

Quetiapine versus clozapine:

See treatment option on clozapine, p 20 .

Quetiapine versus haloperidol:

See treatment option on haloperidol, p 37 .

Quetiapine versus olanzapine:

See treatment option on olanzapine, p 55 .

Quetiapine versus paliperidone:

We found one RCT (314 people) comparing quetiapine versus paliperidone. [41]

Symptom severity

Compared with paliperidone Quetiapine seems less effective at improving positive and negative symptoms in people with schizophrenia at 14 days (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[41] RCT **3-armed trial**	314 people The remaining arm assessed placebo	**Mean difference in change from baseline in Positive and Negative Symptom Scale (PANSS) positive score , 14 days** with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg) with paliperidone (mean daily dose during monotherapy phase of trial 10.4 mg) Absolute results not reported	Mean difference –1.8 P <0.05	○○○	paliperidone
[41] RCT **3-armed trial**	314 people The remaining arm assessed placebo	**Mean difference in change from baseline in PANSS negative score , 14 days** with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg) with paliperidone (mean daily dose during monotherapy phase of trial 10.4 mg) Absolute results not reported	Mean difference –1.4 P <0.05	○○○	paliperidone

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[41] RCT **3-armed trial**	314 people The remaining arm assessed placebo	**Change from baseline in least squares mean of Simpson-Angus Scale** –0.5 with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg) 0.4 with paliperidone (mean daily dose during monotherapy phase of trial 10.4 mg)	P <0.05	○○○	quetiapine
[41] RCT **3-armed trial**	314 people The remaining arm assessed placebo	**Use of antiparkinsonism medication** 37% with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg) 58% with paliperidone (mean daily dose during monotherapy phase of trial 10.4 mg) Absolute numbers not reported	P <0.05	○○○	quetiapine
[41] RCT **3-armed trial**	314 people The remaining arm assessed placebo	**Change from baseline in least squares mean of prolactin value, men** –5.8 with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg)	P <0.05	○○○	quetiapine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		19.2 with paliperidone (mean daily dose during monotherapy phase of trial 10.4 mg)			
[41] RCT **3-armed trial**	314 people The remaining arm assessed placebo	**Change from baseline in least squares mean of prolactin value, women** –16.1 with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg) +74.4 with paliperidone (mean daily dose during monotherapy phase of trial 10.4 mg)	P <0.05	○○○	quetiapine
[41] RCT **3-armed trial**	314 people The remaining arm assessed placebo	**Change from baseline in least squares mean of weight (kg)** 0.8 with quetiapine (mean daily dose during monotherapy phase of trial 690.9 mg) 0.4 with paliperidone (mean daily dose during monotherapy phase of trial 10.4 mg)	P <0.05	○○○	paliperidone

Quetiapine versus risperidone:

We found one systematic review (search date 2007, 11 RCTs, 3770 people). [20]

Symptom severity

Compared with risperidone Quetiapine seems less effective at improving Positive and Negative Symptom Scale (PANSS) positive symptom subscore and Brief Psychiatric Rating Scale (BPRS) positive and negative symptom subscores. However, quetiapine seems equally effective at improving PANSS negative symptom subscores (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[20] Systematic review	1264 people 7 RCTs in this analysis	**Mean difference in Positive and Negative Syndrome Scale (PANSS) positive subscore , endpoint** with quetiapine (dose range 50–800 mg/day) with risperidone (dose range 0.5–12 mg/day) Absolute results not reported	Mean difference 1.82 95% CI 1.16 to 2.48	○○○	risperidone
[20] Systematic review	25 people Data from 1 RCT	**Mean difference in Brief Psychiatric Rating Scale (BPRS) positive subscore , short term** with quetiapine (dose range 300–500 mg/day) with risperidone (dose range 3–5 mg/day) Absolute results not reported	Mean difference 1.10 95% CI 0.18 to 2.02	○○○	risperidone
[20] Systematic review	1183 people 7 RCTs in this analysis	**Mean difference in PANSS negative subscore , endpoint** with quetiapine (dose range 50–800 mg/day)	Mean difference –0.35 95% CI –1.95 to +1.26	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with risperidone (dose range 0.5–12 mg/day) Absolute results not reported			
[20] Systematic review	25 people Data from 1 RCT	**Mean difference in BPRS negative subscore , short term** with quetiapine (dose range 300–500 mg/day) with risperidone (dose range 3–5 mg/day) Absolute results not reported	Mean difference 0.57 95% CI 0.17 to 0.97	○○○	risperidone

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[20] Systematic review	1351 people 2 RCTs in this analysis	**QTc prolongation** with quetiapine (dose range 200–800 mg/day) with risperidone (dose range 1.5–8 mg/day) Absolute results not reported	RR 0.87 95% CI 0.29 to 2.55	⟷	Not significant
[20] Systematic review	940 people 3 RCTs in this analysis	**QTc abnormalities: mean difference in change from baseline (ms)** with quetiapine (dose range 200–800 mg/day) with risperidone (dose range 1.5–8 mg/day) Absolute results not reported	Mean difference 2.21 95% CI –5.05 to +9.48	⟷	Not significant
[20] Systematic review	2226 people 8 RCTs in this analysis	**Sedation** with quetiapine (dose range 50–800 mg/day) with risperidone (dose range 0.5–8 mg/day) Absolute results not reported	RR 1.21 95% CI 1.06 to 1.38	●○○	risperidone
[20] Systematic review	2170 people 6 RCTs in this analysis	**Akathisia** with quetiapine (dose range 50–800 mg/day) with risperidone (dose range 0.5–8 mg/day) Absolute results not reported	RR 0.62 95% CI 0.34 to 1.13	⟷	Not significant
[20] Systematic review	2170 people Data from 1 RCT	**Akinesia** with quetiapine (dose range 100–800 mg/day) with risperidone (dose range 0.5–4 mg/day) Absolute results not reported	RR 0.91 95% CI 0.61 to 1.37	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20] Systematic review	673 people Data from 1 RCT	**Dystonia** with quetiapine (dose range 200–800 mg/day) with risperidone (dose range 2–8 mg/day) Absolute results not reported	RR 0.06 95% CI 0.01 to 0.41	●●●	quetiapine
[20] Systematic review	872 people 2 RCTs in this analysis	**Extrapyramidal symptoms** with quetiapine (dose range 200–800 mg/day) with risperidone (dose range 1.5–8 mg/day) Absolute results not reported	RR 0.59 95% CI 0.43 to 0.81	●○○	quetiapine
[20] Systematic review	717 people 2 RCTs in this analysis	**Parkinsonism** with quetiapine (dose range 50–800 mg/day) with risperidone (dose range 2–8 mg/day) Absolute results not reported	RR 0.06 95% CI 0.00 to 0.96	●●●	quetiapine
[20] Systematic review	309 people Data from 1 RCT	**Rigor** with quetiapine (dose range 50–800 mg/day) with risperidone (dose range 1–6 mg/day) Absolute results not reported	RR 0.45 95% CI 0.16 to 1.25	⟷	Not significant
[20] Systematic review	1715 people 6 RCTs in this analysis	**Use of antiparkinsonism medication** with quetiapine with risperidone Absolute results not reported	RR 0.50 95% CI 0.30 to 0.86	●○○	quetiapine
[20] Systematic review	359 people 4 RCTs in this analysis	**Prolactin-associated adverse effects: amenorrhoea** with quetiapine (dose range 50–800 mg/day) with risperidone (dose range 0.5–6 mg/day) Absolute results not reported	RR 0.47 95% CI 0.28 to 0.79	●●○	quetiapine
[20] Systematic review	163 people Data from 1 RCT	**Prolactin-associated adverse effects: dysmenorrhoea** with quetiapine (dose range 200–800 mg/day) with risperidone (dose range 2–8 mg/day) Absolute results not reported	RR 0.45 95% CI 0.08 to 2.38	⟷	Not significant
[20] Systematic review	1088 people 5 RCTs in this analysis	**Prolactin-associated adverse effects: galactorrhoea** with quetiapine (dose range 100–800 mg/day) with risperidone (dose range 0.5–8 mg/day) Absolute results not reported	RR 0.37 95% CI 0.16 to 0.85	●●○	quetiapine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20] Systematic review	267 people Data from 1 RCT	**Prolactin-associated adverse effects: gynaecomastia** with quetiapine (dose range 100–800 mg/day) with risperidone (dose range 0.5–4 mg/day) Absolute results not reported	RR 0.23 95% CI 0.07 to 0.79	●●○	quetiapine
[20] Systematic review	2157 people 6 RCTs in this analysis	**Prolactin-associated adverse effects: sexual dysfunction** with quetiapine (dose range 50–800 mg/day) with risperidone (dose range 0.5–8 mg/day) Absolute results not reported	RR 0.70 95% CI 0.48 to 1.01	↔	Not significant
[20] Systematic review	1731 people 6 RCTs in this analysis	**Mean difference in change from baseline in prolactin (mg/dL)** with quetiapine (dose range 50–800 mg/day) with risperidone (dose range 0.5–8 mg/day) Absolute results not reported	Mean difference –35.28 mg/dL 95% CI –44.36 mg/dL to –26.19 mg/dL	○○○	quetiapine
[20] Systematic review	940 people 2 RCTs in this analysis	**Significant cholesterol increase** with quetiapine (dose range 100–800 mg/day) with risperidone (dose range 0.5–8 mg/day) Absolute results not reported	RR 1.27 95% CI 0.72 to 2.24	↔	Not significant
[20] Systematic review	1443 people 5 RCTs in this analysis	**Mean difference in change from baseline in cholesterol (mg/dL)** with quetiapine (dose range 100–800 mg/day) with risperidone (dose range 0.5–8 mg/day) Absolute results not reported	Mean difference 8.61 mg/dL 95% CI 4.66 mg/dL to 12.56 mg/dL	○○○	risperidone
[20] Systematic review	1792 people 7 RCTs in this analysis	**Weight gain of 7% or more of body weight** with quetiapine (dose range 50–800 mg/day) with risperidone (dose range 0.5–8 mg/day) Absolute results not reported	RR 0.97 95% CI 0.82 to 1.14	↔	Not significant
[20] Systematic review	1446 people 7 RCTs in this analysis	**Mean difference in change from baseline in weight (kg)** with quetiapine with risperidone Absolute results not reported	Mean difference +0.71 kg 95% CI –1.04 kg to +2.47 kg	↔	Not significant

Quetiapine versus ziprasidone:

We found one systematic review (search date 2007, 2 RCTs, 722 people). [20]

Symptom severity

Compared with ziprasidone Quetiapine seems equally effective at improving positive and negative symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[20] Systematic review	710 people 2 RCTs in this analysis	**Mean difference in endpoint score (Positive and Negative Syndrome Scale [PANSS] total score)** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	Mean difference –0.11 95% CI –6.36 to +6.14	⟷	Not significant
[20] Systematic review	198 people Data from 1 RCT	**Mean difference in endpoint score (PANSS positive symptom subscore) , medium term** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	Mean difference 0.00 95% CI –2.18 to +2.18	⟷	Not significant
[20] Systematic review	198 people Data from 1 RCT	**Mean difference in endpoint score (PANSS negative symptom subscore) , medium term** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	Mean difference +1.60 95% CI –0.34 to +3.54	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[20] Systematic review	522 people Data from 1 RCT	**QTc prolongation** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	RR 1.65 95% CI 0.34 to 8.08	⟷	Not significant
[20] Systematic review	549 people 2 RCTs in this analysis	**QTc abnormalities, mean difference in change from baseline (ms)** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	Mean difference +3.41 ms 95% CI –1.37 ms to +8.18 ms	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20] Systematic review	754 people 2 RCTs in this analysis	**Sedation** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	RR 1.36 95% CI 1.04 to 1.77	●○○	ziprasidone
[20] Systematic review	754 people 2 RCTs in this analysis	**Akathisia** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	RR 0.78 95% CI 0.42 to 1.45	↔	Not significant
[20] Systematic review	232 people Data from 1 RCT	**Extrapyramidal symptoms** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	RR 2.02 95% CI 0.66 to 6.17	↔	Not significant
[20] Systematic review	522 people Data from 1 RCT	**Use of antiparkinsonism medication** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	RR 0.43 95% CI 0.20 to 0.93	●●○	quetiapine
[20] Systematic review	138 people Data from 1 RCT	**Prolactin-associated effects: amenorrhoea** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	RR 0.43 95% CI 0.15 to 1.24	↔	Not significant
[20] Systematic review	572 people 2 RCTs in this analysis	**Prolactin-associated effects: galactorrhoea** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	RR 0.55 95% CI 0.18 to 1.68	↔	Not significant
[20] Systematic review	138 people Data from 1 RCT	**Prolactin associated effects: sexual dysfunction** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	RR 0.96 95% CI 0.64 to 1.42	↔	Not significant
[20] Systematic review	754 people 2 RCTs in this analysis	**Mean difference in change from baseline in prolactin (ng/mL)** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day)	Mean difference –4.77 ng/mL 95% CI –8.16 ng/mL to –1.37 ng/mL	○○○	quetiapine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
[20] Systematic review	754 people 2 RCTs in this analysis	**Mean difference in change from baseline in cholesterol (mg/dL)** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	Mean difference 16.01 mg/dL 95% CI 8.57 mg/dL to 23.46 mg/dL	○○○	ziprasidone
[20] Systematic review	754 people 2 RCTs in this analysis	**Mean difference in change from baseline in glucose (mg/dL)** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	Mean difference +3.10 mg/dL 95% CI –3.99 mg/dL to +10.19 mg/dL	⟷	Not significant
[20] Systematic review	754 people 2 RCTs in this analysis	**Weight gain of 7% or more of total body weight** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	RR 2.22 95% CI 1.35 to 3.63	●●○	ziprasidone
[20] Systematic review	466 people Data from 1 RCT	**Mean difference in change from baseline in weight (kg)** with quetiapine (dose range 200–800 mg/day) with ziprasidone (dose range 40–160 mg/day) Absolute results not reported	Mean difference +1.20 kg 95% CI –0.05 kg to +2.45 kg	⟷	Not significant

Quetiapine versus first-generation antipsychotics:

We found one systematic review (search date 2006, 11 RCTs, 2412 people). [11]

Symptom severity

Compared with first-generation antipsychotics Quetiapine seems less effective at improving positive symptoms, but we don't know whether quetiapine is more effective at improving negative symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[11] Systematic review	1742 people 9 RCTs in this analysis	**Hedges' adjusted g effect size for positive symptoms** with quetiapine with first-generation antipsychotic drugs Absolute results not reported	Effect size 0.14 95% CI 0.03 to 0.26	○○○	first-generation antipsychotic drugs

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[11] Systematic review	1926 people 10 RCTs in this analysis	**Hedges' adjusted g effect size for negative symptoms** with quetiapine with first-generation antipsychotic drugs Absolute results not reported	Effect size 0 95% CI –0.09 to +0.09	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	422 people 2 RCTs in this analysis	**Extrapyramidal symptoms** with quetiapine with low-potency first-generation antipsychotic drugs Absolute results not reported	RR 0.66 95% CI 0.19 to 2.23	⟷	Not significant
[11] Systematic review	201 people Data from 1 RCT	**Mean difference in weight gain (kg)** with quetiapine with low-potency first-generation antipsychotics Absolute results not reported	Mean difference +0.5 kg 95% CI –1.00 kg to +2.00 kg	⟷	Not significant
[11] Systematic review	659 people 3 RCTs in this analysis	**Sedation** with quetiapine with low-potency first-generation antipsychotic drugs Absolute results not reported	RR 0.49 95% CI 0.23 to 1.03	⟷	Not significant

Further information on studies

[11] Some first-generation comparators were not included in the current review, but first-generation antipsychotics were grouped together; thus, it is not possible to do individual comparisons. Some studies included patients that had disorders with diagnoses other than schizophrenia (e.g., schizophreniform disorder, schizoaffective disorder, psychotic state).

[20] The comparison between quetiapine and risperidone for extrapyramidal symptoms contained one large study with no reports of such symptoms in either group and one very small study with no reports of extrapyramidal symptoms in the quetiapine group but 8 reports in the risperidone group, leading to a significant difference between the groups. This difference, however, should not be taken as conclusive. In general, there was a high rate of withdrawal overall and most studies in the review were considered to be at high risk of bias, in terms of treatment of incomplete data, selective reporting, and possible other biases.

[41] The analysis used data to day 14 only, since beyond that point patients were allowed to be prescribed additional treatment. Loss to follow-up was appropriately accounted for in the study by corroborating the last observation carried forward (LOCF) analysis with results from mixed models, the latter being presented here.

[40] The RCT used LOCF to account for loss to follow-up.

Comment: For positive symptoms, in one study immediate-release (IR) quetiapine (fixed dose) and extended-release (XR) quetiapine at high doses showed superiority over placebo, while in a second short-term study there was no evidence of a difference between groups. There is evidence that quetiapine is inferior to olanzapine (medium and long term), paliperidone, risperidone, and first-generation antipsychotics, and no evidence of a difference between quetiapine and clozapine or ziprasidone.

For negative symptoms, there is evidence of superiority of quetiapine XR at higher doses over placebo but no evidence of a difference in the short-term study or for quetiapine IR. There is no clear evidence regarding the difference between clozapine and quetiapine, with evidence of superiority of quetiapine on Positive and Negative Syndrome Scale (PANSS) scores but no difference on Scale for the Assessment of Negative Symptoms (SANS). Paliperidone showed superiority over quetiapine, while there was no clear evidence of any difference for olanzapine, risperidone, ziprasidone, or first-generation antipsychotics.

Quetiapine may be associated with a greater extent of weight gain than placebo, haloperidol, and other second-generation antipsychotics, apart from olanzapine and risperidone. Quetiapine may be associated with a lesser extent of parkinsonism than most other second-generation antipsychotics and a reduced level of extrapyramidal symptoms than risperidone, haloperidol, and paliperidone. There is no evidence of an increase in extrapyramidal symptoms, parkinsonism, and prolactin over placebo, while quetiapine may be associated with fewer prolactin-associated effects compared with risperidone, ziprasidone, and olanzapine. Quetiapine may be better than clozapine and haloperidol for sedation and worse than risperidone and ziprasidone for both sedation and change in cholesterol. Quetiapine may be associated with fewer cardiac effects compared with clozapine, but there was no evidence of a difference between quetiapine and olanzapine, risperidone, or ziprasidone.

Clinical guide:
Perhaps surprisingly, quetiapine XR may be more effective than IR in treating negative symptoms, although quetiapine is less effective than first-generation antipsychotics for positive symptoms. When choosing between quetiapine and other second-generation antipsychotics, adverse-effect profiles should be taken into consideration. For many patients, quetiapine may have a preferable adverse-effect profile.

OPTION RISPERIDONE

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Risperidone shows a similar efficacy profile to other second-generation antipsychotics and, while also similar to haloperidol, is superior to first-generation antipsychotics as a whole. Risperidone is associated with more hyperprolactinaemia, extrapyramidal symptoms, and weight gain than most other second-generation antipsychotics and may be associated with fewer extrapyramidal symptoms than haloperidol.

Benefits and harms

Risperidone versus placebo:

We found two systematic reviews (search date 2008, 10 RCTs, 1363 people; [42] search date 2007, 1 RCT, 160 people [43]).

Symptom severity

Compared with placebo Risperidone seems more effective at improving positive and negative symptoms at 6 weeks in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[42] Systematic review	266 people 3 RCTs in this analysis	**Weighted mean difference in Positive and Negative Syndrome Scale (PANSS) positive endpoint score** with risperidone (dose range 2–16 mg/day) with placebo Absolute results not reported	Mean difference +1.67 95% CI –2.93 to +6.28	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[42] Systematic review	266 people 3 RCTs in this analysis	**Weighted mean difference in PANSS negative endpoint score** with risperidone (dose range 2–16 mg/day) with placebo Absolute results not reported	Mean difference –0.90 95% CI –3.06 to +1.27	⟷	Not significant
[42] Systematic review	233 people Data from 1 RCT	**Weighted mean change from baseline in PANSS positive score** with risperidone (mean dose 4.7 mg/day [SD 0.9 mg/day]) with placebo Absolute results not reported	Mean difference 2.8 95% CI 2.62 to 2.98	○○○	risperidone
[43] Systematic review	233 people Data from 1 RCT	**Weighted mean change from baseline in PANSS negative score** with risperidone (mean dose 4.7 mg/day [SD 0.9 mg/day]) with placebo Absolute results not reported	Mean difference 0.5 95% CI 0.35 to 0.65	○○○	risperidone
[43] Systematic review	160 adolescents Data from 1 RCT 3-armed trial; the other arm assessed risperidone (4–6 mg/day)	**Mean change from baseline in PANSS positive symptom score , 6 weeks** with risperidone (1–3 mg/day) with placebo Absolute results not reported	Mean difference –3.6 95% CI –5.6 to –1.5	○○○	risperidone
[43] Systematic review	160 adolescents Data from 1 RCT 3-armed trial; the other arm assessed risperidone (1–3 mg/day)	**Mean change from baseline in PANSS positive symptom score , 6 weeks** with risperidone (4–6 mg/day) with placebo Absolute results not reported	Mean difference –4.1 95% CI –6.2 to –2.0	○○○	risperidone
[43] Systematic review	160 adolescents Data from 1 RCT 3-armed trial; the other arm assessed risperidone (4–6 mg/day)	**Mean change from baseline in PANSS negative symptom score , 6 weeks** with risperidone (1–3 mg/day) with placebo Absolute results not reported	Mean difference –3.2 95% CI –4.8 to –1.5	○○○	risperidone
[43] Systematic review	160 adolescents Data from 1 RCT 3-armed trial; the other arm assessed risperidone (1–3 mg/day)	**Mean change from baseline in PANSS negative symptom score , 6 weeks** with risperidone (4–6 mg/day) with placebo Absolute results not reported	Mean difference –2.8 95% CI –4.5 to –1.1	○○○	risperidone

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[42] Systematic review	482 people 4 RCTs in this analysis	**Any adverse effect** with risperidone (dose range 2–10 mg/day) with placebo Absolute results not reported	RR 1.04 95% CI 0.94 to 1.15	⟷	Not significant
[42] Systematic review	198 people Data from 1 RCT	**QTc prolongation (corrected QT interval >450 ms or >10% increase from baseline)** with risperidone (6 mg/day) with placebo Absolute results not reported	RR 7.58 95% CI 0.40 to 144.9	⟷	Not significant
[42] Systematic review	655 people 5 RCTs in this analysis	**Agitation** with risperidone (dose range 2–16 mg/day) with placebo Absolute results not reported	RR 0.96 95% CI 0.73 to 1.26	⟷	Not significant
[42] Systematic review	290 people 2 RCTs in this analysis	**Sedation** with risperidone with placebo Absolute results not reported	RR 1.31 95% CI 0.83 to 2.04	⟷	Not significant
[42] Systematic review	911 people 6 RCTs in this analysis	**Somnolence** with risperidone with placebo Absolute results not reported	RR 1.39 95% CI 0.97 to 1.98	⟷	Not significant
[42] Systematic review	323 people 2 RCTs in this analysis	**Serum prolactin increase >23 ng/mL** with risperidone (6 mg/day) with placebo Absolute results not reported	RR 12.54 95% CI 5.11 to 30.79	●●●	placebo
[42] Systematic review	202 people Data from 1 RCT	**Dry mouth** with risperidone (6 mg/day) with placebo Absolute results not reported	RR 2.43 95% CI 0.65 to 9.12	⟷	Not significant
[42] Systematic review	376 people 3 RCTs in this analysis	**Any significant extrapyramidal symptom** with risperidone (dose range 2–16 mg/day) with placebo Absolute results not reported	RR 1.40 95% CI 0.93 to 2.10	⟷	Not significant
[42] Systematic review	42 people Data from 1 RCT	**No improvement on Abnormal Involuntary Movement Scale (AIMS) score** with risperidone (6 mg/day) with placebo Absolute results not reported	RR 0.30 95% CI 0.15 to 0.61	●●○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[42] Systematic review	223 people Data from 1 RCT	**No improvement on Barnes Akathisia Scale score** with risperidone (mean dose 4.7 mg/day [SD 0.9 mg/day]) with placebo Absolute results not reported	RR 0.06 95% CI 0.03 to 0.12	●●●	placebo
[42] Systematic review	44 people Data from 1 RCT	**Needing medication for extrapyramidal symptoms** with risperidone (dose range 2–16 mg/day) with placebo Absolute results not reported	RR 1.17 95% CI 0.47 to 2.92	↔	Not significant
[42] Systematic review	428 people 2 RCTs in this analysis	**Akathisia** with risperidone with placebo Absolute results not reported	RR 2.20 95% CI 0.88 to 5.49	↔	Not significant
[42] Systematic review	202 people Data from 1 RCT	**Dystonia** with risperidone (6 mg/day) with placebo Absolute results not reported	RR 11.44 95% CI 0.64 to 204.21	↔	Not significant
[42] Systematic review	323 people 2 RCTs in this analysis	**Hypertonia** with risperidone (6 mg/day) with placebo Absolute results not reported	RR 2.01 95% CI 0.87 to 4.64	↔	Not significant
[42] Systematic review	428 people 2 RCTs in this analysis	**Tremor** with risperidone with placebo Absolute results not reported	RR 1.34 95% CI 0.14 to 12.69	↔	Not significant
[42] Systematic review	42 people Data from 1 RCT	**Mean difference in average endpoint score for AIMS** with risperidone (6 mg/day) with placebo Absolute results not reported	Mean difference –5.4 95% CI –8.48 to –2.32	○○○	placebo
[42] Systematic review	223 people Data from 1 RCT	**Mean difference in change from baseline in AIMS** with risperidone (4.7 mg/day [SD 0.9 mg/day]) with placebo Absolute results not reported	Mean difference 0.4 95% CI 0.32 to 0.48	○○○	placebo
[42] Systematic review	223 people Data from 1 RCT	**Mean difference in change from baseline in Simpson-Angus Scale** with risperidone (4.7 mg/day [SD 0.9 mg/day]) with placebo Absolute results not reported	Mean difference 0.5 95% CI 0.42 to 0.58	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[42] Systematic review	61 people Data from 1 RCT	**Mean difference in white blood cell count** with risperidone (3 mg/day) with placebo Absolute results not reported	Mean difference +0.66 95% CI –0.20 to +1.52	⟷	Not significant
[42] Systematic review	56 people Data from 1 RCT	**Mean difference in cholesterol (mg/dL)** with risperidone (3 mg/day) with placebo Absolute results not reported	Mean difference –6.60 mg/dL 95% CI –29.05 mg/dL to +15.85 mg/dL	⟷	Not significant
[42] Systematic review	64 people Data from 1 RCT	**Weight gain** with risperidone (3 mg/day) with placebo Absolute results not reported	RR 1.00 95% CI 0.40 to 2.52	⟷	Not significant
[42] Systematic review	303 people 2 RCTs in this analysis	**>7% increase in weight from baseline** with risperidone (6 mg/day) with placebo Absolute results not reported	RR 5.14 95% CI 1.79 to 14.73	●●●	placebo
[42] Systematic review	64 people Data from 1 RCT	**Mean weight gain (kg)** with risperidone (3 mg/day) with placebo Absolute results not reported	Mean difference +3.10 kg 95% CI –6.57 kg to +12.77 kg	⟷	Not significant
[43] Systematic review	160 people Data from 1 RCT 3-armed trial	**Somnolence** 24% with risperidone (1–3 mg/day) 12% with risperidone (4–6 mg/day) 4% with placebo Absolute numbers not reported	Significance assessment not performed		
[43] Systematic review	160 people Data from 1 RCT 3-armed trial	**Extrapyramidal symptoms** 9% with risperidone (1–3 mg/day) 16% with risperidone (4–6 mg/day) 4% with placebo Absolute numbers not reported	Significance assessment not performed		

Risperidone versus amisulpride:

See treatment option on amisulpride, p 4 .

Risperidone versus chlorpromazine:

See treatment option on chlorpromazine, p 14 .

Risperidone versus clozapine:
See treatment option on clozapine, p 20

Risperidone versus haloperidol:
See treatment option on haloperidol, p 37 .

Risperidone versus olanzapine:
See treatment option on olanzapine, p 55 .

Risperidone versus quetiapine:
See treatment option on quetiapine, p 80 .

Risperidone versus sertindole:
We found one systematic review (search date 2007, 2 RCTs, 508 people). [44]

Symptom severity

Compared with sertindole We don't know whether risperidone is more effective at improving positive or negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[44] Systematic review	172 people Data from 1 RCT	**Mean difference in Positive and Negative Syndrome Scale (PANSS) positive score , short term** with risperidone (dose 4–10 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	Mean difference –0.80 95% CI –2.95 to +1.35	⟷	Not significant
[44] Systematic review	172 people Data from 1 RCT	**Mean difference in PANSS negative score , short term** with risperidone (dose 4–10 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	Mean difference –1.30 95% CI –3.13 to +0.53	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[44] Systematic review	508 people 2 RCTs in this analysis	**At least 1 adverse effect** with risperidone (dose 4–12 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	RR 1.03 95% CI 0.95 to 1.11	⟷	Not significant
[44] Systematic review	187 people Data from 1 RCT	**Suicide** with risperidone (dose 4–10 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	RR 0.30 95% CI 0.01 to 7.34	⟷	Not significant
[44] Systematic review	508 people 2 RCTs in this analysis	**QTc prolongation** with risperidone (dose 4–12 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	RR 4.86 95% CI 1.94 to 12.18	●●○	risperidone
[44] Systematic review	495 people 2 RCTs in this analysis	**Mean difference in QTc change from baseline (ms)** with risperidone (dose 4–12 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	Mean difference 18.60 ms 95% CI 14.83 ms to 22.37 ms	○○○	risperidone
[44] Systematic review	508 people 2 RCTs in this analysis	**Sedation** with risperidone (dose 4–12 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	RR 0.87 95% CI 0.52 to 1.44	⟷	Not significant
[44] Systematic review	321 people Data from 1 RCT	**Akathisia** with risperidone (dose 6–12 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	RR 0.45 95% CI 0.20 to 0.98	●●○	sertindole
[44] Systematic review	187 people Data from 1 RCT	**Extrapyramidal symptoms** with risperidone (dose 4–10 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	RR 0.65 95% CI 0.38 to 1.11	⟷	Not significant
[44] Systematic review	321 people Data from 1 RCT	**Parkinsonism** with risperidone (dose 6–12 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	RR 0.24 95% CI 0.09 to 0.69	●●○	sertindole

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[44] Systematic review	187 people Data from 1 RCT	**Tremor** with risperidone (dose 4–10 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	RR 1.51 95% CI 0.37 to 6.15	⟷	Not significant
[44] Systematic review	477 people 2 RCTs in this analysis	**Mean difference in Abnormal Involuntary Movement Scale** with risperidone (dose 4–12 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	Mean difference –0.31 95% CI –0.86 to +0.25	⟷	Not significant
[44] Systematic review	500 people 2 RCTs in this analysis	**Mean difference in Barnes Akathisia Scale** with risperidone (dose 4–12 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	Mean difference –0.22 95% CI –0.41 to –0.03	○○○	sertindole
[44] Systematic review	500 people 2 RCTs in this analysis	**Mean difference in Simpson-Angus Scale** with risperidone (dose 4–12 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	Mean difference –0.46 95% CI –1.24 to +0.32	⟷	Not significant
[44] Systematic review	176 people Data from 1 RCT	**Mean difference in cholesterol (mg/dL)** with risperidone (dose 6–12 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	Mean difference –4.90 mg/dL 95% CI –13.53 mg/dL to +3.73 mg/dL	⟷	Not significant
[44] Systematic review	187 people Data from 1 RCT	**Significant weight gain** with risperidone (dose 4–10 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	RR 1.30 95% CI 0.70 to 2.41	⟷	Not significant
[44] Systematic review	328 people 2 RCTs in this analysis	**Mean difference in change from baseline in weight (kg)** with risperidone (dose 4–12 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	Mean difference 0.99 kg 95% CI 0.12 kg to 1.86 kg	○○○	risperidone
[44] Systematic review	187 people Data from 1 RCT	**Sexual dysfunction** with risperidone (dose 4–10 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	RR 4.54 95% CI 1.02 to 20.16	●●○	risperidone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[44] Systematic review	250 people Data from 1 RCT	**Abnormal ejaculation** with risperidone (dose 6–12 mg/day) with sertindole (dose 12–24 mg/day) Absolute results not reported	RR 2.44 95% CI 0.97 to 6.14	⟷	Not significant

Risperidone versus aripiprazole:

We found one systematic review (search date 2007, 3 RCTs, 1063 people). [45]

Symptom severity

Compared with aripiprazole Risperidone seems as effective at improving positive and negative symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[45] Systematic review	372 people 2 RCTs in this analysis	**Mean difference in Positive and Negative Syndrome Scale (PANSS) positive subscore , short term** with risperidone (6 mg/day) with aripiprazole (15–30 mg/day) Absolute results not reported	Mean difference +1.24 95% CI –0.26 to +2.74	⟷	Not significant
[45] Systematic review	372 people 2 RCTs in this analysis	**Mean difference in PANSS negative subscore , short term** with risperidone (6 mg/day) with aripiprazole (15–30 mg/day) Absolute results not reported	Mean difference –0.45 95% CI –1.78 to +0.87	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] Systematic review	384 people 2 RCTs in this analysis	**At least 1 adverse effect** with risperidone (6 mg/day) with aripiprazole (15–30 mg/day) Absolute results not reported	RR 0.98 95% CI 0.92 to 1.05	⟷	Not significant
[45] Systematic review	301 people Data from 1 RCT	**QTc prolongation** with risperidone (6 mg/day) with aripiprazole (20–30 mg/day) Absolute results not reported	RR 0.07 95% CI 0.00 to 1.35	⟷	Not significant
[45] Systematic review	383 people 2 RCTs in this analysis	**QTc abnormalities: mean difference in change from baseline (ms)** with risperidone (6 mg/day)	Mean difference –7.19 ms 95% CI –12.19 ms to –2.19 ms	○○○	aripiprazole

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with aripiprazole (15–30 mg/day) Absolute results not reported			
[45] Systematic review	83 people Data from 1 RCT	**Mean difference in change from baseline in cholesterol (mg/dL)** with risperidone (6 mg/day) with aripiprazole (15 mg/day) Absolute results not reported	Mean difference –22.3 mg/dL 95% CI –39.69 mg/dL to –4.91 mg/dL	○○○	aripiprazole
[45] Systematic review	384 people 2 RCTs in this analysis	**Akathisia** with risperidone (6 mg/day) with aripiprazole (15–30 mg/day) Absolute results not reported	RR 0.64 95% CI 0.09 to 4.72	⟷	Not significant
[45] Systematic review	301 people Data from 1 RCT	**Dystonia** with risperidone (6 mg/day) with aripiprazole (20–30 mg/day) Absolute results not reported	RR 0.14 95% CI 0.05 to 0.41	●●●	aripiprazole
[45] Systematic review	384 people 2 RCTs in this analysis	**Extrapyramidal symptoms** with risperidone (6 mg/day) with aripiprazole (15–30 mg/day) Absolute results not reported	RR 0.84 95% CI 0.49 to 1.47	⟷	Not significant
[45] Systematic review	301 people Data from 1 RCT	**Parkinsonism** with risperidone (6 mg/day) with aripiprazole (20–30 mg/day) Absolute results not reported	RR 7.39 95% CI 0.43 to 128.08	⟷	Not significant
[45] Systematic review	301 people Data from 1 RCT	**Tremor** with risperidone (6 mg/day) with aripiprazole (20–30 mg/day) Absolute results not reported	RR 4.66 95% CI 1.11 to 19.59	●●○	risperidone
[45] Systematic review	83 people Data from 1 RCT	**Use of antiparkinsonian medication** with risperidone (6 mg/day) with aripiprazole (15 mg/day) Absolute results not reported	RR 0.59 95% CI 0.32 to 1.12	⟷	Not significant
[45] Systematic review	301 people Data from 1 RCT	**Abnormally high prolactin value** with risperidone (6 mg/day) with aripiprazole (20–30 mg/day) Absolute results not reported	RR 0.04 95% CI 0.02 to 0.08	●●●	aripiprazole
[45] Systematic review	91 people Data from 1 RCT	**Dysmenorrhoea** with risperidone (6 mg/day) with aripiprazole (20–30 mg/day) Absolute results not reported	RR 3.17 95% CI 0.17 to 59.43	⟷	Not significant
[45] Systematic review	383 people 2 RCTs in this analysis	**Mean difference in change from baseline in prolactin (ng/mL)** with risperidone (6 mg/day)	Mean difference –54.71 ng/mL 95% CI –60.06 ng/mL to –49.36 ng/mL	○○○	aripiprazole

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with aripiprazole (15–30 mg/day) Absolute results not reported			
[45] Systematic review	384 people 2 RCTs in this analysis	**Weight gain of 7% or more of total body weight** with risperidone (6 mg/day) with aripiprazole (15–30 mg/day) Absolute results not reported	RR 0.77 95% CI 0.33 to 1.82	⟷	Not significant
[45] Systematic review	383 people 2 RCTs in this analysis	**Mean change from baseline in weight (kg)** with risperidone (6 mg/day) with aripiprazole (15–30 mg/day) Absolute results not reported	Mean difference –0.54 kg 95% CI –1.24 kg to +0.15 kg	⟷	Not significant

Risperidone versus ziprasidone:

We found one systematic review (search date 2007, 3 RCTs, 1063 people). [25]

Symptom severity

Compared with ziprasidone Risperidone seems as effective at improving positive and negative symptoms in the short to medium term in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[25] Systematic review	204 people Data from 1 RCT	**Mean difference in Positive and Negative Syndrome Scale (PANSS) positive subscore , medium term** with risperidone (1.5–6 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	Mean difference 2.5 95% CI 0.38 to 4.62	○○○	risperidone
[25] Systematic review	296 people Data from 1 RCT	**Mean difference in Brief Psychiatric Rating Scale (BPRS) positive subscore , short term** with risperidone (6–10 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	Mean difference +0.5 95% CI –0.15 to +1.15	⟷	Not significant
[25] Systematic review	500 people 2 RCTs in this analysis	**Mean difference in PANSS negative subscore , short/medium term** with risperidone (1.5–10 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	Mean difference +0.04 95% CI –1.12 to +1.20	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[25] Systematic review	1063 people 3 RCTs in this analysis	**At least 1 adverse effect** with risperidone (1.5–10 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.93 95% CI 0.86 to 1.02	↔	Not significant
[25] Systematic review	822 people 2 RCTs in this analysis	**QTc prolongation** with risperidone (1.5–10 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.53 95% CI 0.11 to 2.51	↔	Not significant
[25] Systematic review	793 people 3 RCTs in this analysis	**QTc abnormalities: mean change from baseline (ms)** with risperidone (1.5–10 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	Mean difference +2.24 ms 95% CI –1.92 ms to +6.39 ms	↔	Not significant
[25] Systematic review	767 people 2 RCTs in this analysis	**Mean change from baseline in cholesterol (mg/dL)** with risperidone (1.5–6 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	Mean difference –8.58 mg/dL 95% CI –16.04 mg/dL to –1.11 mg/dL	○○○	ziprasidone
[25] Systematic review	767 people 2 RCTs in this analysis	**Suicide or attempted suicide** with risperidone (1.5–6 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 1.18 95% CI 0.22 to 6.42	↔	Not significant
[25] Systematic review	1063 people 3 RCTs in this analysis	**Akathisia** with risperidone (1.5–10 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.98 95% CI 0.53 to 1.81	↔	Not significant
[25] Systematic review	241 people Data from 1 RCT	**Extrapyramidal symptoms** with risperidone (1.5–6 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.32 95% CI 0.12 to 0.87	●●○	ziprasidone
[25] Systematic review	296 people Data from 1 RCT	**Tremor** with risperidone (6–10 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	RR 1.06 95% CI 0.53 to 2.11	↔	Not significant
[25] Systematic review	822 people 2 RCTs in this analysis	**Use of antiparkinsonian medication** with risperidone (1.5–10 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.70 95% CI 0.51 to 0.97	●○○	ziprasidone
[25] Systematic review	296 people Data from 1 RCT	**Mean difference in Abnormal Involuntary Movement Scale** with risperidone (6–10 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	Mean difference –0.21 95% CI –0.25 to –0.17	○○○	ziprasidone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[25] Systematic review	296 people Data from 1 RCT	**Mean difference in Barnes Akathisia Scale** with risperidone (6–10 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	Mean difference –0.56 95% CI –0.61 to –0.51	○○○	ziprasidone
[25] Systematic review	296 people Data from 1 RCT	**Mean difference in Simpson-Angus Scale** with risperidone (6–10 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	Mean difference –0.34 95% CI –0.42 to –0.26	○○○	ziprasidone
[25] Systematic review	215 people Data from 1 RCT	**Abnormal ejaculation** with risperidone (6–10 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	RR 0.48 95% CI 0.15 to 1.54	↔	Not significant
[25] Systematic review	225 people 2 RCTs in this analysis	**Amenorrhoea** with risperidone (1.5–10 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.84 95% CI 0.42 to 1.68	↔	Not significant
[25] Systematic review	296 people Data from 1 RCT	**Decreased libido** with risperidone (6–10 mg/day with ziprasidone (80–160 mg/day) Absolute results not reported	RR 0.61 95% CI 0.26 to 1.42	↔	Not significant
[25] Systematic review	215 people Data from 1 RCT	**Erectile dysfunction** with risperidone (6–10 mg/day) with ziprasidone (80–160 mg/day) Absolute results not reported	RR 0.95 95% CI 0.35 to 2.63	↔	Not significant
[25] Systematic review	303 people 3 RCTs in this analysis	**Galactorrhoea** with risperidone (1.5–10 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.56 95% CI 0.25 to 1.28	↔	Not significant
[25] Systematic review	822 people 2 RCTs in this analysis	**Sexual dysfunction** with risperidone (1.5–10 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.69 95% CI 0.50 to 0.97	●○○	ziprasidone
[25] Systematic review	767 people 2 RCTs in this analysis	**Mean change from baseline in prolactin (ng/mL)** with risperidone (1.5–6 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	Mean difference –21.97 ng/mL 95% CI –27.34 ng/mL to –16.60 ng/mL	○○○	ziprasidone
[25] Systematic review	1063 people 3 RCTs in this analysis	**Sedation** with risperidone (1.5–10 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.87 95% CI 0.63 to 1.20	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[25] Systematic review	1063 people 3 RCTs in this analysis	**Weight gain of 7% or more of total body weight** with risperidone (1.5–10 mg/day) with ziprasidone (40–160 mg/day) Absolute results not reported	RR 0.49 95% CI 0.33 to 0.74	●●○	ziprasidone

Risperidone versus zotepine:

We found one systematic review (search date 2009, 1 RCT, 60 people). [26]

Symptom severity

Compared with zotepine We don't know whether risperidone is more effective at improving Brief Psychiatric Rating Scale scores, or cognitive functioning in the short term in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[26] Systematic review	40 people Data from 1 RCT	**Mean difference in Brief Psychiatric Rating Scale (BPRS) total score at endpoint , short term** with risperidone (4 mg/day) with zotepine (225 mg/day) Absolute results not reported	Mean difference +1.40 95% CI –9.82 to +12.62	⟷	Not significant
[26] Systematic review	40 people Data from 1 RCT	**Mean difference in BPRS total score at endpoint , short term** with risperidone (8 mg/day) with zotepine (225 mg/day) Absolute results not reported	Mean difference –1.30 95% CI –12.95 to +10.35	⟷	Not significant
[26] Systematic review	40 people Data from 1 RCT	**No improvement in cognitive functioning (SKT) , short term** with risperidone (4 mg/day) with zotepine (225 mg/day) Absolute results not reported	RR 0.80 95% CI 0.25 to 2.55	⟷	Not significant
[26] Systematic review	40 people Data from 1 RCT	**No improvement in cognitive functioning (SKT) , short term** with risperidone (8 mg/day) with zotepine (225 mg/day) Absolute results not reported	RR 1.00 95% CI 0.29 to 3.45	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[26] Systematic review	40 people Data from 1 RCT	**Mean difference in extrapyramidal symptoms score at endpoint , short term** with risperidone (4 mg/day)	Mean difference +1.80 95% CI –0.64 to +4.24	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with zotepine (225 mg/day) Absolute results not reported			
[26] Systematic review	40 people Data from 1 RCT	**Mean difference in extrapyramidal symptoms score at end-point , short term** with risperidone (8 mg/day) with zotepine (225 mg/day) Absolute results not reported	Mean difference +2.50 95% CI –0.05 to +5.05	⟷	Not significant
[26] Systematic review	40 people Data from 1 RCT	**Use of antiparkinsonism medication , short term** with risperidone (4 mg/day) with zotepine (225 mg/day) Absolute results not reported	RR 6.00 95% CI 0.79 to 45.42	⟷	Not significant
[26] Systematic review	40 people Data from 1 RCT	**Use of antiparkinsonism medication , short term** with risperidone (8 mg/day) with zotepine (225 mg/day) Absolute results not reported	RR 3.00 95% CI 0.69 to 13.12	⟷	Not significant

Risperidone versus flupentixol:

We found one RCT (107 people) comparing risperidone versus flupentixol. [46]

Symptom severity

Compared with flupentixol We don't know whether risperidone is more effective at improving positive and negative symptoms at 8 to 16 weeks in people with predominantly negative symptoms of schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[46] RCT	107 people with predominantly negative symptoms	**Mean change from baseline in Positive and Negative Syndrome Scale (PANSS) negative subscore , 8 weeks** with risperidone (2–6 mg/day) with flupentixol (4–12 mg/day) Absolute results not reported	Mean difference –1.11 95% CI –3.30 to +1.07	⟷	Not significant
[46] RCT	107 or fewer people with predominantly negative symptoms Unclear how many people remained at this time point	**Mean change from baseline in PANSS negative subscore , 16 weeks** with risperidone (2–6 mg/day) with flupentixol (4–12 mg/day) Absolute results not reported	Mean difference +0.10 95% CI –2.69 to +2.90	⟷	Not significant
[46] RCT	107 or fewer people with predominantly negative symptoms Unclear how many people remained at this time point	**Mean change from baseline in PANSS negative subscore , 24 weeks** with risperidone (2–6 mg/day) with flupentixol (4–12 mg/day) Absolute results not reported	Mean difference +1.60 95% CI –1.63 to +4.83	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[46] RCT	107 people with predominantly negative symptoms	**Change from baseline in PANSS positive score , 24 weeks** with risperidone (2–6 mg/day) with flupentixol (4–12 mg/day) Absolute results not reported	P >0.05	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[46] RCT	153 people with predominantly negative symptoms	**Any adverse effect** 60% with risperidone (2–6 mg/day) 75% with flupentixol (4–12 mg/day) Absolute numbers not reported	P = 0.038	○○○	risperidone
[46] RCT	153 people with predominantly negative symptoms	**Akathisia** 5% with risperidone (2–6 mg/day) 8% with flupentixol (4–12 mg/day) Absolute numbers not reported	P >0.05	⟷	Not significant
[46] RCT	153 people with predominantly negative symptoms	**Extrapyramidal symptoms** 5% with risperidone (2–6 mg/day) 7% with flupentixol (4–12 mg/day) Absolute numbers not reported	P >0.05	⟷	Not significant
[46] RCT	153 people with predominantly negative symptoms	**Insomnia** 5% with risperidone (2–6 mg/day) 7% with flupentixol (4–12 mg/day) Absolute numbers not reported	P >0.05	⟷	Not significant
[46] RCT	153 people with predominantly negative symptoms	**Tremor** 0% with risperidone (2–6 mg/day) 5% with flupentixol (4–12 mg/day) Absolute numbers not reported	P >0.05	⟷	Not significant

Risperidone versus first-generation antipsychotic drugs:

We found three systematic reviews (search date 2002, 17 RCTs and 2 open-label studies, 3643 people; [47] search date 2002, 11 RCTs, 3227 people; [48] and search date 2006, 34 RCTs, 4173 people [11]) and one additional RCT. [49] It is likely that there is overlap in RCTs included in the systematic reviews; however, as two reviews do not report which trials are included in the pooled results, we have reported results from all of the reviews here.

Symptom severity

Compared with first-generation antipsychotic drugs Risperidone seems more effective at improving positive and negative symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[47] Systematic review	3663 people 15 RCTs in this analysis	**Mean difference in Hedges-Olkin score for Positive and Negative Syndrome Scale (PANSS) positive improvement** with risperidone with first-generation antipsychotic drugs Absolute results not reported	Effect size 0.16 95% CI 0.09 to 0.24 P <0.001	○○○	risperidone
[47] Systematic review	3663 people 15 RCTs in this analysis	**Mean difference in Hedges-Olkin score for PANSS negative improvement** with risperidone with first-generation antipsychotic drugs Absolute results not reported	Effect size 0.20 95% CI 0.13 to 0.28 P <0.001	○○○	risperidone
[48] Systematic review	2368 people 9 RCTs in this analysis	**No clinically important improvement , 12 weeks** 789/1809 (44%) with risperidone 292/559 (52%) with first-generation antipsychotic drugs Clinical improvement defined as 20% improvement on PANSS	RR 0.85 95% CI 0.77 to 0.93	●○○	risperidone
[48] Systematic review	859 people 2 RCTs in this analysis	**No clinically important improvement , 26 weeks** 191/442 (43%) with risperidone 246/417 (59%) with first-generation antipsychotic drugs Clinical improvement defined as 20% improvement on PANSS	RR 0.73 95% CI 0.65 to 0.83	●○○	risperidone
[11] Systematic review	3286 people 28 RCTs in this analysis	**Hedges' adjusted g effect size for positive symptoms (PANSS)** with risperidone with first-generation antipsychotic drugs Absolute results not reported	Effect size –0.13 95% CI –0.20 to –0.05	○○○	risperidone
[11] Systematic review	3455 people 30 RCTs in this analysis	**Hedges' adjusted g effect size for negative symptoms (PANSS)** with risperidone with first-generation antipsychotic drugs Absolute results not reported	Effect size –0.13 95% CI –0.21 to –0.06	○○○	risperidone
[49] RCT	99 people	**Response to treatment , 8 weeks** with risperidone with haloperidol Absolute results reported graphically Response defined as 20% reduction in PANSS	Reported as non-significant	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	108 people 2 RCTs in this analysis	**Extrapyramidal symptoms** with risperidone with first-generation antipsychotic drugs Absolute results not reported	RR 0.47 95% CI 0.22 to 0.99	●○○	risperidone
[11] Systematic review	108 people 2 RCTs in this analysis	**Sedation** with risperidone with first-generation antipsychotic drugs Absolute results not reported	RR 2.59 95% CI 0.29 to 22.94	⟷	Not significant
[48] Systematic review	2243 people 11 RCTs in this analysis	**Proportion of people who withdrew because of adverse effects** 142/1619 (9%) with risperidone 70/624 (11%) with first-generation antipsychotic drugs	RR 0.82 95% CI 0.61 to 1.09	⟷	Not significant
[48] Systematic review	2738 people 10 RCTs in this analysis	**Extrapyramidal symptoms** 384/1937 (20%) with risperidone 289/765 (38%) with first-generation antipsychotic drugs	RR 0.63 95% CI 0.56 to 0.71	●○○	risperidone
[48] Systematic review	2524 people 11 RCTs in this analysis	**Antiparkinsonian medication** 461/1856 (25%) with risperidone 289/668 (43%) with first-generation antipsychotic drugs	RR 0.66 95% CI 0.58 to 0.74	●○○	risperidone
[48] Systematic review	1708 people 4 RCTs in this analysis	**Weight gain** 420/1320 (32%) with risperidone 71/388 (18%) with first-generation antipsychotic drugs	RR 1.55 95% CI 1.25 to 1.93	●●○	first-generation antipsychotic drugs

No data from the following reference on this outcome. [47] [49]

Further information on studies

[11] Some first-generation comparators are not included in the current review, but first-generation antipsychotics are grouped together; thus, it is not possible to do individual comparisons. Some studies included patients that had disorders with diagnoses other than schizophrenia (e.g., schizophreniform disorder, schizoaffective disorder, psychotic state).

[25] Studies had high attrition, and most used last observation carried forward (LOCF) and had selective reporting. The authors of the review consider all studies to be at high risk of bias. One study used higher risperidone doses than would generally be used (7.4 mg/day), although results are similar to studies using lower doses.

[42] Studies were all between 8 and 12 weeks and there was high attrition overall. Most trials were funded by the drug manufacturer and the review authors state that poor reporting "suggests that any positive findings in favour of risperidone cannot be fully trusted".

[43] The single included study in this systematic review was incompletely reported and from a conference abstract, so the results have been taken from the presumed corresponding publication. [50] The study had 22% attrition and used LOCF in the analysis. Adverse events were selectively reported (only most common). The study was short term (6 weeks). Sufficient randomisation and blinding details were given.

[44] Included studies were considered poor quality and at high risk of bias by the review authors since both studies had reasonably high attrition, used LOCF, had selective reporting, and were sponsored by the manufacturer of sertindole.

[45] Both studies were sponsored by the manufacturer of aripiprazole. Attrition was reasonably high and both studies used LOCF. The authors of the review considered that both reviews had a high risk of bias because of selective reporting. The studies were short term (4–6 weeks).

[46] In this RCT, there was high attrition in the longer term (45%) and LOCF was used in the analysis. The study gave no information regarding the method of randomisation. Otherwise, it was well reported.

[47] Because of inconsistencies in the review, it is unclear whether for the efficacy comparison the comparator first-generation antipsychotics is actually just haloperidol, or whether there is a minority of included studies that use other drugs. Two studies were open label. The review did not report adverse effects. Several trials were also included in other reviews.

Comment: For positive and negative symptoms, there is mixed evidence about whether risperidone is superior to placebo. There is strong evidence that risperidone is superior to first-generation antipsychotics as a group, but little evidence of a difference between risperidone and haloperidol alone. Risperidone showed superiority over quetiapine and, in the medium term, ziprasidone, for positive symptoms, whereas risperidone may be inferior to olanzapine for negative symptoms in the longer term. There was little evidence of any other differences between risperidone and other second-generation antipsychotics, as a group, for either positive or negative symptoms. There is no evidence of a difference between risperidone and clozapine or olanzapine in global neurocognitive score, while one small study showed superiority of risperidone over haloperidol.

There is strong evidence that risperidone is associated with prolactin increase to a greater extent than ziprasidone, aripiprazole, olanzapine, and quetiapine, and with weight gain to a greater extent than placebo, amisulpride, haloperidol, sertindole, and ziprasidone. Only olanzapine is associated with greater weight gain than risperidone, while there is no evidence of any other antipsychotic being associated with more prolactin increase than risperidone. Risperidone may also be associated with greater levels of prolactin-associated adverse effects, such as sexual dysfunction, than some other antipsychotics. Risperidone may be associated with a greater extent of extrapyramidal symptoms, including akathisia, dystonia, and dyskinesia, and parkinsonism than most other second-generation antipsychotics, while it is comparable or superior to haloperidol for these adverse effects. Risperidone does not seem to be associated with cardiac effects or sedation any more than placebo or other antipsychotics.

Clinical guide:
Risperidone and other second-generation antipsychotics have not been shown consistently in RCTs to differ in efficacy. However, risperidone seems to be associated with an increase in extrapyramidal symptoms, prolactin, and weight gain, which may be problematic. When choosing between risperidone and other second-generation antipsychotics, adverse-effect profiles should be taken into consideration.

OPTION SULPIRIDE

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- A systematic review found no significant difference between the newer antipsychotic drug, sulpiride, and standard antipsychotic drugs in symptom improvement, and showed that they have different profiles of adverse effects. However, like all antipsychotic drugs, harms may include parkinsonism, dystonia, cholinergic effects, and weight gain.

Benefits and harms

Sulpiride versus first-generation antipsychotic drugs:

We found one systematic review (search date 1998, 7 RCTs, 514 people). [51]

Symptom severity

Compared with first-generation antipsychotic drugs Sulpiride is as effective at improving global clinical impression scores at 4 to 10 weeks in people with schizophrenia (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[51] Systematic review	514 people 7 RCTs in this analysis	**No improvement in global clinical impression , 4 to 10 weeks** 74/248 (30%) with sulpiride 96/266 (36%) with first-generation antipsychotic drugs First-generation antipsychotic drugs included: haloperidol, chlorpromazine, or perphenazine	RR 0.82 95% CI 0.64 to 1.05	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[51] Systematic review	511 people 7 RCTs in this analysis	**Use of antiparkinsonian drugs , 4 to 10 weeks** 84/253 (33%) with sulpiride 115/258 (45%) with first-generation antipsychotic drugs	RR 0.73 95% CI 0.59 to 0.90	●○○	sulpiride

Further information on studies

[51] The review stated that the other two RCTs it identified reported improvement in mental state with sulpiride compared with placebo, but that no raw data could be obtained because of poor reporting in the RCTs.

Comment: **Clinical guide:**
A systematic review showed no evidence of differences in efficacy between sulpiride and other antipsychotics. Observational evidence and clinical experience suggest that sulpiride may be associated with galactorrhoea, but RCT data did not quantify the risk. [52]

OPTION ZIPRASIDONE

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Ziprasidone may be less effective than olanzapine and risperidone in treating the positive symptoms of schizophrenia, and has a similar adverse effects profile to other antipsychotic drugs. Ziprasidone is not currently licensed in the UK.

Benefits and harms

Ziprasidone versus aripiprazole:

We found one RCT comparing ziprasidone versus aripiprazole. [53]

Symptom severity

Compared with aripiprazole We don't know whether ziprasidone is more effective at improving positive and negative symptoms in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[53] RCT	247 people Non-inferiority study: null hypothesis of inferiority of ziprasidone	**Brief Psychiatric Rating Scale (BPRS) total score , 4 weeks** with ziprasidone (mean modal dose 149 mg/day) with aripiprazole (mean modal dose 20.9 mg/day) Absolute results not reported A difference of 3.5 was defined as therapeutic equivalence	P = 0.098 Cannot reject the null hypothesis of the inferiority of ziprasidone	⟷	Not significant
[53] RCT	247 people	**Effect size for Positive and Negative Syndrome Scale (PANSS) positive score , 4 weeks** 1.0 with ziprasidone (mean modal dose 149 mg/day) 1.2 with aripiprazole (mean modal dose 20.9 mg/day)	P = 0.16	⟷	Not significant
[53] RCT	247 people	**Effect size for PANSS negative score , 4 weeks** 0.73 with ziprasidone (mean modal dose 149 mg/day) 0.77 with aripiprazole (mean modal dose 20.9 mg/day)	P = 0.71	⟷	Not significant
[53] RCT	247 people	**Mean change from baseline in PANSS total score over time , 2 days** –7.0 with ziprasidone (mean modal dose 149 mg/day) –5.5 with aripiprazole (mean modal dose 20.9 mg/day)	P >0.05	⟷	Not significant
[53] RCT	247 people	**Mean change from baseline in PANSS total score over time , 4 days** –11.5 with ziprasidone (mean modal dose 149 mg/day) –9.6 with aripiprazole (mean modal dose 20.9 mg/day)	P <0.05	○○○	ziprasidone
[53] RCT	247 people	**Mean change from baseline in PANSS total score over time , 1 week** –12.5 with ziprasidone (mean modal dose 149 mg/day) –14.0 with aripiprazole (mean modal dose 20.9 mg/day)	P >0.05	⟷	Not significant
[53] RCT	247 people	**Mean change from baseline in PANSS total score over time , 2 weeks** –17.5 with ziprasidone (mean modal dose 149 mg/day) –18.1 with aripiprazole (mean modal dose 20.9 mg/day)	P >0.05	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[53] RCT	247 people	**Mean change from baseline in PANSS total score over time , 3 weeks** –19.7 with ziprasidone (mean modal dose 149 mg/day) –22.5 with aripiprazole (mean modal dose 20.9 mg/day)	P >0.05	⟷	Not significant
[53] RCT	247 people	**Mean change from baseline in PANSS total score over time , 4 weeks** –21.6 with ziprasidone (mean modal dose 149 mg/day) –24.6 with aripiprazole (mean modal dose 20.9 mg/day)	P >0.05	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[53] RCT	247 people	**Mean change from baseline in Simpson-Angus Scale** 0 with ziprasidone (mean modal dose 149 mg/day) 0 with aripiprazole (mean modal dose 20.9 mg/day)	P = 0.99	⟷	Not significant
[53] RCT	247 people	**Mean change from baseline in Barnes Akathisia Scale** +0.1 with ziprasidone (mean modal dose 149 mg/day) –0.1 with aripiprazole (mean modal dose 20.9 mg/day)	P = 0.05	⟷	Not significant
[53] RCT	247 people	**Mean change from baseline in Abnormal Involuntary Movement Scale** 0 with ziprasidone (mean modal dose 149 mg/day) –0.4 with aripiprazole (mean modal dose 20.9 mg/day)	P = 0.04	○○○	aripiprazole
[53] RCT	247 people	**Median weight gain (kg)** 0.45 kg with ziprasidone (mean modal dose 149 mg/day) 0.45 kg with aripiprazole (mean modal dose 20.9 mg/day)	Significance assessment not performed		
[53] RCT	247 people	**Median change from baseline in prolactin concentration (ng/mL)** –2.6 ng/mL with ziprasidone (mean modal dose 149 mg/day) –9.8 ng/mL with aripiprazole (mean modal dose 20.9 mg/day)	Significance assessment not performed		
[53] RCT	247 people	**Median change from baseline in QTc interval (ms)**	Significance assessment not performed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		9.0 ms with ziprasidone (mean modal dose 149 mg/day) 2.5 ms with aripiprazole (mean modal dose 20.9 mg/day)			
[53] RCT	247 people	**Percentage of people with akathisia** 6% with ziprasidone (mean modal dose 149 mg/day) 7% with aripiprazole (mean modal dose 20.9 mg/day) Absolute numbers not reported	Significance assessment not performed		
[53] RCT	247 people	**Percentage of people with somnolence** 26% with ziprasidone (mean modal dose 149 mg/day) 13% with aripiprazole (mean modal dose 20.9 mg/day) Absolute numbers not reported	Significance assessment not performed		
[53] RCT	247 people	**Percentage of people with dyspepsia** 10% with ziprasidone (mean modal dose 149 mg/day) 18% with aripiprazole (mean modal dose 20.9 mg/day) Absolute numbers not reported	Significance assessment not performed		

Ziprasidone versus first-generation antipsychotic drugs:

We found one systematic review (search date 2006, 5 RCTs, 980 people). [11]

Symptom severity

Compared with first-generation antipsychotic drugs Ziprasidone seems as effective at improving positive and negative symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[11] Systematic review	728 people 4 RCTs in this analysis	**Hedges' adjusted g effect size for positive symptoms** with ziprasidone with first-generation antipsychotic drugs Absolute results not reported	Effect size +0.04 95% CI –0.08 to +0.17	⟷	Not significant
[11] Systematic review	691 people 3 RCTs in this analysis	**Hedges' adjusted g effect size for negative symptoms** with ziprasidone with first-generation antipsychotic drugs Absolute results not reported	Effect size –0.09 95% CI –0.29 to +0.11	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	306 people Data from 1 RCT	**Use of antiparkinsonism medication** with ziprasidone with low-potency first-generation antipsychotics Absolute results not reported	RR 1.13 95% CI 0.91 to 1.41	⟷	Not significant
[11] Systematic review	306 people Data from 1 RCT	**Mean difference in weight gain (kg)** with ziprasidone with low-potency first-generation antipsychotics Absolute results not reported	Mean difference –1.1 kg 95% CI –2.3 kg to +0.2 kg	⟷	Not significant
[11] Systematic review	306 people Data from 1 RCT	**Sedation** with ziprasidone with low-potency first-generation antipsychotics Absolute results not reported	RR 0.67 95% CI 0.44 to 1.01	⟷	Not significant

Ziprasidone versus amisulpride:
See treatment option on amisulpride, p 4 .

Ziprasidone versus clozapine:
See treatment option on clozapine, p 20 .

Ziprasidone versus haloperidol:
See treatment option on haloperidol , p 37 .

Ziprasidone versus olanzapine:
See treatment option on olanzapine, p 55 .

Ziprasidone versus quetiapine:
See treatment option on quetiapine, p 80 .

Ziprasidone versus risperidone:
See treatment option on risperidone, p 92 .

Further information on studies

[11] The review did not include a comparison of ziprasidone versus some first-generation drugs alone, but grouped first-generation antipsychotics together; thus, it is not possible to do individual comparisons. Some studies included patients that had disorders with diagnoses other than schizophrenia (e.g., schizophreniform disorder, schizoaffective disorder, psychotic state).

[53] This was a non-inferiority trial funded by the manufacturer of ziprasidone. The primary outcome was non-inferiority of ziprasidone compared with aripiprazole on Brief Psychiatric Rating Scale and the null hypothesis of ziprasidone being inferior to aripiprazole was not rejected. The secondary outcomes were two-sided tests of superiority of either drug and mainly showed no significant differences. The study did not reach its anticipated sample size and was thus underpowered. This study was therefore inconclusive since it failed to show that ziprasidone was non-inferior to aripiprazole and also failed to show any significant difference between the two drugs. Furthermore, the analyses of the main outcomes used last observation carried forward (LOCF) and only the most common adverse events were reported.

Comment: Ziprasidone may be inferior to olanzapine for positive symptoms and cognitive score, although some olanzapine doses studied were above the UK licence limit. Ziprasidone may also be inferior to risperidone for medium-term positive symptoms. There is no conclusive evidence regarding any difference between ziprasidone and aripiprazole. There is no evidence of any further differences between ziprasidone and other antipsychotics for positive or negative symptoms.

Ziprasidone may be associated with a similar level of weight gain to other antipsychotics, although it is likely to be better than olanzapine, risperidone, and possibly quetiapine. There is evidence that ziprasidone is better than haloperidol for extrapyramidal symptoms and better than risperidone and aripiprazole for some extrapyramidal symptoms, although similar to most other second-generation antipsychotics. Ziprasidone may be associated with a greater level of parkinsonism than olanzapine and quetiapine, but a lesser level than risperidone. The cardiac effects, prolactin changes, and sedation associated with ziprasidone seems be similar to those associated with other antipsychotics, although ziprasidone shows superiority to risperidone for prolactin changes.

Clinical guide:
Ziprasidone currently does not have a UK licence.

OPTION ZOTEPINE

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Zotepine is likely to be as effective as first-generation antipsychotic drugs when treating positive and negative symptoms of schizophrenia. Zotepine has been withdrawn from the UK market.

Benefits and harms

Zotepine versus first-generation antipsychotic drugs:

We found one systematic review (search date 2006, 15 RCTs, 1125 people). [11]

Symptom severity

Compared with first-generation antipsychotic drugs Zotepine seems as effective at improving positive and negative symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[11] Systematic review	1125 people 15 RCTs in this analysis	**Hedges' adjusted g effect size for overall symptoms (Positive and Negative Syndrome Scale [PANSS])** with zotepine	Effect size –0.10 95% CI –0.27 to +0.06	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with first-generation antipsychotic drugs Absolute results not reported			
[11] Systematic review	192 people 2 RCTs in this analysis	**Hedges' adjusted g effect size for positive symptoms (PANSS)** with zotepine with first-generation antipsychotic drugs Absolute results not reported	Effect size +0.12 95% CI –0.16 to +0.40	⟷	Not significant
[11] Systematic review	450 people 5 RCTs in this analysis	**Hedges' adjusted g effect size for negative symptoms (PANSS)** with zotepine with first-generation antipsychotic drugs Absolute results not reported	Effect size –0.23 95% CI –0.46 to +0.00	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] Systematic review	322 people 5 RCTs in this analysis	**Extrapyramidal symptoms** with zotepine with low-potency first-generation antipsychotic drugs Absolute results not reported	RR 1.04 95% CI 0.76 to 1.42	⟷	Not significant
[11] Systematic review	106 people Data from 1 RCT	**Mean difference in weight gain (kg)** with zotepine with low-potency first-generation antipsychotic drugs Absolute results not reported	Mean difference +1.0 kg 95% CI –0.9 kg to +2.9 kg	⟷	Not significant
[11] Systematic review	146 people 2 RCTs in this analysis	**Sedation** with zotepine with low-potency first-generation antipsychotic drugs Absolute results not reported	RR 1.09 95% CI 0.69 to 1.73	⟷	Not significant

Zotepine versus clozapine:

See treatment option on clozapine, p 20 .

Zotepine versus haloperidol:

See treatment option on haloperidol, p 37 .

Further information on studies

[11] The review did not include a comparison of zotepine versus some first-generation drugs alone, but grouped first-generation antipsychotics together; thus, it is not possible to do individual comparisons. Some studies included patients that had disorders with diagnoses other than schizophrenia (e.g., schizophreniform disorder, schizoaffective disorder, psychotic state).

Comment: Zotepine is likely to have a similar effect on positive and negative symptoms to first-generation antipsychotics. There is very little reliable evidence comparing zotepine with other second-generation antipsychotics for treatment of positive and negative symptoms. Zotepine is likely to be associated with a similar level of extrapyramidal symptoms, weight gain, and sedation to low-potency first-generation antipsychotics. Zotepine may, however, be associated with a lesser extent of extrapyramidal symptoms than haloperidol and a greater level of weight gain and sedation. Zotepine may be worse than clozapine for parkinsonism and prolactin increase, although the mean zotepine dose in the single study for this comparison was above the UK license dose limit. There is little other reliable evidence regarding adverse effects of zotepine compared with other second-generation antipsychotics.

Clinical guide:
There is evidence of similar benefit with zotepine compared with first-generation antipsychotics in the treatment of both positive and negative symptoms of schizophrenia. The evidence comparing zotepine with second-generation antipsychotics is poor. Well-controlled RCTs comparing zotepine with other second-generation antipsychotics would be feasible and should be undertaken. Zotepine was withdrawn from the UK market from 1 January 2011.

OPTION ARIPIPRAZOLE

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Aripiprazole may be more effective than placebo for treatment of positive symptoms.
- Aripiprazole may be as effective as first-generation antipsychotic drugs, risperidone, and ziprasidone.
- Aripiprazole may be less effective than olanzapine.
- Aripiprazole is associated with akathisia, extrapyramidal symptoms, parkinsonism, and a decrease in prolactin.

Benefits and harms

Aripiprazole versus placebo:

We found three RCTs. [54] [55] [56]

Symptom severity

Compared with placebo Aripiprazole (10–30 mg/day) may be more effective at improving positive symptoms in people with schizophrenia; however, we don't know whether aripiprazole is more effective at improving negative symptoms, or if lower doses are more effective than placebo (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[54] RCT **3-armed trial**	197 adolescents The remaining arm assessed aripiprazole (30 mg/day)	**Mean change from baseline in Positive and Negative Syndrome Scale (PANSS) positive subscale score , 1 week** –2.1 with aripiprazole (10 mg/day) –1.8 with placebo	P = 0.59	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[54] RCT **3-armed trial**	195 adolescents The remaining arm assessed aripiprazole (10 mg/day)	**Mean change from baseline in PANSS positive subscale score , 1 week** –2.9 with aripiprazole (30 mg/day) –1.8 with placebo	P = 0.03	○○○	aripiprazole
[54] RCT **3-armed trial**	197 adolescents The remaining arm assessed aripiprazole (30 mg/day)	**Mean change from baseline in PANSS positive subscale score , 6 weeks** –7.6 with aripiprazole (10 mg/day) –5.6 with placebo	P = 0.02	○○○	aripiprazole
[54] RCT **3-armed trial**	195 adolescents The remaining arm assessed aripiprazole (10 mg/day)	**Mean change from baseline in PANSS positive subscale score , 6 weeks** –8.1 with aripiprazole (30 mg/day) –5.6 with placebo	P = 0.002	○○○	aripiprazole
[54] RCT **3-armed trial**	197 adolescents The remaining arm assessed aripiprazole (30 mg/day)	**Mean change from baseline in PANSS negative subscale score , 1 week** –1.5 with aripiprazole (10 mg/day) –2.0 with placebo	P = 0.28	↔	Not significant
[54] RCT **3-armed trial**	195 adolescents The remaining arm assessed aripiprazole (10 mg/day)	**Mean change from baseline in PANSS negative subscale score , 1 week** –2.5 with aripiprazole (30 mg/day) –2.0 with placebo	P = 0.29	↔	Not significant
[54] RCT **3-armed trial**	197 adolescents The remaining arm assessed aripiprazole (30 mg/day)	**Mean change from baseline in PANSS negative subscale score , 6 weeks** –6.9 with aripiprazole (10 mg/day) –5.4 with placebo	P = 0.05	●●○	aripiprazole
[54] RCT **3-armed trial**	195 adolescents The remaining arm assessed aripiprazole (10 mg/day)	**Mean change from baseline in PANSS negative subscale score , 6 weeks** –6.6 with aripiprazole (30 mg/day) –5.4 with placebo	P = 0.10	↔	Not significant
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (15 mg/day and 20 mg/day)	**Mean difference in change from baseline in PANSS positive score , 1 week** with aripiprazole (10 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.05	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (15 mg/day and 20 mg/day)	**Mean difference in change from baseline in PANSS positive score , 2 weeks** with aripiprazole (10 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.001	○○○	aripiprazole

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (15 mg/day and 20 mg/day)	**Mean difference in change from baseline in PANSS positive score , 3 weeks** with aripiprazole (10 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.001	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (10 mg/day and 20 mg/day)	**Mean change from baseline in PANSS positive score , 1 week** with aripiprazole (15 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.05	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (10 mg/day and 20 mg/day)	**Mean change from baseline in PANSS positive score , 2 weeks** with aripiprazole (15 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.05	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (10 mg/day and 20 mg/day)	**Mean change from baseline in PANSS positive score , 3 weeks** with aripiprazole (15 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.05	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (10 mg/day and 15 mg/day)	**Mean change from baseline in PANSS positive score , 1 week** with aripiprazole (20 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.05	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (10 mg/day and 15 mg/day)	**Mean change from baseline in PANSS positive score , 2 weeks** with aripiprazole (20 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.01	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (10 mg/day and 15 mg/day)	**Mean change from baseline in PANSS positive score , 3 weeks** with aripiprazole (20 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.01	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (15 mg/day and 20 mg/day)	**Mean change from baseline in PANSS negative score , 1 week** with aripiprazole (10 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.05	○○○	aripiprazole

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (15 mg/day and 20 mg/day)	**Mean change from baseline in PANSS negative score , 2 weeks** with aripiprazole (10 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.001	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (15 mg/day and 20 mg/day)	**Mean change from baseline in PANSS negative score , 3 weeks** with aripiprazole (10 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.001	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (10 mg/day and 20 mg/day)	**Mean change from baseline in PANSS negative score , 1 week** with aripiprazole (15 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.05	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (10 mg/day and 20 mg/day)	**Mean change from baseline in PANSS negative score , 2 weeks** with aripiprazole (15 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.05	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (10 mg/day or 20 mg/day)	**Mean change from baseline in PANSS negative score , 3 weeks** with aripiprazole (15 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.05	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (10 mg/day and 15 mg/day)	**Mean change from baseline in PANSS negative score , 1 week** with aripiprazole (20 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.01	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (10 mg/day and 15 mg/day)	**Mean change from baseline in PANSS negative score , 2 weeks** with aripiprazole (20 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.001	○○○	aripiprazole
[55] RCT **4-armed trial**	420 hospitalised people The remaining arms assessed aripiprazole (10 mg/day and 15 mg/day)	**Mean change from baseline in PANSS negative , 3 weeks** with aripiprazole (20 mg/day) with placebo Absolute results not reported	P less-than or equal to 0.001	○○○	aripiprazole

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[56] RCT **4-armed trial**	367 hospitalised people The remaining arms assessed aripiprazole (2 mg/day and 5 mg/day)	**Change from baseline in PANSS positive score at end-point , 6 weeks** –4.2 with aripiprazole (10 mg/day) –2.3 with placebo	P = 0.03	○○○	aripiprazole
[56] RCT **4-armed trial**	367 hospitalised people The remaining arms assessed aripiprazole (2 mg/day and 10 mg/day)	**Change from baseline in PANSS positive score at end-point , 6 weeks** with aripiprazole (5 mg/day) with placebo Absolute results not reported	P >0.05	⟷	Not significant
[56] RCT **4-armed trial**	367 hospitalised people The remaining arms assessed aripiprazole (5 mg/day and 10 mg/day)	**Change from baseline in PANSS positive score at end-point , 6 weeks** with aripiprazole (2 mg/day) with placebo Absolute results not reported	P >0.05	⟷	Not significant
[56] RCT **4-armed trial**	367 hospitalised people The remaining arms assessed aripiprazole (2 mg/day and 5 mg/day)	**Change from baseline in PANSS negative score at end-point , 6 weeks** with aripiprazole (10 mg/day) with placebo Absolute results not reported	P >0.05	⟷	Not significant
[56] RCT **4-armed trial**	367 hospitalised people The remaining arms assessed aripiprazole (2 mg/day and 10 mg/day)	**Change from baseline in PANSS negative score at end-point , 6 weeks** with aripiprazole (5 mg/day) with placebo Absolute results not reported	P >0.05	⟷	Not significant
[56] RCT **4-armed trial**	367 hospitalised people The remaining arms assessed aripiprazole (5 mg/day and 10 mg/day)	**Change from baseline in PANSS negative score at end-point , 6 weeks** with aripiprazole (2 mg/day) with placebo Absolute results not reported	P >0.05	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[54] RCT **3-armed trial**	302 adolescents	**Percentage with akathisia** 5% with aripiprazole (10 mg/day) 12% with aripiprazole (30 mg/day) 5% with placebo Absolute numbers not reported	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[54] RCT **3-armed trial**	302 adolescents	**Percentage with extrapyramidal symptoms** 13% with aripiprazole (10 mg/day) 22% with aripiprazole (30 mg/day) 5% with placebo Absolute numbers not reported	P value not reported		
[54] RCT **3-armed trial**	302 adolescents	**Percentage with nausea** 9% with aripiprazole (10 mg/day) 10% with aripiprazole (30 mg/day) 6% with placebo Absolute numbers not reported	P value not reported		
[54] RCT **3-armed trial**	302 adolescents	**Percentage with somnolence** 11% with aripiprazole (10 mg/day) 22% with aripiprazole (30 mg/day) 6% with placebo Absolute numbers not reported	P value not reported		
[54] RCT **3-armed trial**	302 adolescents	**Percentage with tremor** 2% with aripiprazole (10 mg/day) 12% with aripiprazole (30 mg/day) 2% with placebo Absolute numbers not reported	P value not reported		
[54] RCT **3-armed trial**	302 adolescents	**Percentage with insomnia** 11% with aripiprazole (10 mg/day) 10% with aripiprazole (30 mg/day) 15% with placebo Absolute numbers not reported	P value not reported		
[54] RCT **3-armed trial**	302 adolescents	**Percentage with a parkinsonism event (including extrapyramidal symptoms and tremor)** 15% with aripiprazole (10 mg/day) 30% with aripiprazole (30 mg/day) 7% with placebo Absolute numbers not reported	P value not reported		
[54] RCT **3-armed trial**	295 adolescents	**Mean change from baseline in weight (kg)** 0 kg with aripiprazole (10 mg/day) +0.2 kg with aripiprazole (30 mg/day) –0.8 kg with placebo	P = 0.009	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[54] RCT **3-armed trial**	286 adolescents The remaining arm assessed aripiprazole (30 mg/day)	**Mean change from baseline in prolactin (ng/mL)** –11.93 ng/mL with aripiprazole (10 mg/day) –8.45 ng/mL with placebo	P = 0.003	○○○	placebo
[54] RCT **3-armed trial**	286 adolescents The remaining arm assessed aripiprazole (10 mg/day)	**Mean change from baseline in prolactin (ng/mL)** –15.14 ng/mL with aripiprazole (30 mg/day) –8.45 ng/mL with placebo	P <0.0001	○○○	placebo
[54] RCT **3-armed trial**	296 adolescents The remaining arm assessed aripiprazole (30 mg/day)	**Mean change from baseline in Simpson-Angus Scale (SAS)** +0.5 with aripiprazole (10 mg/day) –0.3 with placebo	P = 0.007	○○○	placebo
[54] RCT **3-armed trial**	296 adolescents The remaining arm assessed aripiprazole (10 mg/day)	**Mean change from baseline in SAS** +0.3 with aripiprazole (30 mg/day) –0.3 with placebo	P = 0.05	○○○	placebo
[54] RCT **3-armed trial**	296 adolescents	**Mean change from baseline in Barnes Rating Scale for Drug-Induced Akathisia** with aripiprazole (10 mg/day) with aripiprazole (30 mg/day) with placebo Absolute results not reported	P >0.05	↔	Not significant
[54] RCT **3-armed trial**	296 adolescents	**Mean change from baseline in Abnormal Involuntary Movement Scale (AIMS)** with aripiprazole (10 mg/day) with aripiprazole (30 mg/day) with placebo Absolute results not reported	P >0.05	↔	Not significant
[54] RCT **3-armed trial**	302 adolescents The remaining arm assessed aripiprazole (30 mg/day)	**Percentage with low prolactin** 34% with aripiprazole (10 mg/day) 8% with placebo Absolute numbers not reported	P <0.0001	○○○	placebo
[54] RCT **3-armed trial**	302 adolescents The remaining arm assessed aripiprazole (10 mg/day)	**Percentage with low prolactin** 26% with aripiprazole (30 mg/day) 8% with placebo Absolute numbers not reported	P = 0.001	○○○	placebo
[56] RCT **4-armed trial**	340 hospitalised people	**Mean change in SAS score** –0.4 with aripiprazole (2 mg/day) –0.4 with aripiprazole (5 mg/day) +0.9 with aripiprazole (10 mg/day) 0 with placebo	P >0.05	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[56] RCT **4-armed trial**	340 hospitalised people	**Mean change in AIMS score** 0 with aripiprazole (2 mg/day) –0.4 with aripiprazole (5 mg/day) –0.4 with aripiprazole (10 mg/day) 0 with placebo	P >0.05	⟷	Not significant
[56] RCT **4-armed trial**	340 hospitalised people	**Mean change in Barnes Akathisia Scale score** –0.1 with aripiprazole (2 mg/day) –0.1 with aripiprazole (5 mg/day) –0.1 with aripiprazole (10 mg/day) –0.1 with placebo	P >0.05	⟷	Not significant

No data from the following reference on this outcome. [55]

Aripiprazole versus haloperidol:

See treatment option on haloperidol, p 37 .

Aripiprazole versus olanzapine:

See treatment option on olanzapine, p 55 .

Aripiprazole versus risperidone:

See treatment option on risperidone, p 92 .

Aripiprazole versus ziprasidone:

See treatment option on ziprasidone, p 111 .

Aripiprazole versus first-generation antipsychotic drugs:

We found one systematic review (search date 2006, 5 RCTs, 2049 people). [11]

Symptom severity

Compared with first-generation antipsychotic drugs Aripiprazole seems as effective at improving positive and negative symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[11] Systematic review	1983 people 4 RCTs in this analysis	**Hedges' adjusted g effect size for positive symptoms (Positive and Negative Syndrome Scale [PANSS])**	Effect size +0.03 95% CI –0.06 to +0.12	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with aripiprazole with first-generation antipsychotic drugs Absolute results not reported			
[11] Systematic review	2409 people 5 RCTs in this analysis	**Hedges' adjusted g effect size for negative symptoms (PANSS)** with aripiprazole with first-generation antipsychotic drugs Absolute results not reported	Effect size –0.09 95% CI –0.19 to +0.01	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [11]

Further information on studies

[11] The first-generation antipsychotics may all be haloperidol but it is not clear from the systematic review. Adverse effects were reported for haloperidol only. Some studies included patients that had disorders with diagnoses other than schizophrenia (e.g., schizophreniform disorder, schizoaffective disorder, psychotic state).

[54] The study was funded by the manufacturers of aripiprazole. Missing data were accounted for by last observation carried forward (LOCF). There is selective reporting in that only the most common adverse effects (occurring in 5% or more patients) were reported. No details of the blinding procedures were reported. The effect of aripiprazole reducing prolactin more than placebo is unexpected and unexplained. It may be related to the antipsychotics that the patients were on previously, but these were not reported.

[55] The study was funded by the manufacturers of aripiprazole. There was high attrition (47%) and missing data were accounted for by LOCF. There is selective reporting in that only the most common adverse effects (occurring in 5% or more patients) were reported. No details of the randomisation or blinding procedures were reported. Only results to week 3 are reported here because patients that were not responding were allowed to transfer to treatment with open-label aripiprazole at this point. No adverse events are reported here because all adverse events assessments were reported in the study at week 6.

Comment: There is some evidence that aripiprazole is superior to placebo at doses of at least 10 mg daily for positive symptoms. Evidence regarding the efficacy over placebo for negative symptoms is equivocal and there is no clear dose-response relationship. Aripiprazole may be inferior to olanzapine for treatment of overall symptoms and there is no evidence of a difference between aripiprazole and risperidone or first-generation antipsychotics for positive or negative symptoms. There is no conclusive evidence regarding any difference between ziprasidone and aripiprazole.

Aripiprazole may be associated with akathisia, extrapyramidal symptoms, parkinsonism, and tremor, although adverse effects are not systematically tested in the placebo-controlled trials. Aripiprazole may be superior to haloperidol for extrapyramidal symptoms and sedation and similar to other second-generation antipsychotics for extrapyramidal symptoms and cardiac effects. Aripiprazole may be associated with decrease in prolactin, although we are unclear as to whether this effect is clinically significant. The extent of weight gain associated with aripiprazole seems comparable to that with haloperidol and risperidone and less than that with olanzapine.

Most studies are short term, which makes it difficult to draw robust conclusions regarding the efficacy or adverse effects of aripiprazole in the longer term.

Clinical guide:
There is evidence of efficacy in some RCTs using a range of doses in different populations. When choosing between aripiprazole and other antipsychotics, adverse-effect profiles should be taken into consideration. Long-term RCTs looking at aripiprazole treatment would be feasible and should be undertaken.

OPTION SERTINDOLE New

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Sertindole may be as effective as either haloperidol or risperidone for positive or negative symptoms. Sertindole may be associated with fewer extrapyramidal symptoms than haloperidol and less akathisia and parkinsonism than risperidone. However, sertindole may be associated with more weight gain than either haloperidol or risperidone and substantially more cardiac effects and sexual dysfunction than risperidone.
- Following safety concerns regarding possible risks of cardiac arrhythmias in some patients, it is recommended that sertindole should only be used if regular cardiac monitoring takes place to help minimise any risks.

Benefits and harms

Sertindole versus haloperidol:
See treatment option on haloperidol, p 37 .

Sertindole versus risperidone:
See treatment option on risperidone , p 92 .

Further information on studies

Comment: We only found a small number of studies of sertindole and these showed no evidence of a difference compared with either haloperidol or risperidone for positive or negative symptoms. Sertindole may be associated with fewer extrapyramidal symptoms than haloperidol and less akathisia and parkinsonism than risperidone. Sertindole may be associated with more weight gain than either haloperidol or risperidone and substantially more cardiac effects and sexual dysfunction than risperidone.

Clinical guide:
Following safety concerns regarding possible risks of cardiac arrhythmias in some patients, it is recommended that sertindole should only be used if regular cardiac monitoring takes place to help minimise any risks.

OPTION PALIPERIDONE New

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Paliperidone is more effective than placebo for overall symptoms of schizophrenia, is as effective as olanzapine, and may be more effective than quetiapine in the short term.
- Paliperidone may be associated with increased salivation, tachycardia, sleepiness, extrapyramidal symptoms, hypertonia, increased prolactin, and weight gain.

Benefits and harms

Paliperidone versus placebo:
We found one systematic review (search date 2008, 8 RCTs, 2567 people). [37]

Symptom severity

Compared with placebo Paliperidone seems more effective at improving overall symptoms in people with schizophrenia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[37] Systematic review	1305 people 7 RCTs in this analysis	**Mean difference in average change in Positive and Negative Syndrome Scale (PANSS) total score** with paliperidone with placebo Absolute results not reported	Mean difference –7.80 95% CI –8.38 to –7.22	○○○	paliperidone

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[37] Systematic review	767 people 3 RCTs in this analysis	**Use of anticholinergic medication** with paliperidone (3–15 mg/day) with placebo Absolute results not reported	RR 1.33 95% CI 1.00 to 1.78	⟷	Not significant
[37] Systematic review	508 people 2 RCTs in this analysis	**Decreased salivation** with paliperidone (6–12 mg/day) with placebo Absolute results not reported	RR 4.12 95% CI 0.96 to 17.73	⟷	Not significant
[37] Systematic review	793 people 2 RCTs in this analysis	**Increased salivation** with paliperidone (6–12 mg/day) with placebo Absolute results not reported	RR 5.41 95% CI 1.30 to 22.42	●●●	placebo
[37] Systematic review	156 people 2 RCTs in this analysis	**Hypertension** with paliperidone with placebo Absolute results not reported	RR 2.27 95% CI 0.39 to 13.35	⟷	Not significant
[37] Systematic review	605 people 2 RCTs in this analysis	**Hypotension** with paliperidone with placebo Absolute results not reported	RR 4.66 95% CI 0.89 to 24.46	⟷	Not significant
[37] Systematic review	683 people 3 RCTs in this analysis	**Prolonged QTc LD** with paliperidone with placebo Absolute results not reported	RR 2.19 95% CI 0.48 to 9.96	⟷	Not significant
[37] Systematic review	1638 people 5 RCTs in this analysis	**Tachycardia** with paliperidone with placebo Absolute results not reported	RR 1.88 95% CI 1.28 to 2.76	●○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[37] Systematic review	216 people Data from 1 RCT	**Mean difference in change from baseline in QTc LD (ms)** with paliperidone (6 mg/day) with placebo Absolute results not reported	Mean difference 1.50 ms 95% CI 1.12 ms to 1.88 ms	○○○	placebo
[37] Systematic review	216 people Data from 1 RCT	**Mean difference in change from baseline in QTc LD (ms)** with paliperidone (12 mg/day) with placebo Absolute results not reported	Mean difference –1.80 ms 95% CI –2.16 ms to –1.44 ms	○○○	paliperidone
[37] Systematic review	877 people 5 RCTs in this analysis	**Mean difference in change from baseline in cholesterol (mmol/L)** with paliperidone with placebo Absolute results not reported	Mean difference 0.12 mmol/L 95% CI 0.00 mmol/L to 0.24 mmol/L	↔	Not significant
[37] Systematic review	1876 people 6 RCTs in this analysis	**Agitation or aggression** with paliperidone with placebo Absolute results not reported	RR 0.64 95% CI 0.44 to 0.95	●○○	paliperidone
[37] Systematic review	1918 people 7 RCTs in this analysis	**Insomnia** with paliperidone with placebo Absolute results not reported	RR 0.89 95% CI 0.69 to 1.15	↔	Not significant
[37] Systematic review	1715 people 5 RCTs in this analysis	**Sleepiness** with paliperidone with placebo Absolute results not reported	RR 1.50 95% CI 1.03 to 2.17	●○○	placebo
[37] Systematic review	352 people 2 RCTs in this analysis	**Fatigue** with paliperidone with placebo Absolute results not reported	RR 0.90 95% CI 0.35 to 2.27	↔	Not significant
[37] Systematic review	568 people 4 RCTs in this analysis	**Mean difference in change from baseline in prolactin (ng/mL), men** with paliperidone (3–15 mg/day) with placebo Absolute results not reported	Mean difference 22.12 ng/mL 95% CI 21.34 ng/mL to 22.89 ng/mL	●○○	placebo
[37] Systematic review	335 people 4 RCTs in this analysis	**Mean difference in change from baseline in prolactin (ng/mL), women** with paliperidone (3–15 mg/day) with placebo Absolute results not reported	Mean difference 82.50 ng/mL 95% CI 78.88 ng/mL to 86.13 ng/mL	○○○	placebo
[37] Systematic review	592 people 4 RCTs in this analysis	**Nausea** with paliperidone with placebo	RR 0.49 95% CI 0.25 to 0.93	●●○	paliperidone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
[37] Systematic review	1007 people 5 RCTs in this analysis	**Mean difference in change from baseline in weight (kg)** with paliperidone with placebo Absolute results not reported	Mean difference 0.13 kg 95% CI 0.06 kg to 0.20 kg	○○○	placebo
[37] Systematic review	573 people 3 RCTs in this analysis	**Mean difference in change from baseline in BMI** with paliperidone with placebo Absolute results not reported	Mean difference 0.46 95% CI 0.30 to 0.63	○○○	placebo
[37] Systematic review	1680 people 6 RCTs in this analysis	**Extrapyramidal symptoms** with paliperidone with placebo Absolute results not reported	RR 2.27 95% CI 1.31 to 3.95	●●○	placebo
[37] Systematic review	1360 people 4 RCTs in this analysis	**Hyperkinesia** with paliperidone (3–15 mg/day) with placebo Absolute results not reported	RR 1.67 95% CI 0.97 to 2.89	↔	Not significant
[37] Systematic review	1225 people 5 RCTs in this analysis	**Hypotonia** with paliperidone with placebo Absolute results not reported	RR 3.24 95% CI 1.46 to 7.22	●●○	placebo
[37] Systematic review	352 people 2 RCTs in this analysis	**Tremor** with paliperidone with placebo Absolute results not reported	RR 1.36 95% CI 0.75 to 2.47	↔	Not significant
[37] Systematic review	352 people 2 RCTs in this analysis	**Akathisia** with paliperidone with placebo Absolute results not reported	RR 1.43 95% CI 0.58 to 3.52	↔	Not significant
[37] Systematic review	156 people 2 RCTs in this analysis	**Tardive dyskinesia** with paliperidone with placebo Absolute results not reported	RR 3.00 95% CI 0.13 to 69.70	↔	Not significant
[37] Systematic review	1032 people 4 RCTs in this analysis	**Gynaecomastia, men** with paliperidone with placebo Absolute results not reported	RR 0.99 95% CI 0.04 to 23.90	↔	Not significant
[37] Systematic review	1187 people 5 RCTs in this analysis	**Impotence, men** with paliperidone with placebo Absolute results not reported	RR 0.70 95% CI 0.16 to 3.03	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[37] Systematic review	938 people 5 RCTs in this analysis	**Amenorrhoea/dysmenorrhoea, women** with paliperidone with placebo Absolute results not reported	RR 1.46 95% CI 0.31 to 6.92	⟷	Not significant
[37] Systematic review	1763 people 5 RCTs in this analysis	**Abnormal sexual function** with paliperidone with placebo Absolute results not reported	RR 0.61 95% CI 0.12 to 3.11	⟷	Not significant
[37] Systematic review	1566 people 5 RCTs in this analysis	**Suicide attempt** with paliperidone with placebo Absolute results not reported	RR 0.62 95% CI 0.22 to 1.77	⟷	Not significant

Paliperidone versus olanzapine:

See treatment option on olanzapine, p 55 .

Paliperidone versus quetiapine:

See treatment option on quetiapine, p 80 .

Further information on studies

[37] All studies were considered at high risk of selective reporting and other bias. All studies were funded by the company that makes paliperidone and most were short term. For the paliperidone versus placebo comparison, the data from one study [41] included in the meta-analysis is presumed to be from the entire study period — i.e., including the phase during which patients were allowed to receive additive therapy.

Comment:

Most paliperidone studies are placebo-controlled and show evidence of paliperidone being efficacious for overall symptoms. A systematic review containing three studies showed no evidence of a difference between paliperidone and olanzapine for overall symptoms, while one RCT showed evidence of superiority of paliperidone over quetiapine for positive and negative symptoms at 14 days.

Paliperidone may be associated with increased salivation, tachycardia, sleepiness, extrapyramidal symptoms, hypertonia, and prolactin, although there is no evidence of a corresponding increase in prolactin-associated adverse effects over placebo. Paliperidone may also be associated with a small amount of weight gain compared with placebo, although less than that with olanzapine or quetiapine. Evidence regarding cardiac effects is equivocal. Paliperidone may be associated with less agitation/aggression and nausea than placebo and less sleepiness and cholesterol increase than olanzapine. Paliperidone does not seem to be associated with akathisia, although there is evidence that it is associated with more extrapyramidal symptoms in general and with more parkinsonism than olanzapine and quetiapine.

Most studies were short term, making it difficult to draw robust conclusions about efficacy or adverse effects in the longer term.

Clinical guide:
Paliperidone is a metabolite of risperidone, and it is reasonable to assume that its efficacy will be similar. When choosing between paliperidone and other antipsychotics, adverse-effect profiles should be taken into consideration. Long-term RCTs looking at paliperidone treatment would be feasible and should be undertaken.

OPTION FLUPENTIXOL New

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Flupentixol may be as effective as risperidone for treatment of positive or negative symptoms, in people with predominantly negative symptoms. Flupentixol may be associated with more adverse effects than risperidone; however, evidence is limited.

Benefits and harms

Flupentixol versus risperidone:
See treatment option on risperidone, p 92 .

Further information on studies

[46] In this RCT, there was high attrition in the longer term (45%) and last observation carried forward was used in the analysis. The study gave no information regarding the method of randomisation. Otherwise, it was well reported.

Comment: We found very little evidence regarding flupentixol. One small RCT showed no difference between flupentixol and risperidone for treatment of positive or negative symptoms, in patients with predominantly negative symptoms. Flupentixol may be associated with more adverse effects in general than risperidone, but there is no evidence of any difference for specific adverse effects, such as akathisia, extrapyramidal symptoms, insomnia, or tremor.

OPTION DEPOT FLUPENTIXOL DECANOATE New

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- We found no systematic review or RCTs that fulfilled the inclusion criteria for this *Clinical Evidence* review.

Benefits and harms

Depot flupentixol decanoate:
We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
On the basis of observational evidence and experience, most clinicians regard depot flupentixol decanoate to be effective, despite the absence of strong evidence from RCTs of efficacy. RCTs looking at depot flupentixol decanoate therapy would be feasible and should be undertaken.

OPTION ZUCLOPENTHIXOL New

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- We found no systematic review or RCTs that fulfilled the inclusion criteria for this *Clinical Evidence* review.

Benefits and harms

Zuclopenthixol:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
On the basis of observational evidence and experience, most clinicians regard zuclopenthixol to be effective, despite the absence of strong evidence from RCTs of efficacy. RCTs looking at zuclopenthixol therapy would be feasible and should be undertaken.

OPTION DEPOT ZUCLOPENTHIXOL DECANOATE New

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- We found no systematic review or RCTs that fulfilled the inclusion criteria for this *Clinical Evidence* review.

Benefits and harms

Depot zuclopenthixol decanoate:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
On the basis of observational evidence and experience, most clinicians regard depot zuclopenthixol decanoate to be effective, despite the absence of strong evidence of efficacy from RCTs. RCTs looking at depot zuclopenthixol decanoate therapy would be feasible and should be undertaken.

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

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

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- In people resistant to standard antipsychotic drugs, clozapine may improve symptoms compared with first-generation antipsychotic agents.
- Clozapine has been associated with agranulocytosis.

Benefits and harms

Clozapine versus first-generation antipsychotic drugs:

We found one systematic review (search date 2008, 6 RCTs) comparing clozapine versus first-generation antipsychotic drugs in people resistant to standard treatment. [19]

Symptom severity

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[19] Systematic review	370 people 4 RCTs in this analysis 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	**Proportion of people who improved , 6 to 12 weeks** with clozapine with standard antipsychotic drugs Absolute results not reported	RR for no improvement compared with standard antipsychotic drugs 0.71 95% CI 0.64 to 0.79	●○○	clozapine
[19] Systematic review	648 people 2 RCTs in this analysis 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	**Proportion of people who improved , 12 to 24 months** with clozapine with standard antipsychotic drugs Absolute results not reported	RR for no improvement compared with standard antipsychotic drugs 0.83 95% CI 0.76 to 0.91	●○○	clozapine

Relapse

Compared with first-generation antipsychotic drugs Clozapine may be more effective at reducing the proportion of people who relapse in the long term (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Relapse					
[19] Systematic review	396 people 4 RCTs in this analysis 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	**Relapse , short term** with clozapine with first-generation antipsychotics Absolute results not reported Haloperidol and chlorpromazine used as comparators	RR 1.04 95% CI 0.61 to 1.78	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	423 people Data from 1 RCT 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	**Relapse , long term** with clozapine (100–900 mg/day) with haloperidol (5–30 mg/day) Absolute results not reported	RR 0.17 95% CI 0.10 to 0.30	●●●	clozapine

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] Systematic review	827 people 5 RCTs in this analysis 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	**Blood problems** with clozapine with haloperidol/chlorpromazine Absolute results not reported	RR 1.90 95% CI 0.97 to 3.71	⟷	Not significant
[19] Systematic review	827 people 5 RCTs in this analysis 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	**Drowsiness** with clozapine with haloperidol/chlorpromazine Absolute results not reported	RR 1.22 95% CI 1.11 to 1.34	●○○	first-generation antipsychotic drugs
[19] Systematic review	827 people 5 RCTs in this analysis 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	**Too much salivation** with clozapine with haloperidol/chlorpromazine Absolute results not reported	RR 2.01 95% CI 1.74 to 2.32	●●○	first-generation antipsychotic drugs

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	383 people 3 RCTs in this analysis 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	**Too little salivation** with clozapine with haloperidol/chlorpromazine Absolute results not reported	RR 0.27 95% CI 0.16 to 0.45	●●○	clozapine
[19] Systematic review	484 people 3 RCTs in this analysis 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	**Weight gain** with clozapine with haloperidol/chlorpromazine Absolute results not reported	RR 1.33 95% CI 1.11 to 1.59	●○○	first-generation antipsychotic drugs
[19] Systematic review	521 people 4 RCTs in this analysis 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	**Movement disorder** with clozapine with haloperidol/chlorpromazine Absolute results not reported	RR 0.77 95% CI 0.67 to 0.90	●○○	clozapine

Further information on studies

[19] The updated systematic review is unchanged for the benefits. In the previous update of this review, adverse effects were not included from this systematic review, but we now consider that they are worth including. Blood problems were broadly defined as any blood problem requiring withdrawal from the trial, leukopenia, or neutropenia. Two of the included trials used dose ranges of chlorpromazine above the UK licensed dose (up to 1.8 g/day).

Comment: There is some evidence of efficacy of clozapine over first-generation antipsychotics for clinical improvement of treatment-resistant patients in the short and long term, and in prevention of relapse in the long term. However, the authors of the systematic review state that the studies were weak and may be prone to bias in favour of clozapine. Clozapine may be associated with more weight gain, drowsiness, and hypersalivation than first-generation antipsychotics, although less hyposalivation and movement disorder. There may be an increase in blood problems with clozapine com-

pared with first-generation antipsychotics, but the statistical and clinical significance of this effect in the systematic review may have been compromised by its broad definition.

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. [57]

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

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- In people resistant to standard antipsychotic drugs, we don't know whether clozapine is more effective than other second-generation antipsychotic drugs as we found insufficient evidence.

Benefits and harms

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. [58]

Symptom severity

Compared with olanzapine, risperidone, and 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).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[58] Systematic review	315 people 4 RCTs in this analysis 5 (595 people) out of the total of 8 RCTs identified by the review were in people with treatment-resistant schizophrenia (see Comment)	**Change in Clinical Global Impression scale (CGI)** with clozapine with olanzapine, risperidone, and zotepine Absolute results not reported	WMD –0.10 95% CI –0.34 to +0.15 The number of people studied was too small to detect a clinically important difference between groups	⟷	Not significant
[58] Systematic review	351 people 5 RCTs in this analysis 5 (595 people) out of the total of 8 RCTs identified by the review were in people with treatment-resistant schizophrenia (see Comment)	**Proportion with <20% improvement in Brief Psychiatric Rating Scale (BPRS) or Positive and Negative Syndrome Scale (PANSS)** 83/173 (48%) with clozapine 81/178 (46%) with olanzapine, risperidone, and zotepine	RR 0.93 95% CI 0.75 to 1.16 The number of people studied was too small to detect a clinically important difference between groups	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[58] Systematic review	305 people 5 (595 people) out of the total of 8 RCTs identified by the review were in people with treatment-resistant schizophrenia (see Comment)	**Extrapyramidal adverse effects** with clozapine with other second-generation antipsychotic agents (mainly olanzapine and risperidone) Absolute results not reported See also further information on studies for additional information on adverse effects	RR 0.3 95% CI 0.1 to 0.6 NNT 6 95% CI 4 to 9	●●○	clozapine
[58] Systematic review	558 people 4 RCTs in this analysis 5 (595 people) out of the total of 8 RCTs identified by the review were in people with treatment-resistant schizophrenia	**Rate of blood dyscrasias** 7/281 (3%) with clozapine 5/277 (2%) with other second-generation antipsychotic agents (mainly olanzapine and risperidone)	RR 0.76 95% CI 0.27 to 2.18	↔	Not significant

Clozapine versus olanzapine:

We found one systematic review [35] (search date 2004, 2 RCTs, 330 people; including one RCT identified by the previous review [58]) and two subsequent RCTs comparing clozapine versus olanzapine. [59] [60]

Symptom severity

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[35] Systematic review	330 people 2 RCTs in this analysis	**Proportion with no important clinical response (defined as a 40% reduction on Clinical Global Impression scale [CGI]) , 18 weeks** 86/166 (52%) with olanzapine 96/164 (59%) with clozapine	RR 0.89 95% CI 0.73 to 1.08	↔	Not significant
[59] RCT	25 children and adolescents aged 7 to 16 years with onset of symptoms of schizophrenia before age 13 years and no response to treatment with 2 antipsychotic medications	**Change in Brief Psychiatric Rating Scale (BPRS) score , 8 weeks** –9 with clozapine –1 with olanzapine	P = 0.12 The RCT reported a trend in improved symptoms that favoured clozapine	↔	Not significant
[59] RCT	25 children and adolescents aged 7 to 16 years with onset of symptoms of schizophrenia before age 13 years and no response to treat-	**Change in Schedule for the Assessment of Negative symptom score , 8 weeks** –22 with clozapine –8 with olanzapine	P = 0.08 The RCT reported a trend in improved symptoms that favoured clozapine	↔	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	ment with 2 antipsychotic medications				
[59] RCT	25 children and adolescents aged 7 to 16 years with onset of symptoms of schizophrenia before age 13 years and no response to treatment with 2 antipsychotic medications	**Change in Schedule for the Assessment of Positive symptom score , 8 weeks** –12 with clozapine +3 with olanzapine	P = 0.14 The RCT reported a trend in improved symptoms that favoured clozapine	⟷	Not significant
[59] RCT	25 children and adolescents aged 7 to 16 years with onset of symptoms of schizophrenia before age 13 years and no response to treatment with 2 antipsychotic medications	**Change in CGI Severity scale , 8 weeks** –1.1 with clozapine –0.5 with olanzapine	P = 0.39 The RCT reported a trend in improved symptoms that favoured clozapine	⟷	Not significant
[60] RCT	40 people with continual positive symptoms despite trials of 2 or more antipsychotic medications from different chemical classes	**Least-squares mean difference in Positive and Negative Syndrome Scale (PANSS) total score , 6 weeks** with clozapine (dose range 75–700 mg) with olanzapine (dose range 20–40 mg) Absolute results not reported	Mean difference –1.90 P = 0.61	⟷	Not significant
[60] RCT	40 people with continual positive symptoms despite trials of 2 or more antipsychotic medications from different chemical classes	**Least-squares mean difference in PANSS total score , 6 months** with clozapine (dose range 275–900 mg) with olanzapine (dose range 30–45 mg) Absolute results not reported	Mean difference 0.41 P = 0.92	⟷	Not significant
[60] RCT	40 people with continual positive symptoms despite trials of 2 or more antipsychotic medications from different chemical classes	**Least-squares mean difference in CGI score , 6 weeks** with clozapine (dose range 75–700 mg) with olanzapine (dose range 20–40 mg) Absolute results not reported	Mean difference –0.26 P = 0.75	⟷	Not significant
[60] RCT	40 people with continual positive symptoms despite trials of 2 or more antipsychotic medications from different chemical classes	**Least-squares mean difference in CGI score , 6 months** with clozapine (dose range 275–900 mg) with olanzapine (dose range 30–45 mg) Absolute results not reported	Mean difference 0.32 P = 0.76	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[59] RCT	25 children and adolescents aged 7 to 16 years with onset of symptoms of schizophrenia before age 13 years and no response to treatment with 2 antipsychotic medications	**Proportion of total adverse effects that were considered to be treatment related** 55/386 (14%) with clozapine 28/418 (7%) with olanzapine	P <0.001	○○○	olanzapine
[59] RCT	25 children and adolescents aged 7 to 16 years with onset of symptoms of schizophrenia before age 13 years and no response to treatment with 2 antipsychotic medications	**Hypertension** 7/11 (64%) with clozapine 1/11 (9%) with olanzapine	P = 0.02	○○○	olanzapine
[59] RCT	25 children and adolescents aged 7 to 16 years with onset of symptoms of schizophrenia before age 13 years and no response to treatment with 2 antipsychotic medications	**Tachycardia (>100 bpm)** 7/10 (70%) with clozapine 2/12 (17%) with olanzapine	P = 0.03	○○○	olanzapine
[60] RCT	40 people with continual positive symptoms despite trials of 2 or more antipsychotic medications from different chemical classes	**Least-squares mean difference in Abnormal Involuntary Movement Scale (AIMS) total score , 6 weeks** with clozapine (dose range 75–700 mg) with olanzapine (dose range 20–40 mg) Absolute results not reported	Mean difference 1.44 P = 0.07	⟷	Not significant
[60] RCT	40 people with continual positive symptoms despite trials of 2 or more antipsychotic medications from different chemical classes	**Least-squares mean difference in AIMS total score , 6 months** with clozapine (dose range 275–900 mg) with olanzapine (dose range 30–45 mg) Absolute results not reported	Mean difference –0.89 P = 0.30	⟷	Not significant
[60] RCT	40 people with continual positive symptoms despite trials of 2 or more antipsychotic medications from different chemical classes	**Least-squares mean difference in Simpson-Angus Scale (SAS) total score , 6 weeks** with clozapine (dose range 75–700 mg) with olanzapine (dose range 20–40 mg) Absolute results not reported	Mean difference 1.50 P = 0.04	○○○	olanzapine
[60] RCT	40 people with continual positive symptoms despite trials of 2 or more antipsychotic medications from differ-	**Least-squares mean difference in SAS total score , 6 months** with clozapine (dose range 275–900 mg)	Mean difference 0.66 P = 0.40	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	ent chemical classes	with olanzapine (dose range 30–45 mg) Absolute results not reported			
[60] RCT	40 people with continual positive symptoms despite trials of 2 or more antipsychotic medications from different chemical classes	**Least-squares mean difference in weight (lb) , 6 weeks** with clozapine (dose range 75–700 mg) with olanzapine (dose range 20–40 mg) Absolute results not reported	Mean difference –2.41 lb P = 0.56	⟷	Not significant
[60] RCT	40 people with continual positive symptoms despite trials of 2 or more antipsychotic medications from different chemical classes	**Least-squares mean difference in weight (lb) , 6 months** with clozapine (dose range 275–900 mg) with olanzapine (dose range 30–45 mg) Absolute results not reported	Mean difference –12.29 lb P = 0.01	○○○	olanzapine

No data from the following reference on this outcome. [35]

Clozapine versus ziprasidone:

We found one RCT comparing clozapine with ziprasidone. [61]

Symptom severity

Compared with ziprasidone Clozapine seems as effective at improving positive and negative symptoms in people with treatment-resistant schizophrenia at 18 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[61] RCT	146 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Mean change from baseline in Positive and Negative Syndrome Scale (PANSS) total score , 18 weeks** –25.0 with clozapine (250–600 mg/day) –24.2 with ziprasidone (80–160 mg/day)	Reported as not significant	⟷	Not significant
[61] RCT	146 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Mean change from baseline in Clinical Global Impression scale (CGI) Severity score , 18 weeks** –0.6 with clozapine (250–600 mg/day) –0.6 with ziprasidone (80–160 mg/day)	Reported as not significant	⟷	Not significant
[61] RCT	146 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**CGI Improvement score at endpoint , 18 weeks** 3.3 with clozapine (250–600 mg/day) 3.2 with ziprasidone (80–160 mg/day)	Reported as not significant	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[61] RCT	134 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Mean change from baseline in Simpson-Angus Scale score** –0.21 with clozapine (250–600 mg/day) –0.6 with ziprasidone (80–160 mg/day)	Reported as not significant	⟷	Not significant
[61] RCT	139 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Mean change from baseline in Barnes Akathisia Scale score** –0.37 with clozapine (250–600 mg/day) –0.22 with ziprasidone (80–160 mg/day)	Reported as not significant	⟷	Not significant
[61] RCT	139 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Mean change from baseline in Abnormal Involuntary Movement Scale (AIMS) score** –0.15 with clozapine (250–600 mg/day) –0.08 with ziprasidone (80–160 mg/day)	Reported as not significant	⟷	Not significant
[61] RCT	146 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Mean difference in change from baseline in weight (kg)** 0.8 kg with clozapine (250–600 mg/day) 2.6 kg with ziprasidone (80–160 mg/day)	P <0.001	○○○	clozapine
[61] RCT	146 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Change from baseline in median prolactin (ng/mL)** –5.0 ng/mL with clozapine (250–600 mg/day) –6.5 ng/mL with ziprasidone (80–160 mg/day)	Significance assessment not performed		
[61] RCT	146 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Mean change from baseline in heart rate (bpm)** 2.0 bpm with clozapine (250–600 mg/day) 8.0 bpm with ziprasidone (80–160 mg/day)	Reported as not significant	⟷	Not significant
[61] RCT	146 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Mean change from baseline in QTc (ms)** +6.0 ms with clozapine (250–600 mg/day) –3.6 ms with ziprasidone (80–160 mg/day)	Reported as not significant	⟷	Not significant
[61] RCT	146 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Mean change from baseline in total cholesterol** –5.0 with clozapine (250–600 mg/day) +2.0 with ziprasidone (80–160 mg/day)	P <0.05	○○○	ziprasidone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[61] RCT	146 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Incidence of increased salivation** 0% with clozapine (250–600 mg/day) 29% with ziprasidone (80–160 mg/day) Absolute numbers not reported	Significance assessment not performed		
[61] RCT	146 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Incidence of tachycardia** 3% with clozapine (250–600 mg/day) 29% with ziprasidone (80–160 mg/day) Absolute numbers not reported	Significance assessment not performed		
[61] RCT	146 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Incidence of somnolence** 4% with clozapine (250–600 mg/day) 23% with ziprasidone (80–160 mg/day) Absolute numbers not reported	Significance assessment not performed		
[61] RCT	146 people with resistance and/or intolerance to at least 3 acute cycles of different antipsychotics in the past 5 years	**Incidence of insomnia** 10% with clozapine (250–600 mg/day) 3% with ziprasidone (80–160 mg/day) Absolute numbers not reported	Significance assessment not performed		

Further information on studies

[58] The review 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. 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.

[60] This RCT was reasonably well carried out with appropriate methods used to account for withdrawal, although relatively few adverse effects were reported on and the sample size was small. The olanzapine doses were above the UK licensed dose range.

[61] The paper for this RCT states that the study was designed as an equivalence study, but only superiority tests are reported. The paper also claims that a repeated measures model was used to analyse the data, but this does not seem to have been reported. Instead, last observation carried forward was used to account for missing data. Withdrawal over 18 weeks was 38%. There may be under-reporting of adverse effects as only those that occurred in at least 10% of patients were reported. The study was sponsored and carried out by the manufacturer of ziprasidone.

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.

Although we found limited evidence on this comparison, in these RCTs we found that clozapine showed a similar level of efficacy to other second-generation antipsychotics in treatment-resistant people. Clozapine may be associated with similar levels of extrapyramidal symptoms and more cardiac effects than other second-generation antipsychotics. Clozapine may be associated with less weight gain than with olanzapine but more than with ziprasidone; and more increased salivation and somnolence but less insomnia than with ziprasidone. Clozapine has been associated with agranulocytosis (see comment of treatment option clozapine versus first-generation antipsychotic drugs (treatment-resistant disease, p 133)

Clinical guide:
The standard measure for improvement in many of the studies reviewed here is defined as at least 20% reduction in Brief Psychiatric Rating Scale (BPRS) or Positive and Negative Syndrome Scale (PANSS) total score. This improvement in BPRS and PANSS scores correlates with only minimal improvement in the severity of clinical symptoms. [62] In treatment-resistant patients, who by definition have shown no improvement in clinical symptoms with previous treatments, even such improvement may or may not be clinically important.

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

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- In people resistant to standard antipsychotic agents, we found insufficient evidence on the effects of second-generation antipsychotics (other than clozapine) versus first-generation antipsychotics.

Benefits and harms

Olanzapine versus chlorpromazine:
We found one systematic review (search date 2004, 1 RCT, 84 people with schizophrenia). [35]

Symptom severity

Olanzapine versus chlorpromazine We don't know how olanzapine and chlorpromazine compare at reducing psychotic symptoms at 8 weeks in people with treatment-resistant schizophrenia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[35] Systematic review	84 people with schizophrenia Data from 1 RCT See further information on studies for further details of population studied	**Proportion with no important response (defined as <20% reduction on the Clinical Global Impression scale [CGI]) , 8 weeks** 39/42 (93%) with olanzapine (25 mg/day) 42/42 (100%) with chlorpromazine	RR 0.93 95% CI 0.85 to 1.01 The RCT is likely to have been too small to detect a clinically important difference between groups	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[35] Systematic review	84 people with schizophrenia Data from 1 RCT See further information on studies for further details of population studied	**Any extrapyramidal adverse effect , 8 weeks** 12/42 (29%) with olanzapine (25 mg/day) 21/42 (50%) with chlorpromazine	RR 0.57 95% CI 0.32 to 1.01 The RCT is likely to have been too small to detect a clinically important difference between groups	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[35] Systematic review	84 people with schizophrenia Data from 1 RCT See further information on studies for further details of population studied	**Nausea and vomiting , 8 weeks** 5/42 (12%) with olanzapine (25 mg/day) 8/42 (19%) with chlorpromazine	RR 0.63 95% CI 0.22 to 1.75 The RCT is likely to have been too small to detect a clinically important difference between groups	⟷	Not significant

Ziprasidone versus chlorpromazine:

We found one RCT (306 treatment-resistant people). [63]

Symptom severity

Ziprasidone versus chlorpromazine We don't know how ziprasidone and chlorpromazine compare at improving psychotic symptoms at 6 to 12 weeks in people with treatment-resistant schizophrenia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[63] RCT	306 treatment-resistant people See further information on studies for further details of population studied	**Clinical Global Impression scale (CGI) Severity scores , 6 weeks** with ziprasidone (80–160 mg/day) with chlorpromazine (200–1200 mg/day) Absolute results not reported	P less-than or equal to 0.05	○○○	ziprasidone
[63] RCT	306 treatment-resistant people See further information on studies for further details of population studied	**Positive and Negative Syndrome Scale (PANSS) negative subscale scores , 12 weeks** with ziprasidone (80–160 mg/day) with chlorpromazine (200–1200 mg/day) Absolute results not reported	P <0.05	○○○	ziprasidone
[63] RCT	306 treatment-resistant people See further information on studies for further details of population studied	**Brief Psychiatric Rating Scale (BPRS) score of 20% or more , 12 weeks** 58% with ziprasidone (80–160 mg/day) 55% with chlorpromazine (200–1200 mg/day) Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant
[63] RCT	306 treatment-resistant people See further information on studies for further details of population studied	**PANSS total score , 12 weeks** with ziprasidone (80–160 mg/day) with chlorpromazine (200–1200 mg/day) Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[63] RCT	306 treatment-resistant people See further information on studies for further details of population studied	**Extrapyramidal symptoms , 6 weeks** 49/152 (32%) with ziprasidone (80–160 mg/day) 54/154 (35%) with chlorpromazine (200–1200 mg/day) Extrapyramidal symptoms were the most frequently reported adverse effects	Significance not assessed		

Aripiprazole versus perphenazine:

We found one RCT. [64]

Symptom severity

Aripiprazole versus perphenazine We don't know how aripiprazole and perphenazine compare at improving symptoms at 6 weeks in people with treatment-resistant schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[64] RCT	300 treatment-resistant people	**Positive and Negative Syndrome Scale (PANSS) total score , 6 weeks** –9.8 with aripiprazole –10.5 with perphenazine Change reported is mean change in score from baseline (last observation carried forward [LOCF] analysis)	Reported as not significant P value not reported	⟷	Not significant
[64] RCT	300 treatment-resistant people	**Brief Psychiatric Rating Scale score , 6 weeks** –2.0 with aripiprazole –2.0 with perphenazine Change reported is mean change in score from baseline (LOCF analysis)	Reported as not significant P value not reported	⟷	Not significant
[64] RCT	300 treatment-resistant people	**Clinical Global Impression scale (CGI) Severity scores , 6 weeks** –0.3 with aripiprazole –0.3 with perphenazine Change reported is mean change in score from baseline (LOCF analysis)	Reported as not significant P value not reported	⟷	Not significant
[64] RCT	300 treatment-resistant people	**Proportion of people classed as responding (defined as a 30% or more decrease in PANSS total score) , 6 weeks** 40/150 (27%) with aripiprazole 36/144 (25%) with perphenazine	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Change reported is mean change in score from baseline (LOCF analysis)			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[64] RCT	300 treatment-resistant people	**Proportion of people with clinically significant high levels of prolactin , 6 weeks** 6/135 (4%) with aripiprazole 79/137 (58%) with perphenazine	P <0.001	○○○	aripiprazole
[64] RCT	300 treatment-resistant people	**Proportion of people with extrapyramidal symptoms** 21/153 (14%) with aripiprazole 28/144 (19%) with perphenazine	Significance not assessed		
[64] RCT	300 treatment-resistant people	**Proportion of people with insomnia** 37/153 (24%) with aripiprazole 30/144 (21%) with perphenazine Insomnia was reported to be the most common adverse effect	Significance not assessed		

Risperidone versus fluphenazine:

We found one RCT. [65]

Symptom severity

Risperidone compared with fluphenazine We don't know whether risperidone is more effective at improving positive and negative symptoms in people with treatment-resistant schizophrenia (very-low quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[65] RCT **3-armed trial**	26 treatment-resistant people The remaining arm assessed quetiapine	**Brief Psychiatric Rating Scale (BPRS) total score , baseline and 12 weeks** with risperidone (mean dose 4.31 mg/day) with fluphenazine (mean dose 13.2 mg/day) Absolute results not reported	Risperidone 56.00 at baseline *v* 52.15 at 12 weeks Fluphenazine 54.69 at baseline *v* 51.85 at 12 weeks P greater-than or equal to 0.05 for difference in change from baseline	⟷	Not significant
[65] RCT **3-armed trial**	26 treatment-resistant people The remaining arm assessed quetiapine	**Clinical Global Impression scale (CGI) Severity score , baseline and 12 weeks** with risperidone (mean dose 4.31 mg/day) with fluphenazine (mean dose 13.2 mg/day)	Risperidone 5.38 at baseline *v* 5.08 at 12 weeks Fluphenazine 5.38 at baseline *v* 5.15 at 12 weeks P greater-than or equal to 0.05 for difference in change from baseline	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
[65] RCT **3-armed trial**	26 treatment-resistance people The remaining arm assessed quetiapine	**Change from baseline in BPRS positive symptom score , 12 weeks** –1.77 with risperidone (mean dose 4.31 mg/day) –0.92 with fluphenazine (mean dose 13.2 mg/day)	P greater-than or equal to 0.05 for difference in change from baseline	⟷	Not significant
[65] RCT **3-armed trial**	26 treatment-resistant people The remaining arm assessed quetiapine	**Change from baseline in BPRS negative symptom score , 12 weeks** –0.15 with risperidone (mean dose 4.31 mg/day) –0.23 with fluphenazine (mean dose 13.2 mg/day)	P value not reported		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed quetiapine	**Change from baseline in Simpson-Angus Scale score , 12 weeks** –0.13 with risperidone (mean dose 4.31 mg/day) –0.69 with fluphenazine (mean dose 13.2 mg/day)	P greater-than or equal to 0.05	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed quetiapine	**Change from baseline in weight (kg) , 12 weeks** –0.65 kg with risperidone (mean dose 4.31 mg/day) –2.60 kg with fluphenazine (mean dose 13.2 mg/day)	P greater-than or equal to 0.05	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed quetiapine	**Incidence of dyspepsia** 7% with risperidone (mean dose 4.31 mg/day) 23% with fluphenazine (mean dose 13.2 mg/day) Absolute numbers not reported	P greater-than or equal to 0.05	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed quetiapine	**Incidence of somnolence** 38% with risperidone (mean dose 4.31 mg/day) 33% with fluphenazine (mean dose 13.2 mg/day) Absolute numbers not reported	P greater-than or equal to 0.05	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed quetiapine	**Incidence of insomnia** 23% with risperidone (mean dose 4.31 mg/day) 42% with fluphenazine (mean dose 13.2 mg/day) Absolute numbers not reported	P greater-than or equal to 0.05	⟷	Not significant

Quetiapine versus fluphenazine:

We found one RCT. [65]

Symptom severity

Quetiapine compared with fluphenazine We don't know whether quetiapine is more effective at improving positive and negative symptoms in people with treatment-resistant schizophrenia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed risperidone	**Brief Psychiatric Scale (BPRS) total score , baseline and 12 weeks** with quetiapine (mean dose 463.6 mg/day) with fluphenazine (mean dose 13.2 mg/day)	Quetiapine 53.50 at baseline *v* 53.83 at 12 weeks Fluphenazine 54.69 at baseline *v* 51.85 at 12 weeks P greater-than or equal to 0.05 for difference in change from baseline	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed risperidone	**Clinical Global Impression scale (CGI) Severity score , baseline and 12 weeks** with quetiapine (mean dose 463.6 mg/day) with fluphenazine (mean dose 13.2 mg/day)	Quetiapine 5.33 at baseline *v* 5.18 at 12 weeks Fluphenazine 5.38 at baseline *v* 5.15 at 12 weeks P greater-than or equal to 0.05 for difference in change from baseline	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed risperidone	**Change from baseline in BPRS positive symptom score , 12 weeks** –0.67 with quetiapine (mean dose 463.6 mg/day) –0.92 with fluphenazine (mean dose 13.2 mg/day)	P greater-than or equal to 0.05 for difference in change from baseline	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed risperidone	**Change from baseline in BPRS negative symptom score , 12 weeks** +0.42 with quetiapine (mean dose 463.6 mg/day) –0.23 with fluphenazine (mean dose 13.2 mg/day)	P value not reported		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[65] RCT **3-armed trial**	24 treatment-resistant people The remaining arm assessed risperidone	**Change from baseline in Simpson-Angus Scale score , 12 weeks** –1.64 with quetiapine (mean dose 463.6 mg/day) –0.69 with fluphenazine (mean dose 13.2 mg/day)	P greater-than or equal to 0.05	⟷	Not significant
[65] RCT	24 treatment-resistant people	**Change from baseline in weight (kg) , 12 weeks**	P greater-than or equal to 0.05	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	The remaining arm assessed risperidone	–1.2 kg with quetiapine (mean dose 463.6 mg/day) –2.6 kg with fluphenazine (mean dose 13.2 mg/day)			
[65] RCT **3-armed trial**	24 treatment-resistant people The remaining arm assessed risperidone	**Incidence of dyspepsia** 8% with quetiapine (mean dose 463.6 mg/day) 23% with fluphenazine (mean dose 13.2 mg/day) Absolute numbers not reported	P >0.05	⟷	Not significant
[65] RCT **3-armed trial**	24 treatment-resistant people The remaining arm assessed risperidone	**Incidence of somnolence** 25% with quetiapine (mean dose 463.6 mg/day) 33% with fluphenazine (mean dose 13.2 mg/day) Absolute numbers not reported	P >0.05	⟷	Not significant
[65] RCT **3-armed trial**	24 treatment-resistant people The remaining arm assessed risperidone	**Incidence of insomnia** 25% with quetiapine (mean dose 463.6 mg/day) 42% with fluphenazine (mean dose 13.2 mg/day) Absolute numbers not reported	P >0.05	⟷	Not significant

Further information on studies

[35] 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. The review did not specify the duration of treatment-resistant illness of the people included in the RCT.

[63] 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 washout period after the 6-week haloperidol-treatment phase.

[65] The RCT defined treatment resistance as continual positive psychotic symptoms or illness severity despite trials of two antipsychotic medications at doses of at least 600 mg chlorpromazine equivalent and no stable period of good social/occupational functioning in the previous 5 years. Before randomisation, patients were enrolled in a 4–6-week open-label qualification phase during which most were treated with first-generation antipsychotics (other than fluphenazine) and the remainder with olanzapine. Patients only continued the study if they showed no response to treatment during this phase. It is not clear whether there was a washout period after this qualification phase. The sample size for this study was very small and withdrawal was high (50%) but was appropriately accounted for in the analysis using repeated measures methods. The overall test of any differences between quetiapine, risperidone, and fluphenazine in change in negative symptoms gave P <0.05 but pairwise comparisons were not reported. Adverse effects were not reported for one patient in the fluphenazine group.

Comment: There is little evidence of any differences in either efficacy or adverse effects between second-generation antipsychotics (other than clozapine) and first-generation antipsychotics in treatment-resistant patients. However, there are few studies and the existing evidence is mainly low quality and so it is difficult to draw robust conclusions.

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 drug.

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

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- In people resistant to standard antipsychotic agents, we found insufficient evidence on the effects of second-generation antipsychotics (other than clozapine) versus each other.

Benefits and harms

Second-generation antipsychotic agents (other than clozapine) versus risperidone:

We found one RCT. [65]

Symptom severity

Compared with second-generation antipsychotic agents (other than clozapine) We don't know whether risperidone is more effective at improving positive and negative symptoms in people with treatment-resistant schizophrenia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed fluphenazine	**Brief Psychiatric Rating Scale (BPRS) total score , baseline and 12 weeks** with risperidone (mean dose 4.31 mg/day) with quetiapine (mean dose 463.6 mg/day)	Risperidone 56.00 at baseline *v* 52.15 at 12 weeks Quetiapine 53.50 at baseline *v* 53.83 at 12 weeks P greater-than or equal to 0.05 for difference in change from baseline	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed fluphenazine	**Clinical Global Impression scale (CGI) Severity score , baseline and 12 weeks** with risperidone (mean dose 4.31 mg/day) with quetiapine (mean dose 463.6 mg/day)	Risperidone 5.38 at baseline *v* 5.08 at 12 weeks Quetiapine 5.33 at baseline *v* 5.18 at 12 weeks P greater-than or equal to 0.05 for difference in change from baseline	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed fluphenazine	**Change from baseline in BPRS positive symptom score , 12 weeks** –1.77 with risperidone (mean dose 4.31 mg/day) –0.67 with quetiapine (mean dose 463.6 mg/day)	P greater-than or equal to 0.05 for difference in change from baseline P value for between-group difference not reported	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed fluphenazine	**Change from baseline in BPRS negative symptom score , 12 weeks** –0.15 with risperidone (mean dose 4.31 mg/day) +0.42 with quetiapine (mean dose 463.6 mg/day)	P value not reported		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed fluphenazine	**Change from baseline in Simpson-Angus Scale score , 12 weeks** –1.3 with risperidone (mean dose 4.31 mg/day) –1.64 with quetiapine (mean dose 463.6 mg/day)	P greater-than or equal to 0.05	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed fluphenazine	**Change from baseline in weight (kg) , 12 weeks** –0.65 kg with risperidone (mean dose 4.31 mg/day) –1.2 kg with quetiapine (mean dose 463.6 mg/day)	P greater-than or equal to 0.05	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed fluphenazine	**Incidence of dyspepsia** 7% with risperidone (mean dose 4.31 mg/day) 8% with quetiapine (mean dose 463.6 mg/day) Absolute numbers not reported	P greater-than or equal to 0.05	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed fluphenazine	**Incidence of somnolence** 38% with risperidone (mean dose 4.31 mg/day) 25% with quetiapine (mean dose 463.6 mg/day) Absolute numbers not reported	P greater-than or equal to 0.05	⟷	Not significant
[65] RCT **3-armed trial**	25 treatment-resistant people The remaining arm assessed fluphenazine	**Incidence of insomnia** 23% with risperidone (mean dose 4.31 mg/day) 25% with quetiapine (mean dose 463.6 mg/day) Absolute numbers not reported	P greater-than or equal to 0.05	⟷	Not significant

Further information on studies

[65] The RCT defined treatment resistance as continual positive psychotic symptoms or illness severity despite trials of two antipsychotic medications at doses of at least 600 mg chlorpromazine equivalent and no stable period of good social/occupational functioning in the previous 5 years. Before randomisation, patients were enrolled in a 4- to 6-week open-label qualification phase during which most were treated with first-generation antipsychotics (other than fluphenazine) and the remainder with olanzapine. Patients only continued the study if they showed no response to treatment during this phase. It is not clear whether there was a washout period after this qualification phase. The sample size for this study was very small and withdrawal was high (50%) but was appropriately accounted for in the analysis using repeated measures methods. The overall test of any differences between quetiapine, risperidone, and fluphenazine in change in negative symptoms gave P <0.05 but pairwise comparisons were not reported. Adverse effects were not reported for one patient in the fluphenazine group.

Comment: We only found one small RCT, which showed no differences between risperidone and quetiapine in treatment-resistant patients.

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**

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Behavioural interventions may improve adherence to antipsychotic medication compared with usual care.

Benefits and harms

Behavioural therapy versus usual care:

We found no systematic review but found two RCTs. [66] [67]

Adherence to treatment

Compared with usual treatment Behavioural therapies may be more effective at increasing adherence to antipsychotic medication at 3 to 15 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adherence to treatment					
[66] RCT **3-armed trial**	36 men with schizophrenia	**Proportion of people with high pill adherence (by pill count) , 3 months** with psychoeducation with behavioural therapy with usual care Absolute results not reported For further details about interventions used, see further information on studies	The RCT reported fewer people had high pill adherence after usual treatment compared with behavioural therapy Significance of difference between groups not assessed		
[67] RCT **3-armed trial**	63 outpatients and recently discharged inpatients with schizophrenia or schizoaffective disorder The remaining arm assessed compliance cognitive adaptation training	**Pill adherence percentage (using a pill count) , 3 months** with full cognitive adaptation training with usual care Absolute results not reported	P = 0.04	○○○	full cognitive adaptation training
[67] RCT **3-armed trial**	63 outpatients and recently discharged inpatients with schizophrenia or schizoaffective disorder The remaining arm assessed compliance cognitive adaptation training	**Pill adherence percentage (using a pill count) , 6 months** with full cognitive adaptation training with usual care Absolute results not reported	P = 0.001	○○○	full cognitive adaptation training
[67] RCT **3-armed trial**	63 outpatients and recently discharged inpatients with schizophrenia or schizoaffective disorder The remaining arm assessed compli-	**Pill adherence percentage (using a pill count) , 9 months** with full cognitive adaptation training with usual care Absolute results not reported	P = 0.001	○○○	full cognitive adaptation training

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	ance cognitive adaptation training				
[67] RCT **3-armed trial**	63 outpatients and recently discharged inpatients with schizophrenia or schizoaffective disorder The remaining arm assessed compliance cognitive adaptation training	**Pill adherence percentage (using a pill count) , 12 months** with full cognitive adaptation training with usual care Absolute results not reported	P = 0.001	○○○	full cognitive adaptation training
[67] RCT **3-armed trial**	63 outpatients and recently discharged inpatients with schizophrenia or schizoaffective disorder The remaining arm assessed compliance cognitive adaptation training	**Pill adherence percentage (using a pill count) , 15 months** with full cognitive adaptation training with usual care Absolute results not reported	P = 0.001	○○○	full cognitive adaptation training

Adverse effects

No data from the following reference on this outcome. [66] [67]

Behavioural therapy versus compliance therapy:

We found one RCT. [67]

Adherence to treatment

Compared with compliance therapy We don't know whether behavioural therapy is more effective at improving treatment adherence in people with schizophrenia at 3 to 15 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adherence to treatment					
[67] RCT **3-armed trial**	63 outpatients and recently discharged inpatients with schizophrenia or schizoaffective disorder The remaining arm assessed usual care	**Pill adherence percentage (using a pill count) , 3 to 15 months** with full cognitive adaptation training with compliance cognitive adaptation training Absolute results not reported	P >0.05	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [67]

Behavioural therapy versus psychoeducational therapy:
See treatment option on psychoeducational interventions, p 155 .

Further information on studies

[66] 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).

[67] Full cognitive adaptation training involved environmental supports for specific functional problems (medication adherence, laundry, and leisure activity), based on a comprehensive assessment of neurocognitive function, behaviour, adaptive functioning, and the environment. Compliance cognitive adaptation training was a subset of full cognitive adaptation training, involving the environmental supports for medication adherence only. Medication adherence was not measured at baseline so it is not possible to assess change from baseline or the effect of pre-existing differences before the intervention. Pill counts were carried out during unannounced visits to patients' homes, but it is still possible that patients threw pills away. An unknown percentage of patients were diagnosed with schizoaffective disorder.

Comment: There is some limited evidence from a small clinical trial that behavioural therapy is more effective than usual care at improving adherence, as measured by pill count, although similar to compliance therapy.

Clinical guide:
Assessing adherence by pill count has potential confounders, in that people may discard pills. [66] There is limited observational evidence from clinical practice that behavioural therapy is effective at improving adherence.

OPTION PSYCHOEDUCATIONAL INTERVENTIONS (IMPROVING ADHERENCE)

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Compliance therapy may be more effective to usual care, though there is no evidence that it differs in effectiveness compared to non-specific therapies

Benefits and harms

Psychoeducational interventions versus usual care:
We found two systematic reviews (search date 2002, 3 RCTs; [68] and search date 2006, 1 RCT [69]) and two subsequent RCTs [70] [71] assessing adherence to medication.

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 other psychoeducational interventions improve adherence (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adherence to treatment					
[68] Systematic review	163 people Data from 1 RCT The review included RCTs that included people with schizophrenia-related disorders (2	**Adherence (measured on a continuous scale of "medication concordance") , 1 year** with brief group psychoeducational intervention with usual care	WMD –0.40 95% CI –0.62 to –0.18	○○○	brief group psychoeducational intervention

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	RCTs, 318 people; proportion of people within these 2 RCTs with schizophrenia not clear)	Absolute results not reported For full details of psychoeducation used, see further information on studies			
[68] Systematic review	82 people Data from 1 RCT 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)	**Compliance with medication , 18 months** 7/41 (17%) with standard-length group psychoeducational intervention 2/41 (5%) with usual care For full details of psychoeducation used, see further information on studies	RR 3.50 95% CI 0.77 to 15.85 P = 0.1	⟷	Not significant
[68] Systematic review	82 people Data from 1 RCT 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)	**Adherence (measured on a continuous scale of "medication concordance") , 1 year** with brief individual psychoeducation with usual care Absolute results not reported For full details of the psychoeducation used, see further information on studies	Reported as not significant P value not reported	⟷	Not significant
[69] Systematic review	89 non-acute inpatients, two-thirds experiencing first admission Data from 1 RCT	**Hedges' g effect size for medication adherence , 26 weeks** with individual psychoeducation for patients and family with usual care Absolute results not reported	Effect size +0.26 95% CI –0.15 to +0.68	⟷	Not significant
[70] RCT	107 people with schizophrenia	**Proportion of people showing "good compliance" to their pharmaceutical regimen (by pill count) , 6 months** 16/39 (41%) with individual psychoeducational programme 26/47 (55%) with usual care For further details about the psychoeducation programme and methods of assessing compliance, see further information on studies	P >0.05	⟷	Not significant
[71] RCT	50 people; 40 with schizophrenia and 10 with schizoaffective or schizophreniform disorder	**Percentage of people with good adherence to oral and depot antipsychotic medication , 2 years** 67% with integrated treatment 70% with standard treatment Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[71] RCT	50 people; 40 with schizophrenia and 10 with schizoaffective or schizophreniform disorder	**Percentage of people with good adherence to oral antipsychotic medication , 2 years** 57% with integrated treatment 55% with standard treatment Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [68] [69] [70] [71]

Psychoeducational interventions versus behavioural therapy:

We found no systematic review but found two RCTs. [66] [72]

Adherence to treatment

Psychoeducational therapies compared with behavioural therapy We don't know how psychoeducational therapies and behavioural therapies compare at improving adherence to antipsychotic medication at 2 to 3 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adherence to treatment					
[66] RCT **3-armed trial**	36 men with schizophrenia The third arm evaluated usual care	**Pill adherence scores of 80% (by pill count) , 3 months** 3/11 (27%) with psychoeducation 8/11 (73%) with behavioural therapy See further information on studies for further details about the interventions and methods of assessing adherence	RR 0.37 (for psychoeducation *v* behavioural therapy) 95% CI 0.13 to 1.05 The RCT is likely to have been too small to detect a clinically important difference between groups	⟷	Not significant
[72] RCT	39 people with schizophrenia	**Pill adherence scores >90% , 2 months** 6/13 (46%) with psychoeducational intervention 25/26 (96%) with behavioural interventions Either an individual or a family-based behavioural intervention was used; see further information on studies for further details	RR 2.08 95% CI 1.15 to 3.77 NNT 2 95% CI 2 to 5	●●○	behavioural interventions

Further information on studies

[66] 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).

[68] The RCTs in the review compared an individual or group psychoeducational intervention of either standard length (11 sessions or more) or brief length (maximum of 10 sessions).

[69] Two other RCTs in this review that recorded medication adherence were already included in the first review. [68]

[70] 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.

[71] Standard treatment was regular case management with antipsychotic drugs, supportive housing and day care, crisis inpatient treatment at one of two psychiatric hospitals, rehabilitation that promoted independent living and work activity, brief psychoeducation, and supportive psychotherapy. Patients on integrated care were treated by a multidisciplinary specialised mental health team with a low caseload, similar pharmacotherapy, and case management as standard treatment, with additional structured family psychoeducation, social skills training (cognitive-behavioural family communication and problem-solving skills training), and individual cognitive-behavioural strategies for residual symptoms and disability. Patients with 1 month or more or 4 single weeks or more without medication were rated as non-adherent (and it is assumed that 'good adherence' was the converse of this).

[72] The RCT compared a psychoeducational intervention, an individual behavioural intervention, and a behavioural intervention involving the person with schizophrenia and their family. 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.

Comment: Assessing adherence by pill count is potentially misleading, as people may throw pills away. [66] [72] Each psychoeducational intervention varied in the protocol used, and few used the same outcome measurements. We found little evidence of superiority of psychological interventions over usual care or behavioural therapy, although studies were small.

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

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- Compliance therapy may improve adherence to antipsychotic medication compared with usual care, though there is no evidence that it differs in effectiveness compared with non-specific therapies.

Benefits and harms

Compliance therapy versus usual care:
We found one RCT. [67]

Adherence to treatment

Compared with usual care Compliance therapy may be more effective at improving adherence to treatment in people with schizophrenia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adherence to treatment					
[67] RCT **3-armed trial**	63 outpatients and recently discharged inpatients with schizophrenia or schizoaffective disorder	**Pill adherence percentage (using a pill count) , 3 months** with compliance cognitive adaptation training with usual care	P = 0.05	○○○	compliance cognitive adaptation training

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm assessed full cognitive adaptation training	Absolute results not reported			
[67] RCT **3-armed trial**	63 outpatients and recently discharged inpatients with schizophrenia or schizoaffective disorder The remaining arm assessed full cognitive adaptation training	**Pill adherence percentage (using a pill count) , 6 months** with compliance cognitive adaptation training with usual care Absolute results not reported	P = 0.0001	○○○	compliance cognitive adaptation training
[67] RCT **3-armed trial**	63 outpatients and recently discharged inpatients with schizophrenia or schizoaffective disorder The remaining arm assessed full cognitive adaptation training	**Pill adherence percentage (using a pill count) , 9 months** with compliance cognitive adaptation training with usual care Absolute results not reported	P = 0.0001	○○○	compliance cognitive adaptation training
[67] RCT **3-armed trial**	63 outpatients and recently discharged inpatients with schizophrenia or schizoaffective disorder The remaining arm assessed full cognitive adaptation training	**Pill adherence percentage (using a pill count) , 12 months** with compliance cognitive adaptation training with usual care Absolute results not reported	P = 0.0001	○○○	compliance cognitive adaptation training
[67] RCT **3-armed trial**	63 outpatients and recently discharged inpatients with schizophrenia or schizoaffective disorder The remaining arm assessed full cognitive adaptation training	**Pill adherence percentage (using a pill count) , 15 months** with compliance cognitive adaptation training with usual care Absolute results not reported	P = 0.0002	○○○	compliance cognitive adaptation training

Adverse effects

No data from the following reference on this outcome. [67]

Compliance therapy versus non-specific therapy or health education:

We found one systematic review (search date 2005) [73] and one subsequent RCT [74] assessing compliance therapy.

Adherence to treatment

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adherence to treatment					
[73] Systematic review	56 people with schizophrenia admitted to hospital and followed post-discharge Data from 1 RCT	**Proportion of people who were non-compliant** 16/28 (57%) with compliance therapy 13/28 (46%) with non-specific therapy Compliance was measured on a 4-point scale where 4 was classified as optimal compliance	RR 1.23 95% CI 0.74 to 2.05	⟷	Not significant
[74] RCT	409 people with schizophrenia	**Patient-rated compliance (change in scores from baseline) , 12 months** From 2.98 to 3.20 with adherence therapy From 2.97 to 3.33 with health education See further information on studies for details of the interventions and outcomes assessed	AR –0.13 CI –0.35 to +0.08 P = 0.23	⟷	Not significant
[74] RCT	409 people with schizophrenia	**Keyworker-rated compliance (change in scores from baseline) , 12 months** From 5.04 to 5.22 with adherence therapy From 4.73 to 5.03 with health education See further information on studies for details of the interventions and outcomes assessed	AR +0.19 CI –0.12 to +0.52 P = 0.24	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [73] [74]

Compliance therapy versus behavioural therapy:

See treatment option on behavioural therapy, p 153 .

Further information on studies

[67] Full cognitive adaptation training involved environmental supports for specific functional problems (medication adherence, laundry, and leisure activity), based on a comprehensive assessment of neurocognitive function, behaviour, adaptive functioning, and the environment. Compliance cognitive adaptation training was a subset of full cognitive adaptation training, involving the environmental supports for medication adherence only. Medication adherence was not measured at baseline so it is not possible to assess change from baseline or the effect of pre-existing differences before the intervention. Pill counts were carried out during unannounced visits to patients' homes, but it is still possible that patients threw pills away. An unknown percentage of patients were diagnosed with schizoaffective disorder.

[74] Adherence therapy and health education consisted of a maximum of 8 once-weekly 30- to 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).

Comment: There are limited studies on the effectiveness of compliance therapy. The RCT identified by the review [73] and a subsequent RCT [74] did not find that compliance therapy was more effective than non-specific therapy, health education, or behavioural therapy. However, one small RCT showed superior effectiveness of compliance therapy over usual care. [67]

Clinical guide:
There are limited studies on the effectiveness of compliance therapy. The RCT identified by the review [73] and a subsequent RCT [74] did not demonstrate effectiveness of compliance therapy. However, other RCTs suggest that compliance therapy may be effective at improving adherence, although these RCTs have methodological weaknesses (e.g., failure to use a standardised measure of adherence or open label in design). Further studies are needed in this area.

OPTION FAMILY INTERVENTIONS (IMPROVING ADHERENCE)

- For GRADE evaluation of interventions for Schizophrenia, see table, p 166 .
- We don't know whether multiple-session family interventions improve adherence to antipsychotic medication.

Benefits and harms

Family interventions compared with usual care, single-session family intervention, or psychoeducational intervention:

We found two systematic reviews (search date 1999; [75] and search date 2005 [76]). The second review identified 16 RCTs identified by the first review, but the meta-analyses carried out by the reviews included different RCTs. [75] [76]

Adherence to treatment

Compared with usual care, single-session family intervention, or psychoeducational intervention Family interventions may be more effective than usual care or other interventions at improving adherence to antipsychotic medication (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adherence to treatment					
[75] Systematic review	393 people with schizophrenia 5 RCTs in this analysis 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	**Compliance with medication , 9 to 24 months** with multiple-session family interventions with other interventions Absolute results not reported Family interventions mainly consisted of education about the illness and training in problem solving over at least 6 weekly sessions. The other interventions included usual care, single-session family interventions, or psychoeducational interventions	OR 0.63 95% CI 0.40 to 1.01	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[76] Systematic review	369 people 7 RCTs in this analysis 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)	**Proportion of people with poor compliance** 78/177 (44%) with family-based psychosocial interventions 114/192 (59%) with usual care	RR 0.74 95% CI 0.61 to 0.91	●○○	family-based psychosocial interventions

Adverse effects

No data from the following reference on this outcome. [75] [76]

Further information on studies

Comment: We found some evidence of effectiveness of family interventions over usual care or other interventions.

Clinical guide:
There is limited evidence of benefit for family therapy in improving antipsychotic medication adherence in schizophrenia. The resources needed for this intervention can limit its availability, and it cannot be applied to people who have little contact with home-based carers.

GLOSSARY

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 A one-item, observer-rated scale for measuring the severity of a condition. It has been investigated for validity and reliability. The scale is scored 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.

Negative symptoms This generally refers to qualities that are abnormal by their absence (e.g., loss of drive, motivation, affective expression, and self-care).

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Sertindole New option added. Categorised as Unknown effectiveness. [11] [30] [44]

Paliperidone New option added. [37] Categorised as Trade-off between benefits and harms.

Flupentixol New option added. [46] Categorised as Unknown effectiveness.

Depot flupentixol decanoate New option added. We found no systematic review or RCTs. Categorised as Unknown effectiveness.

Zuclopenthixol New option added. We found no systematic review or RCTs. Categorised as Unknown effectiveness.

Depot zuclopenthixol decanoate New option added. We found no systematic review or RCTs. Categorised as Unknown effectiveness.

Amisulpride New evidence added. [10] [11] [12] [13] [14] Categorised as Trade-off between benefits and harms.

Aripiprazole New evidence added. [11] [54] [55] [56] Categorised as Trade-off between benefits and harms.

Chlorpromazine New evidence added. [15] [16] [17] [18] Categorised as Trade-off between benefits and harms.

Clozapine New evidence added. [11] [16] [19] [20] [21] [22] [23] [24] [25] [26] Categorised as Trade-off between benefits and harms.

Compliance therapy New evidence added. [67] Categorisation unchanged (Unknown effectiveness), as there remains insufficient good-quality evidence to assess the effects of compliance therapy in people with schizophrenia.

Depot haloperidol decanoate New evidence added. [28] Categorised as Unknown effectiveness as there remains insufficient good-quality evidence to assess the effects of depot haloperidol in people with schizophrenia.

Haloperidol New evidence added. [11] [16] [24] [29] [30] [31] [32] [33] [34] Categorised as Trade-off between benefits and harms

Olanzapine New evidence added. [11] [21] [35] [36] [37] [38] Categorised as Trade-off between benefits and harms.

Pimozide New evidence added. Categorised as Trade-off between benefits and harms. [39]

Quetiapine New evidence added. [11] [20] [40] [41] Categorised as Trade-off between benefits and harms.

Risperidone New evidence added. [11] [25] [26] [42] [43] [44] [45] [46] [47] [48] [49] Categorised as Trade-off between benefits and harms.

Second-generation antipsychotics (other than clozapine) versus each other (treatment-resistant disease) New evidence added. [65] Categorisation unchanged (Unknown effectiveness), as there remains insufficient good-quality evidence.

Second-generation antipsychotics (other than clozapine) versus first-generation antipsychotics (treatment-resistant disease) New evidence added. [65] Categorisation unchanged (Unknown effectiveness), as there remains insufficient good-quality evidence.

Sulpiride New evidence added. [51] Categorised as Unknown effectiveness.

Ziprasidone New evidence added. [11] [53] Categorised as Trade-off between benefits and harms.

Zotepine New evidence added. [11] Categorised as Trade-off between benefits and harms.

Behavioural therapy New evidence added. [67] Categorisation changed from Likely to be beneficial to Unknown effectiveness, as there remains insufficient good-quality evidence to assess the effects of behavioural therapy in people with schizophrenia.

Clozapine versus first-generation antipsychotic drugs (treatment-resistant disease) One systematic review updated. [19] Categorisation changed from Beneficial to Trade-off between benefits and harms.

Clozapine versus other second-generation antipsychotic drugs (treatment-resistant disease) New evidence added. [60] [61] Categorisation changed from Unknown effectiveness to Trade-off between benefits and harms.

Psychoeducational interventions New evidence added. [69] [71] Categorisation changed from Likely to be beneficial to Unknown effectiveness, as there is insufficient good-quality evidence to assess the effects of psychoeducational interventions in people with schizophrenia.

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Disclaimer

GRADE **Evaluation of interventions for Schizophrenia.**

Important outcomes			Adherence to treatment, Relapse, Symptom severity						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of drug treatments for positive, negative, or cognitive symptoms of schizophrenia?									
4 (514) [10]	Symptom severity	Amisulpride versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of people with schizotypal personality disorder in 1 RCT
5 (781) [12] [13]	Symptom severity	Amisulpride versus olanzapine	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of baseline comparisons
at least 4 (at least 624) [12] [14]	Symptom severity	Amisulpride versus risperidone	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 inclusion of a mixed population in 1 RCT
1 (123) [12]	Symptom severity	Amisulpride versus ziprasidone	4	–2	0	0	0	Low	Quality point deducted for sparse data and incomplete reporting of results
at least 10 (at least 929) [11]	Symptom severity	Amisulpride versus first-generation antipsychotics	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
13 (1131) [15]	Symptom severity	Chlorpromazine versus placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, inclusion of open-label trials, and inclusion of RCTs with inadequate blinding and randomisation
1 (164) [16]	Symptom severity	Chlorpromazine versus clozapine	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
at least 5 (at least 241) [17]	Symptom severity	Chlorpromazine versus haloperidol	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and inclusion of trials with inadequate randomisation and blinding
1 (60) [18]	Symptom severity	Chlorpromazine versus risperidone	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and unclear blinding
2 (317) [19]	Symptom severity	Clozapine versus haloperidol	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
at least 2 (at least 142) [20]	Symptom severity	Clozapine versus quetiapine	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
at least 4 (at least 503) [21]	Symptom severity	Clozapine versus olanzapine	4	–2	0	0	0	Low	Quality points deducted for sparse data, and inclusion of trials with a high risk of bias
5 (491) [23] [24]	Symptom severity	Clozapine versus risperidone	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for low-dose clozapine compared with high-dose risperidone noted by the authors of the review

Important outcomes			Adherence to treatment, Relapse, Symptom severity						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (146) [25]	Symptom severity	Clozapine versus ziprasidone	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (57) [26]	Symptom severity	Clozapine versus zotepine	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
unclear (at least 351) [22]	Symptom severity	Clozapine versus newer atypical antipsychotics (risperidone, zotepine, olanzapine, remoxipride, pooled)	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
17 at most (1603 at most) [27] [11]	Symptom severity	Clozapine versus typical/first-generation antipsychotics	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (22) [28]	Symptom severity	Depot haloperidol decanoate versus standard antipsychotic drugs	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for the study being underpowered to detect clinically important differences
1 (32) [28]	Symptom severity	Depot haloperidol decanoate versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
at least 2 (at least 72) [29]	Symptom severity	Haloperidol versus placebo	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
5 (1475) [16] [11] [30] [24] [31]	Symptom severity	Haloperidol versus risperidone	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point for conflicting results
5 (684) [16] [32] [33] [34]	Symptom severity	Haloperidol versus olanzapine	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of data. Consistency point deducted for conflicting results
5 (1480) [30] [11]	Symptom severity	Haloperidol versus sertindole	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
3 (299) [35] [36]	Symptom severity	Olanzapine versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
2 (794) [21]	Symptom severity	Olanzapine versus aripiprazole	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 3 (at least 715) [37]	Symptom severity	Olanzapine versus paliperidone	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 3 (at least 483) [21]	Symptom severity	Olanzapine versus quetiapine	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 5 (at least 810) [21] [38]	Symptom severity	Olanzapine versus risperidone	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
at least 2 (at least 790) [21]	Symptom severity	Olanzapine versus ziprasidone	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes			Adherence to treatment, Relapse, Symptom severity						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
24 (4189) [11]	Symptom severity	Olanzapine versus first-generation antipsychotics	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (206) [39]	Symptom severity	Pimozide versus standard antipsychotic drugs	4	0	0	0	0	High	
2 (812) [40] [41]	Symptom severity	Quetiapine versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (314) [41]	Symptom severity	Quetiapine versus paliperidone	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 7 (at least 1264) [20]	Symptom severity	Quetiapine versus risperidone	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (908) [20]	Symptom severity	Quetiapine versus ziprasidone	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
10 (1926) [11]	Symptom severity	Quetiapine versus first-generation antipsychotics	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (659) [42] [43]	Symptom severity	Risperidone versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (172) [44]	Symptom severity	Risperidone versus sertindole	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (372) [45]	Symptom severity	Risperidone versus aripiprazole	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 2 (at least 500) [25]	Symptom severity	Risperidone versus ziprasidone	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (40) [26]	Symptom severity	Risperidone versus zotepine	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (107) [46]	Symptom severity	Risperidone versus flupentixol	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
at least 30 (at least 3455) [47] [48] [11] [49]	Symptom severity	Risperidone versus first-generation antipsychotic drugs	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (514) [51]	Symptom severity	Sulpiride versus first-generation antipsychotic drugs	4	0	0	0	0	High	
1 (247) [53]	Symptom severity	Ziprasidone versus aripiprazole	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and being underpowered to detect clinically important differences
at least 4 (at least 728) [11]	Symptom severity	Ziprasidone versus first-generation antipsychotic drugs	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 15 (at least 1125) [11]	Symptom severity	Zotepine versus first-generation antipsychotic drugs	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results

Important outcomes			Adherence to treatment, Relapse, Symptom severity						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
3 (984) [54] [55] [56]	Symptom severity	Aripiprazole versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
at least 5 (at least 2409) [11]	Symptom severity	Aripiprazole versus first-generation antipsychotic drugs	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (1305) [37]	Symptom severity	Paliperidone versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of data
What are the effects of drug treatments in people with schizophrenia who are resistant to standard antipsychotic drugs?									
6 (1018) [19]	Symptom severity	Clozapine versus first-generation antipsychotic drugs	4	0	0	–2	0	Low	Directness points deducted for inclusion of partial responders and for unclear comparator
5 (819) [19]	Relapse	Clozapine versus 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) [58]	Symptom severity	Clozapine versus olanzapine, risperidone, and zotepine	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of non-treatment-resistant people
4 (395) [35] [59] [60]	Symptom severity	Clozapine versus olanzapine	4	0	0	0	0	High	
1 (146) [61]	Symptom severity	Clozapine versus ziprasidone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (84) [35]	Symptom severity	Olanzapine versus 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) [63]	Symptom severity	Ziprasidone versus 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) [64]	Symptom severity	Aripiprazole versus 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
1 (26) [65]	Symptom severity	Risperidone versus fluphenazine	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for baseline comparisons
1 (25) [65]	Symptom severity	Quetiapine versus fluphenazine	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for the use of baseline comparisons
1 (25) [65]	Symptom severity	Second-generation antipsychotic agents (other than clozapine) versus risperidone	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for the use of baseline comparisons
What are the effects of interventions to improve adherence to antipsychotic medication in people with schizophrenia?									
2 (99) [66] [67]	Adherence to treatment	Behavioural therapy versus 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)

Important outcomes			Adherence to treatment, Relapse, Symptom severity						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (63) [67]	Adherence to treatment	Behavioural therapy versus compliance therapy	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
4 (328) [68] [70] [71] [69]	Adherence to treatment	Psychoeducational interventions versus usual care	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) [66] [72]	Adherence to treatment	Psychoeducational interventions versus behavioural therapy	4	–2	–1	–2	0	Very low	Quality points deducted for sparse data and poor follow-up. Consistency point deducted for conflicting results. Directness points deducted for use of co-intervention (pill box) and uncertain validity of outcome assessment (pill count)
1 (63) [67]	Adherence to treatment	Compliance therapy versus usual care	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (465) [73] [74]	Adherence to treatment	Compliance therapy versus non-specific therapy or health education	4	0	0	–1	0	Moderate	Directness point deducted for unclear comparator
7 (at least 369) [75] [76]	Adherence to treatment	Family interventions compared with usual care, single-session family intervention, or psychoeducational intervention	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and inclusion of quasi-randomised RCTs. Directness point deducted for inclusion of people with schizophrenia-related disorders

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.