TECHNICAL COMMENTARY

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First versus second-generation antipsychotics

Introduction

First-generation 'typical' antipsychotics are an older class of antipsychotic than second-generation 'atypical' antipsychotics. First-generation antipsychotics are used primarily to treat positive symptoms including the experiences of perceptual abnormalities (hallucinations) and fixed, false, irrational beliefs (delusions). Second-generation antipsychotics are also effective for the positive symptoms of schizophrenia, and it is sometimes claimed that they are more effective than first-generation antipsychotics in treating the negative symptoms of schizophrenia. Negative symptoms include a lack of ordinary mental activities such as emotional expression, social engagement, thinking and motivation.

Antipsychotics may cause side effects which can differ depending on which antipsychotic is being administered and on individual differences in reaction to the drug. Reactions may include extrapyramidal side effects; 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); 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 these drugs. Second-generation antipsychotics may cause less extrapyramidal side effects than first-generation antipsychotics. 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 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.

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

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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).

Results

We found four reviews that met our inclusion criteria[3-6].

Efficacy

- Moderate to high quality evidence suggests a small effect of improved overall symptoms with second-generation antipsychotics, particularly olanzapine, amilsulpride and risperidone, compared to first generation antipsychotics, particularly haloperidol (mostly high doses, > 12mg/day), which are not as effective as lower doses.
- Moderate to high quality suggests a small effect of less all-cause study discontinuation with olanzapine, risperidone or amisulpride compared to haloperidol in the short-term. Moderate quality evidence suggests only olanzapine may result in less long-term discontinuation due to drug intolerability or inefficiency.
- Moderate to high quality evidence suggests olanzapine and risperidone may improve cognition more than haloperidol, and moderate quality evidence suggests amisulpride, clozapine and sertindole may improve quality of life more than first-generation antipsychotics in general.

Side effects

- Moderate quality evidence suggests a medium effect of less extrapyramidal side effects with second-generation antipsychotics, particularly olanzapine and risperadone, than with haloperidol. Clozapine, olanzapine, and risperidone may also produce fewer extrapyramidal side effects when compared to low-potency first-generation antipsychotics.
- Moderate quality evidence suggests clozapine, quetiapine and zotepine may be more sedating, and aripiprazole less sedating than haloperidol. Compared with low-potency first-generation antipsychotics, only clozapine may be more sedating.
- Moderate to high quality evidence suggests less use of benzodiazapines, anticholinergeric medications, and beta-blockers with olanzapine than with haloperidol.
- Moderate quality evidence suggests amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine may be associated with more weight gain than haloperidol, with no differences when compared to low-potency first-generation antipsychotics. Moderate quality evidence suggests more cholesterol change with olanzapine than haloperidol, and more tryglyceride change with amisulpride than haloperidol.

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Geddes J, Freemantle N, Harrison P, Bebbington P

Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis

BMJ 2000; 321: 1371-1376

View review abstract online

Comparison	**First-generation (haloperidol or chlorpromazine) vs. second-generation antipsychotics (amisulpride, clozapine, olanzapine, quetiapine, risperidone, and sertindole) for people with schizophrenia spectrum disorders.**
Summary of evidence	**Moderate quality evidence (unclear sample sizes, unable to assess consistency, precise, direct) suggests a small significant advantage of second-generation antipsychotics compared to haloperidol, but only at high haloperidol doses (> 12mg/day).** **Moderate to low quality evidence (indirect) suggests a lower drop-out rate for second-generation antipsychotics, but only at high haloperidol doses.**

Overall symptoms

Measured by BPRS

A small, significant advantage of second-generation antipsychotics over haloperidol was reported in RCTs using high doses of haloperidol (> 12mg/day), but not in RCTs using low doses (≤ 12mg/day);

Mean haloperidol dose > 12 mg/day: SMD = -0.28, 95%CI - 0.13 to - 0.44, $p < 0.05$

Mean haloperidol dose ≤12mg/day: SMD = -0.09, 95%CI 0.07 to - 0.26, $p > 0.05$

Similarly, meta-regression showed a decreasing effect size as the dose of haloperidol or chlorpromazine decreased.

Haloperidol: 23 RCTs, dose range 6-22.5mg/day, b = -0.021 95%CI -0.003 to -0.038

Chlorpromazine: 7 RCTs, dose range 375-1000mg/day, b = -1.14, 95%CI -1.68 to -0.58

These results were unaffected by the removal of trials including treatment resistant patients, those taking sertindole, or long-term trials.

Risks	There was no significant difference in dropout rates (a proxy for tolerance) between second-generation antipsychotics and haloperidol in the RCTs that used ≤12 mg/day haloperidol (RD = -0.1%, CI - 4.6% to 4.4% $p > 0.05$), but significantly less participants taking second-generation antipsychotics than haloperidol dropped out of RCTs using > 12 mg/day haloperidol (RD = -8.3%, CI - 1.3% to 15.2%, $p < 0.05$).

Consistency in results‡	Consistency measures within subgroups not reported.
Precision in results§	Precise for efficacy, unable to assess risks (RD).
Directness of results‖	Direct for efficacy of overall first vs. second-generation antipsychotics Indirect for risks (proxy measure).

Lepping P, Sambhi RS, Whittington R, Lane S, Poole R

Clinical relevance of findings in trials of antipsychotics: systematic review

The British Journal of Psychiatry 2011; 198: 341–345

View review abstract online

Comparison	**Clinically relevant improvement after treatment with first vs. second-generation antipsychotics.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests second-generation antipsychotics are slightly more effective than first-generation antipsychotics.**

Clinically relevant improvement

Measured by BPRS or PANSS and translated into CGI–C scores

Second-generation antipsychotics resulted in slightly better clinically relevant improvement from baseline to follow-up (6-24 weeks) than first-generation antipsychotics;

Based on PANSS scores

First-generation antipsychotics: 34 datasets, N = 2,670, CGI-C = -0.7

Second-generation antipsychotics: 154 datasets, N = 17,805, CGI-C = -1.0

Range: first-generation chlorpromazine -0.2 to second generation amisulpride -2.2

Based on BPRS scores

First-generation antipsychotics: 31 datasets, N = 2,237, CGI-C = -1.3

Second-generation antipsychotics: 63 datasets, N = 7,159, CGI-C = -1.65

Range: first-generation chlorpromazine-0.1 to second generation olanzapine -2.05

CGI-C conversions: 0 = no change, -1 = threshold for minimal improvement, -2 = much improved

Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.

Directness of results	Direct

Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM

Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis

Lancet 2009; 373: 31-41

View review abstract online

Comparison	**First-generation vs. second-generation antipsychotics for people with schizophrenia spectrum disorders.**
Summary of evidence	**Moderate to high quality evidence (large samples, precise, inconsistent, direct) suggests a small effect of amilsulpride, clozapine, olanzapine and risperidone being more efficacious than first-generation antipsychotics for symptoms.** **Moderate quality evidence (small samples) suggests amisulpride, clozapine and sertindole may improve quality of life more than first-generation antipsychotics.** **Moderate quality evidence (inconsistent, some imprecision) suggests a medium effect of fewer extrapyramidal side effects with second-generation antipsychotics compared to haloperidol, however only clozapine, olanzapine, and risperidone produce fewer extrapyramidal side effects than low-potency first-generation antipsychotics. Amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine may be associated with more weight gain than haloperidol, but there may be no differences in weight gain when compared to low-potency first-generation antipsychotics. Clozapine, quetiapine and zotepine were significantly more sedating than haloperidol, and aripiprazole was significantly less sedating. Compared with low-potency first-generation antipsychotic drugs, only clozapine was significantly more sedating.**
Overall symptoms and relapse **Measured by BPRS or PANSS**	
Second-generation amisulpride showed small effects of being more efficacious for all symptom clusters than first-generation haloperidol, perphenazine, fluphenazine, or flupenthixol; Overall symptoms: 13 double-blind RCTs, N = 1,017, g = -0.31, 95%CI -0.44 to -0.19, $p < 0.0001$ Positive symptoms: 4 double-blind RCTs, N = 703, g = -0.22, 95%CI -0.37 to -0.06, $p < 0.005$	

Negative symptoms: 10 double-blind RCTs, N = 929, *g* = -0.27, 95%CI -0.40 to -0.14, *p* < 0.0001

Depression: 9 double-blind RCTs, N = 900, *g* = -0.37, 95%CI -0.51 to -0.24, *p* < 0.0001

Second-generation clozapine showed small to medium size effects of being more efficacious for all symptom clusters than first-generation haloperidol, chlorpromazine, thioridazine, levomepromazine, clopenthixol or trifluoperazine;

Overall symptoms:23 double-blind RCTs, N = 1,997, *g* = -0.52,95%CI -0.75 to -0.29, *p* < 0.0001

Positive symptoms: 10 double-blind RCTs, N = 1,080, *g* = -0.36, 95%CI -0.56 to -0.16, *p* < 0.0001

Negative symptoms: 17 double-blind RCTs, N = 1,603, *g* = -0.27,95%CI -0.42 to -0.13, *p* < 0.0001

Depression: 6 double-blind RCTs, N = 426, *g* = -0.51,95%CI -0.87 to -0.14, *p* = 0.006

Second-generation olanzapine showed small effects of being more efficacious for all symptom clusters and relapse than first-generation haloperidol, chlorpromazine, perphenazine, fluphenazine, or flupenthixol;

Overall symptoms: 28 double-blind RCTs, N = 4,966, *g* = -0.28, 95%CI -0.38 to -0.18, *p* < 0.0001

Positive symptoms: 24 double-blind RCTs, N = 4,189, *g* = -0.15, 95%CI -0.21 to -0.09, *p* < 0.0001

Negative symptoms: 24 double-blind RCTs, N = 4,187, *g* = -0.32, 95%CI -0.47 to -0.16, *p* < 0.0001

Depression: 12 double-blind RCTs, N = 2,893, *g* = -0.27, 95%CI -0.35 to -0.19, *p* < 0.0001

Relapse: 4 double-blind RCTs, N = 1,008, RR = 0.67, 95%CI 0.49 to 0.92, *p* < 0.05

Second-generation risperidone showed very small effects of being more efficacious for all symptom clusters and relapse, apart from depression, than first-generation haloperidol, chlorpromazine, perphenazine, fluphenazine, levomepromazine, clopenthixol, zuclopenthixol, or flupenthixol;

Overall symptoms: 34 double-blind RCTs, N = 4,173, *g* = -0.13, 95%CI -0.22 to 0.05, *p* = 0.002

Positive symptoms: 28 double-blind RCTs, N = 3,286, *g* = -0.13, 95%CI -0.20 to -0.05, *p* = 0.001

Negative symptoms: 30 double-blind RCTs, N = 3,455, *g* = -0.13, 95%CI -0.21 to -0.06, *p* < 0.0001

Depression: 11 double-blind RCTs, N = 1,611, *g* = -0.10, 95%CI -0.23 to 0.03, *p* = 0.145

Relapse: 5 double-blind RCTs, N = 1,174, RR = 0.74, 95%CI 0.63 to 0.87, *p* < 0.05

Aripiprazole, ziprasidone, and zotepine were not significantly different from first-generation antipsychotics for symptoms. Quetiapine showed a very small effect of *less* efficacy for positive symptoms (9 double-blind RCTs, N = 1,742, *g* = 0.14, 95%CI 0.03 to 0.26, *p* = 0.013). Sertindole reported less relapses (1 double-blind RCT, N = 282, RR = 0.17, 95%CI 0.04 to 0.73, *p* < 0.05).

Note: subgroup analysis using only non-industry sponsored studies of clozapine showed a reduction in the effect size for overall symptoms to -0.22 (*p* < 0.05); no differences in effect size were reported for olanzapine and risperidone. No consistent differences in effect size were reported depending on comparator dose (haloperidol at more or less than 12 mg/day or 7.5 mg/day, or chlorpromazine 600 mg equivalents for low-potency first-generation drugs).

Quality of life

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Only amisulpride, clozapine and sertindole were better than first-generation antipsychotics for quality of life; Amisulpride: 1 double-blind RCT, N = 194, *g* = -0.31, 95%CI -0.60 to -0.03, *p* = 0.03 Clozapine: 1 double-blind RCT, N = 113, *g* = -0.24, 95%CI -0.46 to -0.01, *p* = 0.039 Sertindole: 1 double-blind RCT, N = 105, *g* = -0.44, 95%CI -0.83 to -0.05, *p* = 0.027	
Risks	All second-generation antipsychotic drugs were associated with fewer extrapyramidal side effects than haloperidol, however, only clozapine, olanzapine, and risperidone were better than low-potency first generation antipsychotics (small to medium effects). *Versus Haloperidol;* Amisulpride: 8 RCTs, N = 783, RR = 0.58, 95%CI 0.45 to 0.76, *p* < 0.0001 Aripiprazole: 4 RCTs, N = 1,794, RR = 0.50, 95%CI 0.32 to 0.64, *p* < 0.0001 Clozapine: 3 RCTs, N = 162, RR = 0.17, 95%CI 0.03 to 0.88, *p* < 0.035 Olanzapine: 12 RCTs, N = 3,670, RR = 0.39, 95%CI0.30 to 0.51, *p* < 0.0001 Quetiapine: 5 RCTs, N = 1,167, RR = 0.43, 95%CI 0.25 to 0.74, *p* = 0.002 Risperidone: 21 RCTs, N =2,738, RR0.61, 95%CI 0.52 to 0.72, *p* < 0.0001 Sertindole: 4 RCTs, N = 1,472, RR = 0.36, 95%CI0.29 to 0.45, *p* < 0.0001 Ziprasidone: 3 RCTs, N = 501, RR = 0.50, 95%CI 0.26 to 0.96, *p* = 0.037 Zotepine: 4 RCTs, N = 398, RR = 0.59, 95%CI 0.44 to 0.79, *p* < 0.0001 *Versus low-potency first-generation antipsychotics (e.g. chlorpromazine, chlorprothixene, thioridazine, levomepromazine, perazine);* Clozapine: 11 RCTs, N = 775, RR = 0.66, 95%CI 0.48 to 0.91, *p* = 0.010 Olanzapine: 2 RCTs, N = 152, RR = 0.53, 95%CI 0.32 to 0.89, *p* = 0.016 Risperidone: 2 RCTs, N = 108, RR = 0.47, 95%CI 0.22 to 0.99, *p* = 0.046

	Amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine were associated with significantly more weight gain than haloperidol, and there were no differences in weight gain when compared to low-potency first-generation antipsychotics. *Versus haloperidol;* Amisulpride: 2 RCTs, N = 373, MD = 0.9, 95%CI 0.2 to 1.6, $p = 0.012$ Clozapine: 3 RCTs, N = 170, MD = 3.4, 95%CI 2.0 to 4.9, $p < 0.0001$ Olanzapine: 9 RCTs, N = 2,952, MD = 3.3, 95%CI 2.2 to 4.4, $p < 0.0001$ Quetiapine: 3 RCTs, N = 945, MD = 1.4, 95%CI 0.7 to 2.1, $p < 0.0001$ Risperidone: 9 RCTs, N = 1,366, MD = 1.7, 95%CI 0.9 to 2.4, $p < 0.0001$ Sertindole: 2 RCTs, N = 779, MD = 3.3, 95%CI 0.2 to 6.4, $p = 0.040$ Zotepine: 3 RCTs, N = 321, MD = 2.7, 95%CI 1.7 to 3.7, $p < 0.0001$ Clozapine, quetiapine and zotepine were significantly more sedating than haloperidol, whereas aripiprazole was significantly less sedating. Compared with low-potency first-generation antipsychotic drugs, only clozapine was significantly more sedating (small effects). *Versus haloperidol;* Aripiprazole: 2 RCTs, N = 1,602, RR = 0.65, 95%CI 0.45 to 0.95, $p = 0.024$ Clozapine: 6 RCTs, N = 655, RR = 1.50, 95%CI 1.01 to 2.23, $p = 0.043$ Quetiapine: 4 RCTs, N = 970, RR = 2.07, 95%CI 1.01 to 4.27, $p = 0.047$ Zotepine: 3 RCTs, N = 221, RR = 1.86, 95%CI 1.04 to 3.33, $p = 0.037$ *Versus low-potency first generation antipsychotics.* Clozapine: 9 RCTs, N = 928, RR = 1.32, 95%CI 1.10 to 1.59, $p = 0.003$
Consistency in results	Authors report considerable heterogeneity in some analyses.
Precision in results	Precise for symptoms, quality of life and relapse (apart from sertindole) Precise for side effects, apart from extrapyramidal side effects for clozapine, quetiapine, and ziprasidone vs. haloperidol, risperidone vs. low potency drugs, and all sedation comparisons. Unable to assess MD.
Directness of results	Direct for overall first vs. second-generation antipsychotics.

Zhang J, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU

Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis

International Journal of Neuropsychopharmacology 2013; 16: 1205-1218

View review abstract online

Comparison	**First-generation vs. second-generation antipsychotics for people with first-episode psychosis.**
Summary of evidence	**Moderate to high quality evidence (large samples, precise, inconsistent, direct) suggests a small effect of less all-cause discontinuation with olanzapine, risperidone or amisulpride compared to haloperidol in the short-term. Moderate quality evidence (imprecise) suggests only olanzapine may result in less long-term discontinuation due to intolerability or inefficiency.** **Moderate to high quality evidence (large samples, precise, inconsistent, direct) suggests risperidone may result in less relapses than haloperidol, and moderate quality evidence (imprecise) suggests ziprasidone may also result in less relapses than haloperidol.** **Moderate quality evidence (found only in pharmaceutical company sponsored trials or imprecise) suggests olanzapine and quetiapine may have a small advantage over haloperidol, and clozapine over chlorpromazine for negative symptoms. Olanzapine and amisulpride may be more efficacious for depression and overall symptoms than haloperidol.** **Moderate to high quality evidence (large samples, precise, inconsistent, direct) suggests olanzapine and risperidone may improve cognition more than haloperidol.** **Moderate to high quality evidence (large samples, precise, inconsistent, direct) suggests less extrapyramidal side effects and akathisia with olanzapine and risperidone compared to haloperidol, although olanzapine and risperidone may cause more weight gain. Moderate to high quality evidence suggests less use of benzodiazapines with olanzapine compared to haloperidol, and moderate quality evidence (imprecise) also suggests less use of anticholinergeric medications and beta-blockers with olanzapine, although cholesterol change is higher**

	than haloperidol. For tryglyceride change, amisulpride resulted in greater change than haloperidol. **All other side effects information was rated as low quality due to the small samples involved.**
Discontinuation in the study	
A small effect of less short-term all-cause discontinuation for second-generation antipsychotics compared to first-generation antipsychotics; 12 RCTs, N = 1,952, RR = 0.74, 95%CI 0.62 to 0.87, $p < 0.01$ Individually, only olanzapine (5 RCTs, N = 689, RR = 0.53, 95%CI 0.37 to 0.77, $p = 0.001$), risperidone (5 RCTs, N = 1,146, RR = 0.79, 95%CI 0.63 to 0.97, $p = 0.03$) and amisulpride (1 RCT, N = 207, RR = 0.63, 95%CI 0.47 to 0.85, $p < 0.01$) caused less all-cause discontinuation than haloperidol. *A small effect of less short-term discontinuation due to inefficacy for second-generation antipsychotics compared to first-generation antipsychotics;* 9 RCTs, N = 1,792, RR = 0.60, 95%CI 0.43 to 0.82, $p < 0.01$ Individually, only olanzapine (5 RCTs, N = 689, RR = 0.38, 95%CI 0.25 to 0.59, $p < 0.001$) and amisulpride (1 RCT, N = 207, RR = 0.24, 95%CI 0.12 to 0.49, $p < 0.01$) caused less short-term discontinuation due to inefficacy than haloperidol. *A small to medium effect of less short-term discontinuation due to intolerability for second-generation antipsychotics compared to first-generation antipsychotics;* 9 RCTs, N = 1,792, RR = 0.46, 95%CI 0.31 to 0.68, $p < 0.01$ Individually, only olanzapine (5 RCTs, N = 689, RR = 0.29, 95%CI 0.14 to 0.59, $p = 0.001$), risperidone (4 RCT, N = 1,146, RR = 0.50, 95%CI 0.28 to 0.89, $p = 0.02$), and quetiapine (1 RCT, N = 207, RR = 0.13, 95%CI 0.03 to 0.55, $p < 0.01$) caused less short-term discontinuation due to intolerability than haloperidol. *A small to medium effect of less long-term discontinuation due to intolerability for second-generation antipsychotics compared to first-generation antipsychotics;* 5 RCTs, N =1,295, RR = 0.49, 95%CI 0.32 to 0.75, $p = 0.001$ Individually, only olanzapine caused less long-term discontinuation due to intolerability than haloperidol (RR = 0.31, $p < 0.001$). *No differences in long-term discontinuation due to inefficacy for second-generation antipsychotics compared to first-generation antipsychotics;* 5 RCTs, N =1,295, RR = 0.66, 95%CI 0.37 to 1.17, $p = 0.16$ Individually, only olanzapine caused less long-term discontinuation due to inefficacy than haloperidol (3 RCTs, N = 582, RR = 0.51, 95%CI 0.27 to 0.95, $p = 0.04$). *No differences in discontinuation due to non-adherence for second-generation antipsychotics compared to first-generation antipsychotics;* 9 RCTs, N = 1,792, RR = 0.84, 95%CI 0.57 to 1.24, $p > 0.05$	

Individually, only quetiapine caused less discontinuation due to non-adherence than haloperidol (1 RCT, N = 207, RR = 0.15, 95%CI 0.04 to 0.65, $p < 0.05$).

Authors report no effects of moderators for any discontinuation variable.

Symptoms

A very small effect of improved negatives symptoms for second-generation antipsychotics compared to first-generation antipsychotics;

11 RCTs, N = 1,932, $g = 0.16$, 95%CI 0.04 to 0.28, $p < 0.01$

Individually, only olanzapine (4 RCTs, N = 653, $g = 0.30$, 95%CI 0.15 to 0.46, $p < 0.001$) and quetiapine (1 RCT, N = 207, $g = 0.32$, 95%CI 0.05 to 0.59, $p < 0.05$) were superior to haloperidol and clozapine was superior to chlorpromazine (1 RCT, N = 160, $g = 0.41$, 95%CI 0.10 to 0.72, $p < 0.01$).

Only industry-sponsored studies significantly favouring second-generation antipsychotics ($p = 0.001$), while independently funded or government funded studies did not, although between groups analysis (Q_B) was not significant.

Trend level, very small improvement in depression symptoms for second-generation antipsychotics compared to first-generation antipsychotics;

11 RCTs, N = 1,932, $g = 0.12$, 95%CI 0.00 to 0.24, $p = 0.06$

Individually, only olanzapine (4 RCTs, N = 653, $g = 0.28$, 95%CI 0.11 to 0.44, $p = 0.001$), and amisulpride (1 RCT, N = 207, $g = 0.32$, 95%CI 0.05 to 0.59, $p < 0.05$) were superior to haloperidol.

Industry-sponsored studies more likely favoured second-generation antipsychotics (statistics not reported).

No differences in positive symptoms for second-generation antipsychotics compared to first-generation antipsychotics;

11 RCTs, N = 1,932, $g = 0.09$, 95%CI -0.03 to 0.21, $p > 0.05$

Individually, amisulpride was superior to haloperidol (1 RCT, N = 207, $g = 0.54$, 95%CI 0.27 to 0.82, $p < 0.01$), olanzapine had trend-level superiority over haloperidol (4 RCTs, N = 653, $g = 0.26$, 95%CI -0.03 to 0.54, $p = 0.08$).

No differences in overall symptom reduction for second-generation antipsychotics compared to first-generation antipsychotics;

12 RCTs, N = 1,952, $g = 0.11$, 95%CI -0.02 to 0.24, $p > 0.05$

Individually, olanzapine (5 RCTs, N = 689, $g = 0.26$, 95%CI 0.05 to 0.47, $p = 0.01$) and amisulpride (1 RCT, N = 207, $g = 0.40$, 95%CI 0.13 to 0.68, $p < 0.01$) were superior to haloperidol.

Study sponsorship significantly moderated the effect ($Q_B = 6.68$, $p = 0.01$), with only industry-sponsored studies significantly favouring second-generation antipsychotics (g 0.19, $p = 0.007$), while independently funded or government funded studies did not.

No differences in response rates for second-generation antipsychotics compared to first-generation antipsychotics;

12 RCTs, N = 1,952, RR = 1.13, 95%CI 0.99 to 1.27, $p > 0.05$

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Individually, olanzapine (5 RCTs, N = 689, RR = 1.29, 95%CI 1.05 to 1.58, *p* = 0.02) and amisulpride (1 RCT, N = 207, RR = 1.56, 95%CI 1.13 to 2.15, *p* < 0.01) were superior to haloperidol. Study sponsorship significantly moderated the effect (Q_B =3.97, *p* = 0.046), with only industry-sponsored studies significantly favouring second-generation antipsychotics (RR = 1.23, *p* = 0.005), while independently funded or government funded studies did not. *No differences in overall clinical global impressions(severity) for second-generation antipsychotics compared to first-generation antipsychotics;* 11 RCTs, N = 1,932, *g* = 0.10, 95%CI -0.09 to 0.29, *p* > 0.05 Individually, only amisulpride was superior to haloperidol (1 RCT, N = 207, *g* = 0.38, 95%CI 0.10 to 0.65, *p* < 0.01). Industry-sponsored studies more likely favoured second-generation antipsychotics (statistics not reported).
Remission and relapse
Trend level, very small effect of more long-term remission rates for second-generation antipsychotics compared to first-generation antipsychotics; 9 RCTs, N = 1792, RR = 1.26, 95%CI 0.99 to 1.60, *p* = 0.06 Individually, only olanzapine (5 RCTs, N = 689, RR = 1.57, 95%CI 1.06 to 2.32, *p* = 0.03), and amisulpride (1 RCT, N = 207, RR = 2.35, 95%CI 1.45 to 3.83, *p* = 0.001) were superior to haloperidol. *A small effect of less long-term relapse rates for second-generation antipsychotics compared to first-generation antipsychotics;* 9 RCTs, N = 1792, RR = 0.84, 95%CI 0.72 to 0.99, *p* < 0.05 Individually, only risperidone (4 RCTs, N = 1146, RR = 0.77, 95%CI 0.64 to 0.95, *p* = 0.01), and ziprasidone (1 RCT, N = 185, RR = 0.32, 95%CI 0.11 to 0.89, *p* = 0.03) were superior to haloperidol.
Cognitive function
A small effect of improved global cognition for second-generation antipsychotics compared to first-generation antipsychotics; 11 RCTs, N = 1932, *g* = 0.25, 95%CI 0.10 to 0.40, *p* < 0.01 Individually, only olanzapine (4 RCTs, N = 653, *g* = 0.27, 95%CI 0.06 to 0.49, *p* < 0.01) and risperidone (5 RCT, N = 1136, *g* = 0.23, 95%CI 0.04 to 0.43, *p* < 0.01) were superior to haloperidol.

Risks	Overall, second-generation antipsychotics resulted in less extrapyramidal side effects (9 RCTs, N = 1338, *g* = -0.43, 95%CI -0.64 to -0.22, *p* < 0.01), which was most evident in individual analyses of olanzapine (4 RCTs, N = 609, *g* = -0.69, 95%CI -1.02 to -0.35, *p* < 0.01), and risperidone (3 RCTs, N = 588, *g* = -0.33, 95%CI -

	0.51 to -0.16, $p < 0.01$) compared to haloperidol, and in the comparison of clozapine with chlorpromazine (1 RCT, N = 160, g = -0.72, 95%CI -1.04 to -0.41, $p < 0.01$). More recent studies had smaller effect sizes for extrapyramidal side effects (b = 0.04, p = 0.02), and higher patient age was associated with larger effect sizes (b = -0.04, p = 0.006). Less akathisia was reported with second-generation antipsychotics (7 RCTs, N = 998, g = -0.48, 95%CI -0.62 to -0.34, $p < 0.01$), particularly for olanzapine (4 RCTs, N = 611, g = -0.61, 95%CI -0.79 to -0.42, $p < 0.01$), and risperidone (2 RCTs, N = 406, g = -0.29, 95%CI -0.52 to -0.06, $p < 0.05$) compared to haloperidol. Second-generation antipsychotics resulted in less use of anticholinergeric medications (6 RCTs, N = 999, RR = 0.47, 95%CI 0.29 to 0.77, $p < 0.01$), particularly for olanzapine compared to haloperidol (3 RCTs, N = 445, RR = 0.21, 95%CI 0.09 to 0.51, $p <$ 0.01), or molindone (1 RCT, N = 75, RR = 0.31, 95%CI 0.13 to 0.76, $p < 0.01$). Less use of benzodiazepines (5 RCTs, N = 816, RR = 0.84, 95%CI 0.75 to 0.95, $p < 0.01$), particularly for olanzapine compared to haloperidol (3 RCTs, N = 445, RR = 0.83, 95%CI 0.71 to 0.96, p 0.05). Less use of beta-blockers for olanzapine compared to haloperidol (1 RCT, N = 251, RR = 0.11, 95%CI 0.03 to 0.40, $p <$ 0.01). More patients on first-generation antipsychotics in open-label studies took anticholinergics than in double-blind studies. Less anticholinergic use with second-generation antipsychotics compared to first-generation antipsychotics was associated with smaller sample size, younger age, male sex and longer follow-up. Olanzapine (2 RCTs, N = 362, RR = 3.31, 95%CI 1.83 to 5.98, p <0.01) and risperidone (2 RCTs, N = 485, RR = 1.61, 95%CI 1.25 to 2.09, $p < 0.01$) caused more weight gain than haloperidol (>7% gain). Larger differences in weight gain were associated with shorter follow-up time, smaller sample size, younger age, female sex and schizophrenia diagnosis. Olanzapine (1 RCT, N = 53, g = -1.21, 95%CI -1.79 to -0.63, $p <$ 0.01), risperidone (1 RCT, N = 58, g = -1.99, 95%CI -2.61 to -1.36, p < 0.01), and clozapine (1 RCT, N = 59, g = -1.54, 95%CI -2.12 to -0.97, $p < 0.01$), were associated with lower glucose change than sulpiride. Olanzapine resulted in more total cholesterol change than molindone (1 RCT, N = 35, g = 1.02, 95%CI 1.30 to 1.75, $p < 0.01$), sulpiride (1 RCT, N = 53, g = 5.12, 95%CI 4.01 to 6.23, $p < 0.01$), and haloperidol (3 RCTs, N = 501, g = 0.17, 95%CI 0.00 to 0.35, p = 0.05). Risperidone resulted in less total cholesterol change than sulpiride (1 RCT, N = 58, g = -1.36, 95%CI -1.93 to -0.80, $p < 0.01$). For triglyceride change, olanzapine (1 RCT, N = 53, g = 3.32, 95%CI 2.49 to 4.15, $p < 0.01$) and clozapine (1 RCT, N = 59, g = 5.02,

	95%CI 3.98 to 6.05, $p < 0.01$) were worse than sulpiride, and amisulpride was worse than haloperidol (1 RCT, N = 207, $g = 0.34$, 95%CI 0.06 to 0.61, $p < 0.05$). Risperidone was better than sulpiride (1 RCT, N = 58, $g = -1.18$, 95%CI -1.74 to -0.63, $p < 0.01$).
Consistency in results	Authors report inconsistency in results.
Precision in results	Precise for all efficacy measures apart from; discontinuation due to inefficacy, intolerability or non-adherence; remission rates; relapse rates for ziprasidone; response rates for amisulpride. Precise for extrapyramidal side effects, akathisia and use of benzodiazapines, imprecise for other side effects.
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CGI-C = Clinical Global Improvement-Change, CI = Confidence Interval, *g* = Hedges' *g* standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, Q_B = test for between group differences (heterogeneity between groups of studies for an outcome of interest), RCT = randomised controlled trials, RD = risk difference, RR = relative risk, 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.[7]

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† 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).

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.[7]

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[8]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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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 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;[7]

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

§ 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.[9]

‖ 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. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal*. 2009; **151**(4): 264-9.
2. GRADEWorkingGroup. Grading quality of evidence and strength of recommendations. *British Medical Journal*. 2004; **328**: 1490.
3. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ*. 2000; **321**(7273): 1371-6.
4. Lepping P, Sambhi RS, Whittington R, Lane S, Poole R. Clinical relevance of findings in trials of antipsychotics: systematic review. *British Journal of Psychiatry*. 2011; **198**(5): 341-5.
5. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009; **373**(9657): 31-41.
6. Zhang JP, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: A systematic review and meta-analysis. *International Journal of Neuropsychopharmacology*. 2013; **16**(6): 1205-18.
7. CochraneCollaboration. Cochrane Handbook for Systematic Reviews of Interventions. 2008: Accessed 24/06/2011.
8. Sommer IE, van Westrhenen R, Begemann MJH, de Witte LD, Leucht S, Kahn RS. Efficacy of Anti-inflammatory Agents to Improve Symptoms in Patients With Schizophrenia: An Update. *Schizophrenia Bulletin*. 2014; **40**(1): 181-91.
9. GRADEpro. [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*. 2008.