TECHNICAL COMMENTARY

All antipsychotics versus placebo

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Introduction

Antipsychotics are effective for the symptoms of schizophrenia. Positive symptoms include the experiences of perceptual abnormalities (hallucinations) and fixed, false, irrational beliefs (delusions). Negative symptoms include a lack of ordinary mental activities such as emotional expression, social engagement, and motivation.

Antipsychotics can also cause side effects. These include extrapyramidal symptoms such as dyskinesias (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 (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 antipsychotics. Other side effects may include weight, hormonal and metabolic changes, increased sedation, and ventricular anomalies (QTc prolongation).

This table presents the current evidence for the efficacy and side effects of antipsychotics when compared to placebo in randomised controlled trials.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

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 randomised controlled trials (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 or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

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Results

We found three systematic reviews that met inclusion criteria[3-5].

- Overall, moderate to high quality evidence finds a medium-sized effect of greater total symptom improvement with antipsychotics compared to placebo. There was less variability in the response to antipsychotics than in the response to placebo, with older studies, those with younger patients, higher dose treatments, and greater mean difference in symptom change being associated with the least variability.
- For particular antipsychotics, there were symptom improvements with (in descending order of efficacy): clozapine (for total, positive, negative, and depressive symptoms), amisulpride (for total, positive, negative and depressive symptoms), thiotixene (for total symptoms), zotepine (for total and negative symptoms), olanzapine (for total, positive, negative, and depressive symptoms), perphenazine (for total, positive, and negative symptoms), risperidone (for total, positive, negative, and depressive symptoms), thioridazine (for total symptoms), zuclopenthixol (for total symptoms), paliperidone (for total, positive, negative, and depressive symptoms), sulpiride (for total and depressive symptoms), haloperidol (for total, positive, negative, and depressive symptoms), loxapine (for total symptoms), chlorpromazine (for total, positive, and negative symptoms), flupentixol (for total symptoms), clopenthixol (for total symptoms), molindone (for total symptoms), quetiapine (for total, positive, negative, and depressive symptoms), aripiprazole (for total, positive, negative, and depressive symptoms), ziprasidone (for total, positive, negative, and depressive symptoms), sertindole (for total, positive, and negative symptoms), asenapine (for total, positive, negative, and depressive symptoms), lurasidone (for total, positive, negative, and depressive symptoms), cariprazine (for total, positive, negative, and depressive symptoms), iloperidone (for total, positive, and negative symptoms), and brexpiprazole (for total, positive, negative, and depressive symptoms).
- There were no significant differences in total symptoms between placebo and penfluridol, pimozide, perazine, fluphenazine, trifluoperazine, and levomepromazine.
- For social functioning, there were improvements with (in descending order of efficacy) thioridazine, olanzapine, paliperidone, quetiapine, lurasidone, and brexpiprazole. There were no improvements in social functioning with aripiprazole, sertindole, amisulpride, ziprasidone, flupentixol, or risperidone.
- For all-cause discontinuation (in order of descending effects, first being best), there was less discontinuation with clopenthixol, amisulpride, olanzapine, paliperidone, thiotixene, thioridazine, clozapine, loxapine, iloperidone, perphenazine, aripiprazole, risperidone, zuclopenthixol, zotepine, asenapine, quetiapine, lurasidone, brexpiprazole, haloperidol, and ziprasidone. There were no differences between placebo and perazine, levomepromazine, flupentixol, molindone, fluphenazine, chlorpromazine, cariprazine, sulpiride, sertindole, penfluridol, trifluoperazine, and pimozide.
- For side effects (in ascending order of harm), there was less use of antiparkinson drugs with clozapine, and more use of antiparkinson drugs with paliperidone, ziprasidone, risperidone, lurasidone, zotepine, cariprazine, chlorpromazine, sulpiride, perphenazine, molindone, zuclopenthixol, trifluoperazine, flupentixol, haloperidol, loxapine, penfluridol, fluphenazine, chlorpromazine, thiotixene, and pimozide.
- There was more akathisia with aripiprazole, ziprasidone, thioridazine, asenapine, amisulpride, chlorpromazine, thiotixene, risperidone, cariprazine, loxapine, haloperidol, lurasidone, trifluoperazine,

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sulpiride, molindone, penfluridol, pimozide, fluphenazine, flupentixol, and zuclopenthixol.

- There was more weight gain with haloperidol, amisulpride, asenapine, risperidone, paliperidone, clozapine, quetiapine, iloperidone, chlorpromazine, sertindole, olanzapine, and zotepine.
- There was less prolactin elevation with aripiprazole, clozapine, and zotepine, and more prolactin elevation with olanzapine, asenapine, lurasidone, sertindole, haloperidol, amisulpride, risperidone, and paliperidone.
- There was more sedation with aripiprazole, lurasidone, haloperidol, risperidone, asenapine, loxapine, olanzapine, chlorpromazine, thioridazine, thiotixene, ziprasidone, perazine, clozapine, clopenthixol, quetiapine, sulpiride, zotepine, and zuclopenthixol.
- There was more QTc prolongation with quetiapine, olanzapine, risperidone, iloperidone, ziprasidone, amisulpride, and sertindole.
- There was more anticholinergic side-effects haloperidol, olanzapine, clozapine, chlorpromazine, zotepine, iloperidone, thioridazine, and quetiapine.
- Moderate to high quality evidence shows symptom severity worsened by ~10% over one year in patients continuing antipsychotic treatment, while symptom severity worsened by ~50% over one year in those switching to placebo treatment.

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Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, Arndt T, Backers L, Rothe P, Cipriani A, Davis J, Salanti G, Leucht S

Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis

The Lancet 2019; 394: 918

View review abstract online

Comparison	**All antipsychotics vs. placebo for 3-13 weeks.** **Studies with a high risk of bias were excluded.**
Summary of evidence	**In order of first being best, moderate to high quality evidence (large samples, mostly consistent and precise, some indirectness) finds improvements in symptoms with clozapine (total, positive, negative, and depressive), amisulpride (total, positive, negative and depressive), thiotixene (total), zotepine (total and negative), olanzapine (total, positive, negative, and depressive), perphenazine (total, positive, and negative), risperidone (total, positive, negative, and depressive), thioridazine (total), zuclopenthixol (total), paliperidone (total, positive, negative, and depressive), sulpiride (total and depressive), haloperidol (total, positive, negative, and depressive), loxapine (total), chlorpromazine (total, positive, and negative), flupentixol (total), clopenthixol (total), molindone (total), quetiapine (total, positive, negative, and depressive), aripiprazole (total, positive, negative, and depressive), ziprasidone (total, positive, negative, and depressive), sertindole (total, positive, and negative), asenapine (total, positive, negative, and depressive), lurasidone (total, positive, negative, and depressive), cariprazine (total, positive, negative, and depressive), iloperidone (total, positive, and negative), brexpiprazole (total, positive, negative, and depressive).** **There were no significant differences in total symptoms between placebo and penfluridol, pimozide, perazine, fluphenazine, trifluoperazine, and levomepromazine.** **For social functioning (in order of descending effects, first being best), there were improvements with thioridazine, olanzapine, paliperidone, quetiapine, lurasidone, and brexpiprazole. There were no improvements with aripiprazole, sertindole,**

	amisulpride, ziprasidone, flupentixol, and risperidone. **For all-cause discontinuation (in order of descending effects, first being best), there was less discontinuation with clopenthixol, amisulpride, olanzapine, paliperidone, thiotixene, thioridazine, clozapine, loxapine, iloperidone, perphenazine, aripiprazole, risperidone, zuclopenthixol, zotepine, asenapine, quetiapine, lurasidone, brexpiprazole, haloperidol, and ziprasidone. There were no differences between placebo and perazine, levomepromazine, flupentixol, molindone, fluphenazine, chlorpromazine, cariprazine, sulpiride, sertindole, penfluridol, trifluoperazine, and pimozide.** **For side effects in order of first being best, there was a large effect of less use of antiparkinson drugs with clozapine, and more use of antiparkinson drugs with paliperidone, ziprasidone, risperidone, lurasidone, zotepine, cariprazine, chlorpromazine, sulpiride, perphenazine, molindone, zuclopenthixol, trifluoperazine, flupentixol, haloperidol, loxapine, penfluridol, fluphenazine, chlorpromazine, thiotixene and pimozide.** **There was more akathisia with aripiprazole, ziprasidone, thioridazine, asenapine, amisulpride, chlorpromazine, thiotixene, risperidone, cariprazine, loxapine, haloperidol, lurasidone, trifluoperazine, sulpiride, molindone, penfluridol, pimozide, fluphenazine, flupentixol, and zuclopenthixol.** **There was more weight gain with haloperidol, amisulpride, asenapine, risperidone, paliperidone, clozapine, quetiapine, iloperidone, chlorpromazine, sertindole, olanzapine, and zotepine.** **There was less prolactin elevation with aripiprazole, clozapine, and zotepine, and more prolactin elevation with olanzapine, asenapine, lurasidone, sertindole, haloperidol, amisulpride, risperidone, and paliperidone.** **There was more sedation with aripiprazole, lurasidone, haloperidol, risperidone, asenapine, loxapine, olanzapine, chlorpromazine, thioridazine, thiotixene, ziprasidone, perazine, clozapine, clopenthixol, quetiapine, sulpiride, zotepine, and zuclopenthixol.** **There was more QTc prolongation with quetiapine, olanzapine, risperidone, iloperidone, ziprasidone, amisulpride, and sertindole.** **There was more anticholinergic side-effects haloperidol, olanzapine, clozapine, chlorpromazine, zotepine, iloperidone,**

	thioridazine, and quetiapine.
Symptoms	
218 RCTs, N = 40,815 *Large effects of more improvement in symptoms with (in descending order of effect size);* <u>Clozapine</u> N = 8,337, SMD = -0.89, 95%CrI -1.08 to -0.71, $p < 0.05$ The effects were significant and medium-sized in the subgroup analyses of positive (SMD = -0.64), negative (SMD = -0.62), and depressive (SMD = -0.52) symptoms. *Medium-sized effects of more improvement in symptoms with (in descending order of effect size);* <u>Amisulpride</u> N = 8,712, SMD = -0.73, 95%CrI -0.89 to -0.58, $p < 0.05$ The effects were significant and medium-sized in the subgroup analyses of positive (SMD = -0.69), negative (SMD = -0.50), and depressive (SMD = -0.44) symptoms. <u>Thiotixene</u> N = 8,138, SMD = -0.63, 95%CrI -0.97 to -0.30, $p < 0.05$ The effect was not significant in the subgroup analysis of depressive symptoms (SMD = -0.17). <u>Zotepine</u> N = 8,312, SMD = -0.61, 95%CrI -0.82 to -0.40, $p < 0.05$ The effect was significant and medium-sized in the subgroup analysis of negative symptoms (SMD = -0.54), and non-significant for depressive symptoms (SMD = -0.26). <u>Olanzapine</u> N = 13,669, SMD = -0.56, 95%CrI -0.62 to -0.50, $p < 0.05$ The effects were significant and medium-sized in the subgroup analyses of positive (SMD = -0.53) and negative (SMD = -0.45) symptoms, and small for depressive symptoms (SMD = -0.37). <u>Perphenazine</u> N = 8,445, SMD = -0.56, 95%CrI -0.75 to -0.38, $p < 0.05$ The effects were significant and medium-sized in the subgroup analyses of positive (SMD = -0.45) and negative symptoms (SMD = -0.42), and non-significant for depressive symptoms (SMD = -0.22). <u>Risperidone</u> N = 11,849, SMD = -0.55, 95%CrI -0.62 to -0.48, $p < 0.05$ The effect was significant and medium-sized in the subgroup analysis of positive symptoms (SMD = -0.61), and significant and small for negative (SMD = -0.37), and depressive (SMD = -0.23) symptoms.	

Thioridazine

N = 8,188, SMD = -0.54, 95%CrI -0.82 to -0.27, $p < 0.05$

There were no subgroup analyses of symptom type.

Zuclopenthixol

N = 8,245, SMD = -0.51, 95%CrI -0.75 to -0.27, $p < 0.05$

There were no significant effects in the subgroup analyses of positive (SMD = -0.43), negative (SMD = -0.17), or depressive symptoms (SMD = -0.16).

Paliperidone

N = 9,651, SMD = -0.49, 95%CrI -0.59 to -0.38, $p < 0.05$

The effect was significant and medium-sized in the subgroup analysis of positive symptoms (SMD = -0.53), and significant and small for negative (SMD = -0.37), and depressive (SMD = -0.33) symptoms.

Sulpiride

N = 8,133, SMD = -0.48, 95%CrI -0.87 to -0.09, $p < 0.05$

The effect was significant and large in the subgroup analysis of depressive symptoms (SMD = -0.90)

Haloperidol

N = 12,467, SMD = -0.47, 95%CrI -0.53 to -0.41, $p < 0.05$

The effect was significant and medium-sized in the subgroup analysis of positive symptoms (SMD = -0.49), and significant and small for negative (SMD = -0.29), and depressive (SMD = -0.17) symptoms.

Loxapine

N = 8,356, SMD = -0.45, 95%CrI -0.63 to -0.26, $p < 0.05$

There were no significant effects in the subgroup analyses of positive (SMD = -0.21) or depressive symptoms (SMD = -0.12).

Chlorpromazine

N = 8,808, SMD = -0.44, 95%CrI -0.57 to -0.31, $p < 0.05$

The effect was significant and medium-sized in the subgroup analyses of positive symptoms (SMD = -0.57), significant and small for negative symptoms (SMD = -0.35), and non-significant for depressive symptoms (SMD = -0.18).

Flupentixol

N = 8,155, SMD = -0.43, 95%CrI -0.77 to -0.08, $p < 0.05$

There were no significant effects in the subgroup analyses of positive (SMD = -0.38), negative (SMD = -0.10), or depressive symptoms (SMD = 0.04).

Clopenthixol

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N = 8,127, SMD = -0.42, 95%CrI -0.78 to -0.06, $p < 0.05$

There was no significant effect in the subgroup analysis of depressive symptoms (SMD = -0.06).

Molindone

N = 8,134, SMD = -0.42, 95%CrI -0.78 to -0.04, $p < 0.05$

There was no significant effect in the subgroup analysis of depressive symptoms (SMD = -0.06).

Quetiapine

N = 11,069, SMD = -0.42, 95%CrI -0.50 to -0.33, $p < 0.05$

The effect was significant and medium-sized in the subgroup analyses of positive symptoms (SMD = -0.40), and significant and small for negative (SMD = -0.31) and depressive (SMD = -0.24) symptoms.

Aripiprazole

N = 9,993, SMD = -0.41, 95%CrI -0.50 to -0.32, $p < 0.05$

The effects were significant and small to medium-sized in the subgroup analyses of positive (SMD = -0.38), negative (SMD = -0.33) and depressive (SMD = -0.40) symptoms.

Ziprasidone

N = 9,295, SMD = -0.41, 95%CrI -0.52 to -0.30, $p < 0.05$

The effects were significant and small to medium-sized in the subgroup analyses of positive (SMD = -0.43), negative (SMD = -0.33) and depressive (SMD = -0.21) symptoms.

Sertindole

N = 8,935, SMD = -0.40, 95%CrI -0.54 to -0.26, $p < 0.05$

The effects were significant and small to medium-sized in the subgroup analyses of positive (SMD = -0.40) and negative (SMD = -0.37) symptoms, and non-significant for depressive symptoms (SMD = -0.11).

Small effects of more improvement in symptoms with (in descending order of effect size);

Asenapine

N = 9,094, SMD = -0.39, 95%CrI -0.52 to -0.26, $p < 0.05$

The effects were significant and medium-sized in the subgroup analyses of positive (SMD = -0.47) and negative symptoms (SMD = -0.42), and significant and small for depressive symptoms (SMD = -0.32).

Lurasidone

N = 9,430, SMD = -0.36, 95%CrI -0.48 to -0.24, $p < 0.05$

The effects were significant and small in the subgroup analyses of positive (SMD = -0.33), negative (SMD = -0.29), and depressive (SMD = -0.20) symptoms.

Cariprazine

N = 9,066, SMD = -0.34, 95%CrI -0.49 to -0.20, $p < 0.05$

The effects were significant and small in the subgroup analyses of positive (SMD = -0.30), negative (SMD = -0.32), and depressive (SMD = -0.36) symptoms.

Iloperidone

N = 10,224, SMD = -0.33, 95%CrI -0.44 to -0.22, $p < 0.05$

The effects were significant and small in the subgroup analyses of positive (SMD = -0.30) and negative (SMD = -0.22) symptoms.

Brexpiprazole

N = 9,247, SMD = -0.26, 95%CrI -0.39 to -0.12, $p < 0.05$

The effects were significant and small in the subgroup analyses of positive (SMD = -0.17), negative (SMD = -0.25), and depressive (SMD = -0.16) symptoms.

There were no significant effects for;

Penfluridol

N = 8,071, SMD = -0.39, 95%CrI -1.13 to 0.36, $p > 0.05$

The effect was non-significant in the subgroup analysis of depressive symptoms (SMD = -0.18).

Pimozide

N = 8,111, SMD = -0.30, 95%CrI -0.75 to 0.14, $p > 0.05$

The effect was non-significant in the subgroup analysis of depressive symptoms (SMD = -0.20).

Perazine

N = 8,118, SMD = -0.29, 95%CrI -0.72 to 0.14, $p > 0.05$

The effect was non-significant in the subgroup analysis of depressive symptoms (SMD = -0.26).

Fluphenazine

N = 8,120, SMD = -0.24, 95%CrI -0.62 to 0.13, $p > 0.05$

There were no subgroup analyses of symptom type.

Trifluoperazine

N = 8,190, SMD = -0.24, 95%CrI -0.53 to 0.05, $p > 0.05$

The effect was non-significant in the subgroup analysis of depressive symptoms (SMD = -0.17).

Levomepromazine

N = 8,088, SMD = -0.03, 95%CrI -0.59 to 0.52, $p > 0.05$

The effects were non-significant in the subgroup analyses of positive (SMD = -0.18) and depressive symptoms (SMD = -0.09).

Moderator analyses

Older antipsychotics had less placebo response than newer ones, which had the greatest effect on heterogeneity across studies. The effect sizes of the individual antipsychotics changed after accounting for response to placebo, but the overall hierarchy did not.

Year of publication, mean participants' age, baseline severity, percentage of male patients, sample size, and sponsoring did not affect the hierarchy of treatment effects. Sensitivity analyses removing studies with overall high risk of bias, completer analyses, imputed standard deviations, duration more than six weeks, unfair dose comparisons, failed trials, and trials conducted before 1990 also did not affect the results.
Social functioning
16 RCTs, N = 4,370 *Medium-sized effects of better social functioning with (in descending order of effect size);* Thioridazine N = 1,121, SMD = -0.69, 95%CrI -1.24 to -0.14, $p < 0.05$ Olanzapine N = 1,313, SMD = -0.53, 95%CrI -0.73 to -0.33, $p < 0.05$ Paliperidone N = 1,868, SMD = -0.51, 95%CrI -0.66 to -0.37, $p < 0.05$ Quetiapine N = 1,306, SMD = -0.47, 95%CrI -0.72 to -0.22, $p < 0.05$ Lurasidone N = 1,292, SMD = -0.44, 95%CrI -0.72 to -0.16, $p < 0.05$ *Small effects of better social functioning with;* Brexpiprazole N = 2,012, SMD = -0.25, 95%CrI -0.38 to -0.12, $p < 0.05$ *There were no significant effects of;* Aripiprazole N = 1,144, SMD = -0.23, 95%CrI -0.55 to 0.09, $p > 0.05$ Sertindole N = 1,153, SMD = -0.09, 95%CrI -0.68 to 0.49, $p > 0.05$ Amisulpride N = 1,301, SMD = -0.01, 95%CrI -0.52 to 0.49, $p > 0.05$ Ziprasidone N = 1,219, SMD = 0.04, 95%CrI -0.47 to 0.55, $p > 0.05$ Flupentixol N = 1,156, SMD = 0.11, 95%CrI -0.51 to 0.76, $p > 0.05$ Risperidone

N = 1,519, SMD = 0.10, 95%CrI -0.33 to 0.52, $p > 0.05$
All-cause discontinuation
216 RCTs, N = 42,672 *Small effects of less all-cause discontinuation with (in descending order of effect size);* Clopenthixol N = 8,449, RR = 0.52, 95%CrI 0.12 to 0.95, $p < 0.05$ Amisulpride N = 9,121, RR = 0.67, 95%CrI 0.55 to 0.78, $p < 0.05$ Olanzapine N = 13,762, RR = 0.69, 95%CrI 0.65 to 0.74, $p < 0.05$ Paliperidone N = 9,853, RR = 0.70, 95%CrI 0.62 to 0.77, $p < 0.05$ Thiotixene N = 8,533, RR = 0.71, 95%CrI 0.66 to 0.82, $p < 0.05$ Thioridazine N = 8,647, RR = 0.76, 95%CrI 0.70 to 0.88, $p < 0.05$ Clozapine N = 8,829, RR = 0.76, 95%CrI 0.59 to 0.92, $p < 0.05$ Loxapine N = 8,675, RR = 0.78, 95%CrI 0.60 to 0.95, $p < 0.05$ Iloperidone N = 10,598, RR = 0.79, 95%CrI 0.71 to 0.86, $p < 0.05$ Perphenazine N = 8,961, RR = 0.79, 95%CrI 0.68 to 0.91, $p < 0.05$ Aripiprazole N = 10,131, RR = 0.80, 95%CrI 0.73 to 0.86, $p < 0.05$ Risperidone N = 12,359, RR = 0.82, 95%CrI 0.80 to 0.85, $p < 0.05$ Zuclopenthixol N = 12,359, RR = 0.82, 95%CrI 0.74 to 0.97, $p < 0.05$ Zotepine

N = 8,711, RR = 0.82, 95%CrI 0.76 to 0.93, $p < 0.05$

Asenapine

N = 9,439, RR = 0.84, 95%CrI 0.76 to 0.92, $p < 0.05$

Quetiapine

N = 11,430, RR = 0.85, 95%CrI 0.82 to 0.89, $p < 0.05$

Lurasidone

N = 9,774, RR = 0.88, 95%CrI 0.80 to 0.96, $p < 0.05$

Brexpiprazole

N = 9,589, RR = 0.89, 95%CrI 0.80 to 0.98, $p < 0.05$

Haloperidol

N = 13,033, RR = 0.90, 95%CrI 0.85 to 0.95, $p < 0.05$

Ziprasidone

N = 9,683, RR = 0.90, 95%CrI 0.85 to 0.96, $p < 0.05$

No significant effects for;

Perazine

N = 8,487, RR = 0.79, 95%CrI 0.48 to 1.07, $p > 0.05$

Levomepromazine

N = 8,442, RR = 0.81, 95%CrI 0.46 to 1.11, $p > 0.05$

Flupentixol

N = 8,479, RR = 0.84, 95%CrI 0.53 to 1.10, $p > 0.05$

Molindone

N = 8,503, RR = 0.86, 95%CrI 0.43 to 1.21, $p > 0.05$

Fluphenazine

N = 8,459, RR = 0.89, 95%CrI 0.44 to 1.20, $p < 0.05$

Chlorpromazine

N = 9,421, RR = 0.91, 95%CrI 0.79 to 1.01, $p > 0.05$

Cariprazine

N = 8,418, RR = 0.93, 95%CrI 0.83 to 1.02, $p > 0.05$

Sulpiride

N = 8,552, RR = 0.94, 95%CrI 0.79 to 1.28, $p > 0.05$

Sertindole

N = 9,306, RR = 0.96, 95%CrI 0.89 to 1.06, $p > 0.05$

	Penfluridol N = 8,475, RR = 0.97, 95%CrI 0.45 to 1.31, *p* > 0.05 Trifluoperazine N = 8,595, RR = 0.98, 95%CrI 0.79 to 1.51, *p* > 0.05 Pimozide N = 8,468, RR = 1.15, 95%CrI 0.36 to 1.47, *p* > 0.05
Risks	*The following antipsychotics were significantly associated with;* More use of antiparkinson drugs Small effects: paliperidone, ziprasidone, risperidone, and lurasidone Medium-sized effects: zotepine, cariprazine, chlorpromazine, sulpiride, perphenazine, molindone, zuclopenthixol, trifluoperazine, flupentixol, loxapine, penfluridol, haloperidol, fluphenazine, and chlorpromazine Large effects: thiotixene and pimozide. There was a large effect of less use of antiparkinson drugs with clozapine. Akathisia Small effects: aripiprazole Medium-sized effects: ziprasidone, thioridazine, asenapine, amisulpride, chlorpromazine, thiotixene, risperidone, cariprazine, loxapine, haloperidol, lurasidone, trifluoperazine, and sulpiride, Large effects: molindone, penfluridol, pimozide, fluphenazine, flupentixol, and zuclopenthixol Weight gain In order of increasing effect (measured in kg): haloperidol, amisulpride, asenapine, risperidone, paliperidone, clozapine, quetiapine, iloperidone, chlorpromazine, sertindole, olanzapine, and zotepine Prolactin elevation Less elevation with aripiprazole, clozapine, and zotepine More elevation with olanzapine, asenapine, lurasidone, sertindole, haloperidol, amisulpride, risperidone, and paliperidone Sedation Small effects: aripiprazole, lurasidone, and haloperidol Medium-sized effects: risperidone, thioridazine, asenapine, loxapine, olanzapine, thiotixene, ziprasidone, quetiapine, perazine, chlorpromazine, sulpiride, clopenthixol, and clozapine Large effects: zotepine and zuclopenthixol

	QTc prolongation Medium-sized effects: quetiapine, olanzapine, and risperidone Large effects: iloperidone, ziprasidone, amisulpride, and sertindole Anticholinergic side-effects Small effects: haloperidol and olanzapine Medium-sized effects: clozapine, iloperidone, chlorpromazine, zotepine, thioridazine, and quetiapine
Consistency in results	Authors state that overall heterogeneity was low to moderate.
Precision in results	The significant findings are mostly precise.
Directness of results	Some indirectness; network meta-analysis.

McCutcheon RA, Pillinger T, Mizuno Y, Montgomery A, Pandian H, Vano L, Marques TR, Howes OD

The efficacy and heterogeneity of antipsychotic response in schizophrenia: A meta-analysis

Molecular Psychiatry 2019; doi: 10.1038/s41380-019-0502-5.

View review abstract online

Comparison	**All antipsychotics vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large sample, appears inconsistent, precise, direct) finds a medium-sized effect of greater total symptoms improvement with antipsychotics. There was less variability in response to antipsychotics than in response to placebo, with older studies, those with younger patients, higher dose treatments, and greater mean-difference in symptom-change being associated with less variability.**

Symptoms

A medium-sized significant effects of greater total symptom improvement with antipsychotics;

66 RCTs, N = 17,202, $g = 0.47$, 95%CI 0.42 to 0.51, $p < 0.001$

Authors report that there was less variability in symptomatic improvement in antipsychotic-response relative to placebo. Less variability was associated with older studies, younger patients, higher dose treatments, and greater mean-difference in symptom-change.

Consistency in results	Forest plot appears inconsistent.
Precision in results	Precise
Directness of results	Direct

Takeuchi H, Kantor N, Sanches M, Fervaha G, Agid O, Remington G

One-year symptom trajectories in patients with stable schizophrenia maintained on antipsychotics versus placebo: meta-analysis

The British Journal of Psychiatry 2017; 211: 137-143

View review abstract online

Comparison	**Symptom changes over time (1 year) in people with stable schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample, unable to assess consistency, precise, direct) shows symptom severity worsened by ~10% over one year in patients continuing antipsychotic treatment, while symptom severity worsened by ~50% over one year in those switching to placebo treatment.**
Symptoms	
11 studies, N = 2,826 A placebo replacement was associated with a 49.2% worsening of symptoms from baseline to 52 weeks, in contrast to 10.1% worsening of symptoms in those who continued antipsychotic treatment. Group x time interaction: $F = 10.5$, $p < 0.0001$ The results remained significant after excluding studies that used the BPRS, long-acting injectables, first-generation antipsychotics, low-dose antipsychotics, or those with a severe baseline symptom level.	
Consistency in results	Not reported.
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CrI = credible interval, *g* = Hedges' *g* standardised mean differences (see below for interpretation of effect size), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = risk ratio, SMD = standardised mean difference, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[6].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[6].

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[7]. 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.

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Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect 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.

‡ 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[6];

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

§ 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[8].

‖ 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.

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