TECHNICAL COMMENTARY

Risperidone

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Introduction

Second generation antipsychotics (sometimes referred to as 'atypical' antipsychotics) are a newer class of antipsychotic medication than first generation 'typical' antipsychotics. Second generation antipsychotics are effective for the positive symptoms of schizophrenia. It is sometimes claimed that they are more effective than first generation antipsychotics in treating the negative symptoms of schizophrenia, although the evidence for this is weak. Negative symptoms include a lack of ordinary mental activities such as emotional expression, social engagement, thinking and motivation, whereas positive symptoms include the experiences of perceptual abnormalities (hallucinations) and fixed, false, irrational beliefs (delusions).

Second generation antipsychotics may also cause less extra-pyramidal side effects. These include dyskinesias such as repetitive, involuntary, and purposeless body or facial movements, Parkinsonism (cogwheel muscle rigidity, pill-rolling tremor and reduced or slowed movements), akathisia (motor restlessness, especially in the legs, and resembling agitation) and dystonias such as muscle contractions causing unusual twisting of parts of the body, most often in the neck. These effects are caused by the dopamine receptor antagonist action of these drugs. One explanation for differences in producing these side effects is that high potency first generation antipsychotics are usually selective dopamine receptor antagonists with a high affinity for the dopamine receptor and they induce extrapyramidal effects by the blockade of these dopamine receptors. In contrast, second generation antipsychotics generally have a lower affinity for the dopamine receptor and also block serotonin receptors, both of which mechanisms may play a role in mitigating the effects of dopamine blockade. Amisulpride is an exception to other second generation antipsychotics in that it is a pure dopamine receptor antagonist, however it tends to block dopamine receptors more selectively in the limbic system relative to the nigrostriatal system, which is the site responsible for inducing extrapyramidal symptoms. In addition to amisulpride, olanzapine and quetiapine also tend to selectively block dopamine receptors in the mesolimbic system but target serotonin receptors.

This table summarises overall group effectiveness of risperidone from information gained from randomised controlled trials (RCTs), however individual treatment programs need to be tailored by trained clinicians as response - both in symptoms and adverse effects - can vary between individuals.

Method

Owing to the vast number of reviews on antipsychotics, we have prioritised information reported in the abstracts of Cochrane systematic reviews[1]. This is because the Cochrane internal review process ensures a high level of scientific rigor and meta-analyses are usually conducted, giving treatment effect sizes. Data from the abstracts were supplemented from the full text when clarification was required. When multiple copies of reviews were found and/or when findings conflict, we present the most recent version and the most recent conclusions. Where no Cochrane review exists, other reviews with pooled data are included.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from RCTs may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a

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dose dependent response or if results are reasonably consistent, precise and direct with low associated risks[2]. The resulting table represents an objective summary of the evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found fourteen reviews that met our inclusion criteria[3-16].

Risperidone

Depot vs. oral risperidone

Efficacy: Moderate quality evidence (precise, inconsistent, direct) suggests depot and oral risperidone may not be different for global outcomes, mental state and treatment compliance.

Adverse effects: Moderate quality evidence (precise, inconsistent, direct) suggests depot and oral risperidone may not be significantly different for adverse effects.

Compared to placebo

Efficacy: Moderate quality evidence (imprecise) suggests risperidone may improve symptoms, agitation and reduce relapse compared to placebo. High quality evidence (precise, consistent) suggests risperidone had greater study retention than placebo.

Adverse effects: Moderate quality evidence (imprecise, inconsistent) suggests a small risk of increased extrapyramidal and cardiovascular side effects with risperidone when compared to placebo.

Compared to first generation antipsychotics

Efficacy: High quality evidence (consistent, precise, direct) suggests risperidone is more effective than haloperidol for reducing symptom severity, and increasing study retention, and moderate quality evidence (imprecise) suggests it may reduce the risk of psychotic relapse in chronic patients.

Adverse effects: High quality evidence (consistent, precise, direct) suggests risperidone results in less movement disorders than haloperidol. Moderate quality evidence (imprecise) suggests risperidone may be associated with a higher risk of weight gain and rhinitis than first generation antipsychotics in general.

Compared to second generation antipsychotic amisulpride

Efficacy: Moderate quality evidence (imprecise) suggests no significant differences between risperidone and amisulpride.

Adverse effects: Moderate quality evidence (imprecise or unable to assess) suggests risperidone may result in less agitation and more weight gain than amisulpride.

Compared to second generation antipsychotic clozapine

Efficacy: Moderate quality evidence (imprecise) suggests clozapine had higher dropout due to adverse effects, but risperidone had higher dropout due to inefficacy. The risperidone group showed greater social functioning but there was no significant difference in mental state or negative symptoms.

Adverse effects: Moderate to high quality evidence (some imprecision) suggests risperidone may have less hypersalivation, sedation, seizures, weight gain and lower triglyceride levels, but more extrapyramidal side-effects and altered prolactin levels than clozapine.

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Compared to second generation antipsychotic olanzapine

Efficacy: High quality evidence (consistent, precise, direct) suggests no differences in symptom severity, although risperidone may result in more study attrition. Moderate quality evidence (imprecise) suggests olanzapine may result in a fewer relapses.

Adverse effects: High quality evidence suggests risperidone results in less weight gain than olanzapine. Moderate quality evidence suggests higher levels of extrapyramidal symptoms with risperidone. Moderate quality evidence also suggests olanzapine may result in less insomnia and less abnormal ejaculation.

Compared to second generation antipsychotic quetiapine

Efficacy: Moderate to high quality evidence (consistent, unable to assess precision) suggests risperidone has higher efficacy for reducing symptom severity than quetiapine.

Adverse effects: Moderate quality evidence (inconsistent, imprecise or unable to assess) suggests risperidone has a higher risk of extrapyramidal effects and prolactin increase, but lower cholesterol levels and less sedation (high quality evidence).

Compared to second generation antipsychotic sertindol

Adverse effects: Moderate quality evidence (imprecise or unable to assess) suggests risperidone may produce more extrapyramidal side effects but less weight gain, less QTc prolongation, and less sexual dysfunction in men than sertindol.

Compared to second generation antipsychotic ziprasidone

Efficacy: High quality evidence (consistent, precise, direct) suggests risperidone may result in more study attrition. Moderate quality evidence (some inconsistency, unable to assess precision) suggests risperidone had higher efficacy for reducing symptom severity than ziprasidone.

Adverse effects: Moderate quality evidence (imprecise) suggests risperidone may produce more extrapyramidal side effects and more cholesterol increase than ziprasidone.

Compared to second generation antipsychotic zotepine

Efficacy: Low quality evidence (imprecise, 1 small RCT) is unable to determine any differences between risperidone and zotepine for symptom severity.

Adverse effects: Low quality evidence (imprecise, 1 small RCT) is unable to determine any differences between risperidone and zotepine for extrapyramidal symptoms.

Comparison of different risperidone doses

Efficacy: Moderate quality evidence (imprecise) suggests low dose risperidone (<2 mg/day - <4 mg/day) may result in insufficient treatment response when compared to higher doses. High doses (>=10 mg/day) may result in less improvement than standard-high doses (>=6-<10 mg/day).

Adverse effects: Moderate quality evidence (imprecise) suggests high doses may result in more movement disorders.

Asenjo Lobos, C, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Leucht S. Clozapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of

Systematic Reviews 2010, Issue 11: Art. No.: CD006633 DOI: 10.1002/14651858.CD006633.pub2.	
The review includes 27 blinded RCTs, N = 3099, nine compared clozapine with risperidone. Clozapine had a higher attrition rate due to adverse effects than the risperidone group (6 RCTs, N = 627, RR = 1.88, 95%CI 1.11 to 3.21 p = 0.02, I^2 = 0%). However, fewer participants in the clozapine group left the study early due to inefficacy than in the risperidone group (6 RCTs, N = 627, RR = 0.40 95%CI 0.23 to 0.70, p = 0.0013, I^2 = 0%). No significant difference in mental state (BPRS total score) (3 RCTs, N = 337, MD = -2.98, 95%CI -6.93 to 0.97, p = 0.14, I^2 = 61%) or negative symptoms between clozapine and risperidone (5 RCT, N = 562, MD = 0.13, 95%CI -1.71 to 1.96, p = 0.89, I^2 = 61%). People on risperidone showed greater improvement in social functioning than those on clozapine (1 RCT, N = 19, MD = -47.0, 95%CI -93.55 to -0.45, p = 0.048).	
Risks	Compared to clozapine, risperidone showed more extrapyramidal effects (6 RCTs, N = 304, p < 0.05) and greater weight gain (4 RCTs, N = 459, p < 0.05), but less hypersalivation (3 RCTs, N = 373, p < 0.05); sedation (5 RCTs, N = 479, p = 0.0014); less seizures (2 RCTs, N = 354, p = 0.010); lower triglycerides (1 RCT, N = 26, p < 0.001). Risperidone altered prolactin levels (p < 0.05).
Consistency in results‡	Consistent for all measures except weight gain, mental states and negative symptoms. Unable to assess for 1 RCT.
Precision in results§	Imprecise for all other measures. Unable to assess for mental states, triglyceride levels and social functioning as standardised values not reported.
Directness of results‖	Direct
Hamann J, Kissling W, Leucht S, Rummel-Kluge C. New generation antipsychotics for first episode schizophrenia. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD004410. DOI: 10.1002/14651858.CD004410.	
This review includes 2 RCTs (N = 266). Compared to haloperidol, risperidone had equivalent study retention (N = 183, 1 RCT, RR=0.7 CI 0.4 to 1.1). No difference was reported for global effect measures (N = 183, 1 RCT, RR 1.0 CI 0.6 to 1.5), or mental state (N = 183, 1 RCT, RR 0.85 CI 0.6 to 1.2).	
Risks	Compared to haloperidol, risperidone had significantly fewer adverse events (N = 183, 1 RCT, RR 0.9 CI 0.8 to 0.98, NNH 8 CI 4 to 50). Patients randomised to risperidone required significantly less anticholinergic medication for extrapyramidal effects (N = 183, 1 RCT, RR 0.7 CI 0.5 to 0.9, NNH 4 CI 3 to 9).

Consistency in results	Not applicable, 1 RCT only.
Precision in results	Imprecise for all outcomes except adverse events and extrapyramidal effects.
Directness of results	Direct
Hosalli P, Davis JM. Depot risperidone for schizophrenia. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD004161 DOI: 10.1002/14651858.CD004161.	
This review includes 2 RCTs (N = not reported). Compared to placebo, there was no significant difference for anxiety (N = 400, 1 RCT RR 0.58 CI 0.32 to 1.05) or hallucinations (N = 400, 1 RCT RR 1.23 CI 0.47 to 3.22), but there may be less agitation (N = 400, 1 RCT RR 0.60 CI 0.39 to 0.92) and psychosis relapses (N = 400, 1 RCT RR 0.52 CI 0.33 to 0.83, NNT 9 CI 7 to 26). Risperidone depot may also improve study retention (N = 400, 1 RCT RR 0.74 CI 0.63 to 0.88, NNT 6 CI 4 to 12). Compared to oral risperidone, there was no clear difference in global outcome between the depot group and oral group (N = 640, 1 RCT RR 1.06 CI 0.92 to 1.22) and there was no significant difference in mental state. There was no significant difference in compliance with treatment (N = 640, 1 RCT RR 1.16 CI 0.81 to 1.67).	
Risks	Compared to placebo, severe adverse events were more common in the placebo group (13% to 23%, N = 400, RR 0.59 CI 0.38 to 0.93, NNT 11 CI 7 to 70). Depot risperidone had similar rates of movement disorders to placebo (N = 400, RR 2.38 CI 0.73 to 7.78). Compared to oral risperidone, depot risperidone was associated with similar rates of adverse effects (N = 640, RR 1.04 CI 0.91 to 1.18).
Consistency in results	Not applicable, 1 RCT only per comparison.
Precision in results	Imprecise for all outcomes except study retention compared to placebo, and global outcomes compared to oral administration.
Directness of results	Direct
Hunter R, Kennedy E, Song F, Gadon L, Irving CB. Risperidone versus typical antipsychotic medication for schizophrenia. Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: CD000440. DOI: 10.1002/14651858.CD000440	
This review includes 23 RCTs, (N = 4445). Compared to haloperidol, risperidone was more likely to improve symptom severity in the short term, (N = 2368, 9 RCTs, RR 0.85 CI 0.77 to 0.93 NNT 8, I^2 = 0%, p = 0.63) and long term (N = 859, 2 RCTs RR not improved 20% 0.73 CI 0.65 to 0.83 NNT 4, I^2 = 61%, p = 0.11; N = 675 1 RCT, RR not improved 40% 0.75 CI 0.66 to 0.84 NNT 5; N = 675, 1 RCT, RR not 60% improved 0.90 CI 0.84 to 0.96, NNT 11).	

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Compared to haloperidol, risperidone reduced the risk of relapse (N = 367, 1 RCT, RR 0.64 CI 0.41 to 0.99, NNT 7), and improved study retention in the short term (N = 3066, 18 RCTs, RR 0.76 CI 0.63 to 0.92, NNT 6, I^2 = 8%, *p* = 0.37) and long-term trials (N = 1270, 4 RCTs, RR 0.55 CI 0.42 to 0.73 NNT 4, I^2 = 6%, *p* = 0.36).	
Risks	Compared to first generation antipsychotics, risperidone had a significantly lower risk of movement disorders (including extrapyramidal side effects) (N = 2702, 10 RCTs, RR 0.63 CI 0.56 to 0.71, NNT 3, I^2 = 0%, *p* = 0.50) and lower use of antiparkinsonian medications (N = 2524, 11 RCTs, RR 0.66 CI 0.58 to 0.74, NNT 4, I^2 = 0%, *p* = 0.81). No difference was reported between the groups for sexual problems such as erectile dysfunction (N = 106, 2 RCTs, RR 1.55 CI 0.58 to 4.20, I^2 = 14%, *p* = 0.28). Compared to first generation antipsychotics, risperidone increased the risk of weight gain (N = 1708, RR 1.55 CI 1.25 to 1.93, NNH 3, I^2 = 63%, *p* = 0.04) and rhinitis (N = 656, 3 RCTs, RR 1.99 CI 1.24 to 3.19, NNH 3, I^2 = 61%, *p* = 0.08).
Consistency in results	Consistent for all outcomes except weight gain.
Precision in results	Precise for all outcomes except relapse.
Directness of results	Direct
Jayaram MB, Hosalli P, Stroup TS. Risperidone versus olanzapine for schizophrenia. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD005237 DOI: 10.1002/14651858.CD005237.pub2.	
This review includes 16 RCTs, (N = not reported). Compared with olanzapine, no significant differences were reported for short term global effect, (N = 548, 2 RCTs, RR 1.00 CI 0.88 to 1.15, I^2 = 0%, *p* = 0.52). Olanzapine had a lower relapse rate at 12 months N = 279, 1 RCT, RR 2.16 CI 1.31 to 3.54, NNH 7 CI 3 to 25). No significant differences were reported for symptom severity and mental state (N = 552, 2 RCTs, RR 1.01 CI 0.87 to 1.16, I^2 = 0%, *p* = 0.69). Both drugs were associated with high attrition rates; in the long term 66% of those allocated risperidone left the study early compared with 56% given olanzapine (N = 1440, 5 RCTs, RR 1.17 CI 1.08 to 1.27, NNH 11 CI 7 to 23, I^2 = 7%, *p* = 0.38).	
Risks	Compared to olanzapine, insomnia was higher with risperidone (N = 1588, 5 RCTs, RR 1.41 CI 1.15 to 1.72, NNH 15 CI 9 to 41, I^2 = 0%, *p* = 0.98). Extrapyramidal symptoms were common with both drugs (N = 893, 3 RCTs, RR 1.18 CI 0.75 to 1.88, I^2 = 63%, *p* = 0.07); although risperidone patients had increased requirements for medication to alleviate these symptoms (N = 419, 2 RCTs, RR 1.76 CI 1.25 to 2.48, NNH 8 CI 4 to 25, I^2 = 0%, *p* = 0.44). Patients randomised to risperidone were less likely to gain weight compared to olanzapine (N = 984, 2 RCTs, RR 0.47 CI 0.36 to 0.61, NNH 7 CI

	6 to 10, I^2 = 0%, *p* = 0.98). Patients on risperidone were more likely to experience abnormal ejaculation (N = 370, 2 RCTs, RR 4.36 CI 1.38 to 13.76, NNH 20 CI 6 to 176, I^2 = 0%, *p* = 0.82).
Consistency in results	Consistent for all outcomes.
Precision in results	Precise for all outcomes except relapse, insomnia, extrapyramidal symptoms, sexual dysfunction.
Directness of results	Direct
Komossa K, Rummel-Kluge C, Schwarz S, Schmid F, Hunger H, Kissling W, Leucht S. Risperidone versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD006626. DOI: 10.1002/14651858.CD006626.pub2.	
This review includes 45 RCTs (N = 7760). Compared to clozapine: risperidone resulted in more patients leaving the study early due to inefficacy (7 RCTs, N = 647, RR 2.51, 95%CI 1.43 to 4.40, I^2 = 0%, *p* = 0.48). Compared to olanzapine: risperidone was not as effective for symptom severity (PANSS total score: 15 RCTs, N = 2390, MD 1.94, 95%CI 0.58 to 3.31, I^2 = 0%, *p* = 0.65), however risperidone had slightly more patients leaving the study early for any reason (16 RCTs, N = 2738, RR 1.14, 95%CI 1.07 to 1.21, I^2 = 0%, *p* = 0.75). Compared to quetiapine: risperidone was more effective for symptom severity (PANSS total score: 9 RCTs, N = 1953, MD -3.09, 95%CI -5.16 to -1.01, I^2 = 24%, *p* = 0.23). Compared to ziprasidone: risperidone had less patients leaving the study early for any reason (3 RCTs, N = 1209, RR 0.90, 95%CI 0.83 to 0.98, I^2 = 0%, *p* = 0.37), and was more effective for symptom severity (PANSS total score: 3 RCTs, N = 1016, MD -3.91, 95%CI -7.55 to -0.27, I^2 = 64%, *p* = 0.06). No differences for efficacy were reported in comparisons with amisulpride (4 RCTs), aripiprazole (2 RCT) or sertindole.	
Risks	Compared to amisulpride: risperidone produced more weight gain (3 RCTs, N = 585, MD 0.99, 95%CI 0.37 to 1.61, I^2 = 0%). Compared to aripiprazole: risperidone caused more cholesterol increase (1 RCT, N = 83, MD 22.30, 95%CI 4.91 to 39.69). Compared to clozapine: risperidone produced more extrapyramidal side effects (use of parkinsonism medication: 6 RCTs, N = 304, RR 2.57, 95%CI 1.47 to 4.48, *p* = 0.75, I^2 = 0%). However, risperidone was less sedating (5 RCTs, N = 475, RR 0.58, 95%CI 0.41 to 0.81, I^2 = 0%), produced fewer seizures (2 RCTs, N = 354, RR 0.22, 95%CI 0.07 to 0.70, I^2 = 0%), and resulted in less weight gain (3 RCTs, N = 373, MD -3.30, 95%CI -5.65 to -0.95, I^2 84%, *p* = 0.002). Compared to olanzapine: risperidone produced more extrapyramidal

	side effects (13 RCTs, N = 2599, RR 1.28, 95%CI 1.06 to 1.55, I^2 = 28%, *p* = 0.17), but less weight gain (13 RCTs, N = 2116, MD -2.61, 95%CI -3.74 to -1.48, I^2 = 83%, *p* < 0.00001). Compared to quetiapine: risperidone produced more extrapyramidal side effects (6 RCTs, N = 1715, RR 1.98, 95%CI 1.16 to 3.39, I^2 = 37%, *p* = 0.16), but less cholesterol increase (5 RCTs, N = 1433, MD -8.49, 95%CI -12. 23 to -4.75, I^2 = 6%, *p* = 0.37) and less sedation (8 RCTs, N = 2226, RR .82, 95%CI 0.69 to 0.97, I^2 = 26%, *p* = 0.22). Compared to sertindole: risperidone produced more extrapyramidal side effects (1 RCT, N = 321, RR 4.11, 95%CI 1.44 to 11.73), but less weight gain (2 RCTs, N = 328, MD -0.99, 95%CI -1.86 to -0.12, I^2 = 10%, *p* = 0.29), less QTc prolongation (2 RCTs, N = 495, MD -18.60, 95%CI -22.37 to 14.83, I^2 = 0%), and less sexual dysfunction in men (2 RCTs, N = 437, RR 0.34, 95%CI 0.16 to 0.76, I^2 = 0%). Compared to ziprasidone: risperidone produced more extrapyramidal side effects (2 RCTs, N = 822, RR 1.42, 95%CI 1.03 to 1.96, I^2 = 0%) and more cholesterol increase (2 RCTs, N = 767, MD 8.58, 95%CI 1.11 to 16.04, I^2 = 0%). Authors report that risperidone increased prolactin levels more than all comparators, except amisulpride and sertindole as no data were available.
Consistency in results	Consistent apart from weight gain in the comparisons with clozapine and olanzapine. Moderate inconsistency in ziprasidone efficacy comparison.
Precision in results	Precise for olanzapine and ziprasidone efficacy comparisons for binary variables, imprecise or unable to assess otherwise. Mostly imprecise for side effects.
Directness of results	Direct

Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Duggan L, Kissling W, Leucht S. Olanzapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD006654 DOI: 10.1002/14651858.CD006654.pub2.

The review includes 50 RCTs (N = 9476) of olanzapine compared to amisulpride, aripiprazole, clozapine, quetiapine, risperidone or ziprasidone,

Olanzapine had greater improvement of general mental state (measured by PANSS) compared to risperidone (15 RCTs, N = 2390, WMD -1.94, 95%CI -3.31 to -0.58, I^2 = 0%, *p* = 0.65).

Olanzapine had significantly fewer participants leave the study early due to inefficacy compared to risperidone (14 RCTs, N = 2744, RR 0.78, 95%CI 0.62 to 0.98, NNT 50, I^2 = 11%, *p* = 0.33).

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Risks	Olanzapine induced more weight gain compared to risperidone (13 RCTs, N = 2116, WMD 2.61kg, 95%CI 1.48kg to 3.74kg, I^2 = 83%, p < 0.00001). Related effects such as increases in glucose and cholesterol levels were also more frequent with olanzapine. Olanzapine was associated with less extrapyramidal side effects than risperidone (13 RCTs, N = 2599, RR 0.78, 95%CI 0.65 to 0.95, NNH 17, I^2 = 28%, p = 0.17). Olanzapine increased prolactin less than risperidone (6 RCTs, N = 1291, WMD -22.84, 95%CI -27.98 to -17.69, I^2 = 65%, p = 0.01).
Consistency in results	Consistent for all except weight gain and prolactin.
Precision in results	Precise for dichotomous outcomes, unable to assess continuous measures.
Directness of results	Direct
Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, Srisurapanont M, Kissling W, Leucht S. Quetiapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD006625 DOI: 10.1002/14651858.CD006625.pub2.	
This review includes 21 RCTs (N = 4101) compared quetiapine with clozapine, olanzapine, risperidone or ziprasidone. No significant difference in study attrition was reported between the interventions, both had high numbers of participants leaving the study early. Compared to risperidone, quetiapine had lower efficacy for reducing symptom severity (9 RCTs, N = 1953, WMD 3.09, 95%CI 1.01 to 5.16, I^2 = 24%, p = 0.23).	
Risks	Compared with risperidone, quetiapine induced fewer movement disorders (as measured by use of antiparkinson medication, 6 RCTs, N = 1715, RR 0.5, 95%CI 0.3 to 0.86, NNH 20, I^2 = 37%, p = 0.16), less prolactin increase (6 RCTs, N = 1731, WMD -35.28, 95%CI -44.36 to -26.19, I^2 = 9%, p < 0.00001), but more cholesterol increase (5 RCTs, N = 1433, WMD 8.61, 95%CI 4.66 to 12.56, I^2 = 5%, p = 0.38).
Consistency in results	Consistent, inconsistent for prolactin increase only.
Precision in results	Imprecise for dichotomous outcomes, unable to assess continuous outcomes.
Directness of results	Direct
Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Silveira da Mota Neto JI, Kissling W, Leucht S. Amisulpride versus other atypical antipsychotics for schizophrenia.	

Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD006624. DOI: 10.1002/14651858.CD006624.pub2.	
This review includes 10 RCTs (N = 1549) compared amisulpride to olanzapine, risperidone or ziprasidone. No significant difference was reported between any intervention for study attrition. Compared to ziprasidone, amisulpride was more effective (measured as leaving the study early due to inefficacy: N = 123, 1 RCT, RR 0.21, 95%CI 0.05 to 0.94, NNT 8 CI 5 to 50). No significant differences in efficacy were reported compared to olanzapine and risperidone.	
Risks	Compared to risperidone, amisulpride induced less weight gain (N = 585, 3 RCTs, MD -0.99, 95%CI -1.61 to -0.37, I^2 = 0%, p = 0.80). There was no difference in cardiac effects compared to risperidone (akathisia: N = 586, 3 RCTs, RR 0.80 CI 0.58 to 1.11, I^2 = 0%, p = 0.64). Compared to olanzapine, amisulpride also induced less weight gain (N = 671, 3 RCTs, MD -2.11, 95%CI -2.94 to -1.29, I^2 = 0%, p = 0.58). Olanzapine was also associated with a higher increase of glucose (N =406, 2 RCTs, MD -7.30, 95%CI -7.62 to -6.99, I^2 = 0%, p = 0.52).There was no difference in terms of cardiac effects and extra pyramidal symptoms (EPS) compared with olanzapine (akathisia: N = 587, 2 RCTs, RR 0.66 CI 0.36 to 1.21, I^2 = 0%, p = 0.51). There was no difference in cardiac effects compared to ziprasidone (akathisia: N = 123, 1 RCT, RR 0.63, CI 0.11 to 3.67).
Consistency in results	Consistent, no significant heterogeneity in reported outcomes.
Precision in results	Imprecise for binary data, unable to assess continuous measures.
Directness of results	Direct
Li C, Xia J, Wang J. Risperidone dose for schizophrenia. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.:CD007474. DOI: 10.1002/14651858.CD007474.pub2.	
This review includes 11 RCTs (N = 2498) comparing differing risperidone dosages. Ultra-low dose (<2 mg/day) vs. standard-low doses (4-6 mg/day) resulted in higher attrition due to insufficient response in the ultra-low dose group (1 RCT, N = 456, RR 2.48, 95%CI 1.43 to 4.30). Low doses (2-4 mg/day) vs. standard-high doses (6-10 mg/day) and vs. high doses (≥10 mg/day), resulted in higher attrition due to insufficient response in the low doses group (2 RCTs, N = 173, 6-10 mg/day: RR 4.05, 95%CI 1.09 to 15.07; ≥10 mg/day: RR 1.92, 95%CI 1.36 to 2.70). Standard-low doses (4-6 mg/day) vs. high doses (≥10 mg/day) resulted in less study attrition in the standard-low doses group (1 RCT, N = 677, RR leaving any reason 0.74, 95%CI 0.54 to 1.00; RR	

due to adverse effects 0.56, 95%CI 0.32 to 0.97). Low doses (2-4 mg/day) vs. standard-low doses (4-6 mg/day) resulted in improved endpoint scores on PANSS in the low doses group (1 RCT, N = 124, MD -12.40, 95%CI -17.01 to -7.79). Low doses (2-4 mg/day) vs. standard-high doses (6-10 mg/day) resulted in less clinically important improvement in the low doses group (2 RCT, N = 272, RR 2.26, 95%CI 0.81 to 6.34). Standard-low doses (4-6 mg/day) vs. standard-high doses (6-10 mg/day) resulted in no differences in clinically important improvement (1 RCT, N = 39, RR 0.79, 95%CI 0.29 to 2.17). High doses (≥10 mg/day) vs. low doses (2-4 mg/day) resulted in improvements in more clinically important improvement in the high doses group (2 RCT, N = 257, RR 0.64, 95%CI 0.50 to 0.82). High doses (≥10 mg/day) vs standard-high doses (6-10 mg/day) resulted in less clinically important improvement in the high doses group (2 RCT, N = 255, RR 1.22, 95%CI 1.00 to 1.51).	
Risks	Low doses vs. other higher doses showed no differences in terms of cardiovascular, CNS, endocrine or gastrointestinal adverse effects. Unspecified movement disorders were more frequent with the higher doses vs. low doses group (≥10 mg: N = 262, 2 RCTs, RR 0.45, 95%CI 0.24 to 0.84; 4-6 mg/day 1 RCT, N = 124, 1 RCT, RR 2.28, 95%CI 1.67 to 3.11).
Consistency in results	Consistent where applicable.
Precision in results	Precise only for high doses vs. low doses comparison of clinical improvement.
Directness of results	Direct
Marriott RG, Neil W, Waddingham S. Antipsychotic medication for elderly people with schizophrenia. Cochrane Database of Systematic Reviews 2006; Issue 1. Art. No.: CD005580 DOI: 10.1002/14651858.CD005580.	
This review includes 3 RCTs (N = 252 elderly people with schizophrenia). Compared with second generation antipsychotic, olanzapine there were no differences in global state (N = 171, 1 RCT, RR 1.26 CI 0.8 to 1.9) and mental state (N =171, 1 RCT, RR 0.98 CI 0.76 to 1.26).	
Risks	Not reported.
Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise
Directness of results	Direct

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Rattehalli RD, Jayaram MB, Smith M. Risperidone versus placebo for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD006918. DOI: 10.1002/14651858.CD006918.pub2	
This review includes 10 RCTs (N = 1363) comparing risperidone and placebo. Compared to placebo, risperidone had lower attrition (N = 1363, 10 RCTs, RR 0.70, 95%CI 0.57 to 0.86, NNT 13 CI 9 to 29, I^2 = 36%, *p* = 0.12) and fewer participants on risperidone left the trial due to lack of efficacy (N = 888, 5 RCTs, RR 0.38, 95%CI 0.20 to 0.73, NNT 7 CI 5 to 15, I^2 = 69%, *p* = 0.01). Compared to placebo, risperidone did not significantly improve global state (measured by CGI) (N = 397, 3 RCTs, RR 0.80, 95%CI 0.55 to 1.15, I^2 = 84%, *p* = 0.002), but significantly reduced symptom ratings (measured by BPRS/PANSS) (N = 856, 7 RCTs, RR 0.70, 95%CI 0.62 to 0.79, NNT 7 CI 6 to 10, I^2 = 75%, *p* = 0.0005). Fewer participants on risperidone needed an additional psychotropic medication compared to placebo (N = 186, 1 RCT, RR 0.62, 95%CI 0.45 to 0.85, NNT 10 CI 7 to 28).	
Risks	Increased risk of extrapyramidal side effects for participants on risperidone (N = 723, 5 RCTs, RR 1.40, 95%CI 0.93 to 2.10, I^2 = 0%, *p* = 0.76). One study reported three participants experiencing prolonged QTc (N = 198, 1 RCT, RR 7.5, 95%CI 0.4 to 144). More participants on risperidone gained weight (N = 303, 2 RCTs, RR 5.14, 95%CI 1.79 to 14.73, NNH 10 CI 3 to 51, I^2 = 0%, *p* = 0.84) and had a raised prolactin (N = 323, 2 RCTs, RR 12.54, 95%CI 5.11 to 30.79, NNH 3 CI 2 to 5, I^2 = 42%, *p* = 0.19).
Consistency in results	Inconsistent for efficacy measures apart from attrition, and consistent for all adverse effects.
Precision in results	Precise for attrition and symptom severity only.
Directness of results	Direct

Sivaraman P, Rattehalli RD, Jayaram MB. Levomepromazine for schizophrenia (Review). Cochrane Database of Systematic Reviews 2010, Issue 10. Art No.: CD007779. DOI: 10.1002/14651858.CD007779.pub2.	
The review includes 1 RCT, N = 42 (21 risperidone, 21 levomepromazine) Levomepromazine was not significantly different to risperidone for rates of leaving the study early. Risperidone was better than levomepromazine for CGI endpoint scores (N = 42, 1 RCT, RR 2.33, 95%CI 1.11 to 4.89, *p* = 0.025). Those receiving risperidone showed significant improvement in BPRS endpoint scores (N = 42, 1 RCT, RR 3.33, 95%CI 1.07 to 10.42, NNT 3 CI 2 to 14) over levomepromazine.	
Risks	Compared with risperidone, levomepromazine caused more hypotension (N = 42, 1 RCT, RR = 2.50, 95%CI 1.21 to 5.18, *p* =

	0.014). Dizziness was common with levomepromazine compared with other antipsychotic medications.
Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise
Directness of results	Direct

Subramanian S, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Kissling W, Leucht S, Komossa K. Zotepine versus other atypical antipsychotics for schizophrenia (Review). Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD006628.

This review includes three RCTs (N = 289).

No significant difference in study retention was reported.

There was no difference in symptom severity (BPRS) between zotepine and risperidone (vs 4 mg: N = 40, 1 RCT, MD 1.40, 95%CI -9.82 to 12.62, *p* = 0.81; vs. 8 mg N = 40, 1 RCT, MD -1.30, 95%CI -12.95 to10.35, *p* = 0.83).

Risks	No significant difference between zotepine and risperisone in extrapyramidal symptoms measured as use of antiparkinson medication (vs 4 mg: N = 40, 1 RCT, MD 1.80, 95%CI -0.64 to 4.24, *p* = 0.15; vs 8 mg: N = 40, 1 RCT, MD 2.50 95%CI -0.05 to 5.05, *p* = 0.055).
Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise. Unable to assess as standardised values are not reported.
Directness of results	Direct

Explanation of acronyms

BPRS – Brief Psychiatric Rating Scale, CGI = Clinical Global Impression scale, CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, mg = milligram, N = number of participants, NNH = number of patients needed to treat for one to show one negative effect, NNT = number of patients needed to treat for one to show a positive effect, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = relative risk, vs = versus, WMD = weighted mean difference

Explanation of technical terms

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[1].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[17]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

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‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[1];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

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§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered

imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[18].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

References

1. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Hamann J, Kissling W, Leucht S, Rummel-Kluge C (2003): New generation antipsychotics for first episode schizophrenia. *Cochrane Database of Systematic Reviews*.
4. Hosalli P, Davis JM (2003): Depot risperidone for schizophrenia. *Cochrane Database of Systematic Reviews*.
5. Hunter RH, Joy CB, Kennedy E, Gilbody SM, Song F (2003): Risperidone versus typical antipsychotic medication for schizophrenia. *Cochrane Database of Systematic Reviews*: CD000440.
6. Jayaram MB, Hosalli P, Stroup S (2006): Risperidone versus olanzapine for schizophrenia. *Cochrane Database of Systematic Reviews*: CD005237.
7. Marriott RG, Neil W, Waddingham S (2006): Antipsychotic medication for elderly people with schizophrenia. *Cochrane Database of Systematic Reviews*: CD005580.
8. Rattehalli RD, Jayaram MB, Smith M (2010): Risperidone versus placebo for schizophrenia. *Cochrane Database of Systematic Reviews*: CD006918.
9. Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, Srisurapanont M*, et al.* (2010): Quetiapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*: CD006625.
10. Asenjo Lobos C, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S*, et al.* (2010): Clozapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*: Treatment.
11. Subramanian S, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Kissling W*, et al.* (2010): Zotepine versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*.
12. Sivaraman P, Rattehalli RD, Jayaram MB (2010): Levomepromazine for schizophrenia. *Cochrane Database of Systematic Reviews*.
13. Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Duggan L*, et al.* (2010): Olanzapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews* 3: CD006654.
14. Li C, Xia J, Wang J (2009): Risperidone dose for schizophrenia. *Cochrane Database of Systematic Reviews*: CD007474.
15. Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Silveira da Mota Neto JI*, et al.* (2010): Amisulpride versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*: CD006624.
16. Komossa K, Rummel-Kluge C, Schwarz S, Schmid F, Hunger H, Kissling W*, et al.* (2011): Risperidone versus other atypical antipsychotics for schizophrenia. *Cochrane database of systematic reviews* 1: CD006626.
17. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
18. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*