TECHNICAL COMMENTARY

Extrapyramidal side effects

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Introduction

Extrapyramidal side effects include dyskinesias; repetitive, involuntary, and purposeless body or facial movements. Parkinsonism may occur, involving cogwheel muscle rigidity, pill-rolling tremor and reduced or slowed movements. Akathisia involves motor restlessness, especially in the legs, and dystonias are muscle contractions causing unusual twisting of parts of the body, most often in the neck. These side effects are caused by the dopamine receptor antagonist action of antipsychotics.

Some antipsychotics are more likely to produce extrapyramidal side effects than others. One explanation 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.

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,

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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 ten systematic reviews that met inclusion criteria[3-12].

Overall prevalence rate

- Moderate quality evidence suggests the overall prevalence rate of tardive dyskinesia is around 25%, with rates highest with first generation antipsychotic use and with longer duration of illness. Rates were lowest in Asian countries.

All antipsychotics versus placebo

- Moderate quality evidence shows a small effect of fewer extrapyramidal side effects with clozapine versus placebo. Small effects of increased extrapyramidal side effects were reported with ziprasidone, paliperidone, and risperidone, and medium effects were reported with lurasidone, chlorpromazine, zotepine, and haloperidol. No differences were reported for sertindole, olanzapine, quetiapine, aripiprazole, iloperidone, amisulpride and asenapine.

Antipsychotic dose reduction or switching

- Moderate to low quality evidence suggests no significant differences in tardive dyskinesia with antipsychotic dose reduction compared to antipsychotic dose maintenance. Lower quality evidence is unable to determine any benefit of switching antipsychotics.

First versus second generation antipsychotics

- Moderate to high quality evidence suggests fewer extrapyramidal side effects with second generation antipsychotics, in particular olanzapine and risperidone, when compared to first generation antipsychotic haloperidol. Fewer extrapyramidal side effects are reported with second generation antipsychotic clozapine when compared to first generation antipsychotic chlorpromazine. Moderate quality evidence suggests clozapine, olanzapine, and risperidone also produce fewer extrapyramidal side effects than low-potency first generation antipsychotics.

Second generation antipsychotics

- Moderate to high quality evidence suggests risperidone may be associated with more use of antiparkinson medication than clozapine (medium effect), olanzapine, quetiapine, and ziprasidone (small effects). Ziprasidone may be associated with more use of antiparkinson medication than olanzapine (small effect) and quetiapine (medium effect). Olanzapine may be associated with more use of antiparkinson medication than quetiapine (medium effect), and aripiprazole may be associated with more use of antiparkinson medication than olanzapine (small effect). No differences were found between amisulpride and olanzapine, risperidone, or ziprasidone. No differences were found between aripiprazole and risperidone, or between clozapine and olanzapine or ziprasidone. Low quality evidence is unable to determine if there are differences between zotepine and clozapine.

Schizophrenia versus affective disorders

- Moderate quality evidence suggests patients with affective disorders treated with aripiprazole may show more akathisia than patients with schizophrenia treated with aripiprazole. Patients with schizophrenia treated with olanzapine may show more parkinsonism than patients with bipolar disorder treated with olanzapine.

Ethnic differences

- Moderate to low quality evidence suggests people from China, Japan and Korea who are treated with antipsychotics may show a small increase in extrapyramidal side effects

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compared to people from other countries treated with antipsychotics. No differences were reported between Black and White populations.

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Bergman H, Rathbone J, Agarwal V, Soares-Weiser K

Antipsychotic reduction and/or cessation and antipsychotics as specific treatments for tardive dyskinesia

Cochrane Database of Systematic Reviews 2018; 2: CD000459

View review abstract online

Comparison	**Antipsychotic reduction or switching as a treatment for tardive dyskinesia.**
Summary of evidence	**Moderate to low quality evidence (very small samples, consistent where applicable, imprecise, direct) suggests no significant differences in tardive dyskinesia with antipsychotic dose reduction compared to antipsychotic dose maintenance. Lower quality evidence (smaller samples) is unable to determine the effects of switching antipsychotics for tardive dyskinesia.**

Tardive dyskinesia

There were no significant differences in rates of tardive dyskinesia between dose reduction and dose maintenance;

2 RCTs, N = 17, RR = 0.42, 95%CI 0.17 to 1.04, $p > 0.05$

There was greater clinical improvement with switching to risperidone than antipsychotic cessation;

1 RCT, N = 42, RR = 0.45, 95%CI 0.23 to 0.89, $p < 0.05$

There was greater clinical improvement with switching to quetiapine than switching to haloperidol;

1 RCT, N = 45, RR = 0.45, 95%CI 0.21 to 0.96, $p < 0.05$

Consistency in results‡	Authors report data are consistent where applicable.
Precision in results§	Imprecise
Directness of results‖	Direct

Carbon M, Hsieh CH, Kane JM, Correll CU

Tardive Dyskinesia Prevalence in the Period of Second-Generation Antipsychotic Use: A Meta-Analysis

Journal of Clinical Psychiatry 2017; 78: e264-e78

View review abstract online

Comparison	**Prevalence of tardive dyskinesia with second generation antipsychotic use.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, appears precise, direct) suggests the overall prevalence rate of tardive dyskinesia is around 25%, with rates higher with first generation antipsychotics than with second generation antipsychotics, and higher with longer duration of illness. Rates were lowest in Asian countries.**
Tardive dyskinesia	
41 studies, N = 11,493, prevalence = 25.3%, 95%CI 22.7% to 28.1% Rates were lower with second generation than first generation antipsychotics (20.7% vs. 30%). Prevalence was higher with a longer illness duration and higher frequency of parkinsonism. Asia had lower rates than the United States and other regions.	
Consistency in results	Authors report prevalence rates were inconsistent across studies (range 8.5% to 75%).
Precision in results	Appears precise
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 quality evidence (inconsistent, some imprecision, large samples, direct) 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.**
Extrapyramidal symptoms	
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); <u>Versus Haloperidol</u> Amisulpride: 8 RCTs, N = 783, RR = 0.58, 95%CI 0.45−0.76, $p < 0.0001$ Aripiprazole: 4 RCTs, N = 1794, RR = 0.50, 95%CI 0.32−0.64, $p < 0.0001$ Clozapine: 3 RCTs, N = 162, RR = 0.17, 95%CI 0.03−0.88, $p < 0.035$ Olanzapine: 12 RCTs, N = 3670, RR = 0.39, 95%CI 0.30−0.51, $p < .0.0001$ Quetiapine: 5 RCTs, N = 1167, RR = 0.43, 95%CI 0.25−0.74, $p = 0.002$ Risperidone: 21 RCTs, N = 2738, RR = 0.61, 95%CI 0.52−0.72, $p < 0.0001$ Sertindole: 4 RCTs, N = 1472, RR = 0.36, 95%CI 0.29−0.45, $p < 0.0001$ Ziprasidone: 3 RCTs, N = 501, RR = 0.50, 95%CI 0.26−0.96, $p = 0.037$ Zotepine: 4 RCTs, N = 398, RR = 0.59, 95%CI 0.44−0.79, $p < 0.0001$ <u>Versus low-potency first generation antipsychotics (e.g. chlorpromazine, chlorprothixene, thioridazine, levomepromazine, perazine)</u> Clozapine: 11 RCTs, N = 775, RR = 0.66, 95%CI 0.48−0.91, $p = 0.010$ Olanzapine: 2 RCTs, N = 152, RR = 0.53, 95%CI 0.32−0.89, $p = 0.016$ Risperidone: 2 RCTs, N = 108, RR = 0.47, 95%CI 0.22−0.99, $p = 0.046$	
Consistency in results	Authors report considerable heterogeneity in some analyses.
Precision in results	Imprecise for clozapine, quetiapine, and ziprasidone vs. haloperidol and risperidone vs. low potency drugs.
Directness of results	Direct

Leucht S, Cipriani A, Loukia S, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lassig B, Salanti G, Davis JM

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Lancet 2013; 382: 951- 962

View review abstract online

Comparison	**All antipsychotics vs. placebo for ~6 weeks in people with schizophrenia spectrum disorders.** **Studies on patients with predominant negative symptoms, concomitant medical illness, treatment resistance, or stable illness were excluded.**
Summary of evidence	**Moderate quality evidence (imprecise, some indirectness) shows a small effect of fewer extrapyramidal side effects for clozapine compared to placebo. Small effects of more extrapyramidal side effects were reported for ziprasidone, paliperidone, and risperidone. Medium effects of more extrapyramidal side effects were reported for lurasidone, chlorpromazine, zotepine, and haloperidol. No differences were reported for sertindole, olanzapine, quetiapine, aripiprazole, iloperidone, amisulpride and asenapine.**

Extrapyramidal symptoms

This meta-analysis included 212 studies overall with 43,049 participants

Clozapine showed a significant small effect of fewer extrapyramidal side effects than placebo;

OR = 0.30, 95%CrI 0.12 to 0.62, $p < 0.05$

Small, significant effects of more extrapyramidal side effects than placebo for;

Ziprasidone: OR = 1.61, 95%CrI 1.05 to 2.37, $p < 0.05$

Paliperidone: OR = 1.81, 95%CrI 1.17 to 2.69, $p < 0.05$

Risperidone: OR = 2.09, 95%CrI 1.54 to 2.78, $p < 0.05$

Medium significant effects of more extrapyramidal side effects than placebo for;

Lurasidone: OR = 2.46, 95%CrI 1.55 to 3.72, $p < 0.05$

Chlorpromazine: OR = 2.65, 95%CrI 1.33 to 4.76, $p < 0.05$

Zotepine: OR = 3.01, 95%CrI 1.38 to 5.77, $p < 0.05$

Haloperidol: OR = 4.76, 95%CrI 3.70 to 6.04, $p < 0.05$ No significant differences were reported for sertindole, olanzapine, quetiapine, aripiprazole, iloperidone, amisulpride and asenapine.	
Consistency in results	Authors report disagreement between direct and indirect estimates (a measure of consistency) was identified in only 1/56 studies.
Precision in results	Imprecise
Directness of results	Direct and indirect comparisons combined, with no consistent differences in results across these comparisons.

Moteshafi H, Stip E

Comparing tolerability profile of quetiapine, risperidone, aripiprazole and ziprasidone in schizophrenia and affective disorders: a meta-analysis

Expert Opinion on Drug Safety 2012; 11(5): 713-732

View review abstract online

Comparison	**Extrapyramidal side effects in schizophrenia vs. affective disorders.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests patients with affective disorder treated with aripiprazole may show significantly more akathisia than patients with schizophrenia treated with aripiprazole.**
Extrapyramidal symptoms	
Affective disorder patients treated with aripiprazole showed significantly more akathisia compared with schizophrenia patients treated with aripiprazole. A trend effect was reported for ziprasidone; Aripiprazole - akathisia Schizophrenia: 8 RCTs, N = 2264, incidence rate 5.4% Affective disorder: 8 RCTs, N = 1307, incidence rate 14.6% $p = 0.001$ Ziprasidone - akathisia Schizophrenia: 6 RCTs, N = 875, incidence rate 7.7% Affective disorder: 4 RCTs, N = 584, incidence rate 13.2%	

p = 0.065 *Affective disorder patients treated with aripiprazole showed a trend effect of more parkinsonism (but not antiparkinson medication use) compared with schizophrenia patients treated with aripiprazole;* Aripiprazole - parkinsonism Schizophrenia: 7 RCTs, N = 1979, incidence rate 6.7% Affective disorder: 4 RCTs, N = 701, incidence rate 10.4% p = 0.069 The akathisia or parkinsonism event rate (including antiparkinson medication use) did not differ significantly between the two groups for quetiapine, nor for parkinsonism with risperidone or ziprasidone treatment. Subgroup analyses showed no differences in effect size for differences in age, sex, dose and treatment duration, although the trend effect for aripiprazole, parkinsonism became significant.

Consistency in results	Authors report inconsistency in results (I^2 > 50%).
Precision in results	Unable to assess (no CIs reported).
Directness of results	Direct

Moteshafi H, Zhornitsky S, Brunelle S, Stip E

Comparing Tolerability of Olanzapine in Schizophrenia and Affective disorders: a meta-analysis

Drug Safety 2012; 35(10): 819-836

View review abstract online

Comparison	**Extrapyramidal side effects in schizophrenia vs. affective disorders.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests patients with schizophrenia treated with olanzapine may show significantly more parkinsonism than patients with bipolar disorder treated with olanzapine.**
Extrapyramidal symptoms	

Affective disorder patients treated with olanzapine showed significantly more parkinsonism compared with schizophrenia patients treated with olanzapine; Schizophrenia: 6 RCTs, N = 884, incidence rate 13.9% Bipolar disorder: 7 RCTs, N = 2460, incidence rate 3.1% p = 0.005 The akathisia or antiparkinson medication use did not differ significantly between the two groups. Subgroup analyses showed parkinsonism was inversely related to the ratio of males in the schizophrenia group (more males = less parkinsonism). No differences in effect size were found for differences in age, dose, study sponsorship or treatment duration.

Consistency in results	Authors report inconsistency in results (I^2 > 50%).
Precision in results	Unable to assess (no CIs reported).
Directness of results	Direct

Ormerod S, McDowell SE, Coleman JJ, Ferner RE

Ethnic differences in the risks of adverse reactions to drugs used in the treatment of psychoses and depression: a systematic review and meta-analysis.

Drug Safety 2008; 31(7): 597-607

View review abstract online

Comparison	**Extrapyramidal side effects in different ethnic groups.**
Summary of evidence	**Moderate to low quality evidence (small samples, consistent, imprecise, direct) suggests East Asian patients from China, Japan and Korea may show a small increase in extrapyramidal symptoms than non-East Asian populations.**

Extrapyramidal symptoms

Small, significant increased risk of extrapyramidal symptoms (dystonic reactions, parkinsonism, akathisia) in East Asian populations (China, Japan and Korea) compared with non-East Asian populations;

4 studies, RR = 1.38, N = 230, 95%CI 1.11 to 1.72, p = 0.004, I^2 = 25.1%, p = 0.26

No differences in tardive dyskinesia or in any Black vs. White population comparison.

Authors report that the studies were of low quality.

Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Pagsberg AK, Tarp S, Glintborg D, Stenstrom AD, Fink-Jensen A, Correll CU, Christensen R

Acute Antipsychotic Treatment of Children and Adolescents With Schizophrenia-Spectrum Disorders: A Systematic Review and Network Meta-Analysis

Journal of the American Academy of Child and Adolescent Psychiatry 2017; 56(3): 191-202

View review abstract online

Comparison 1	**Antipsychotics vs. placebo in children and adolescents (8 to 19 years) with schizophrenia spectrum disorders.**
Summary of evidence	**Moderate to low quality evidence (imprecise) suggests large effects of more extrapyramidal side effects with paliperidione, ziprasidone, risperidone, and aripiprazole compared to placebo.**

Extrapyramidal symptoms

Significant, large effects were found in direct comparisons with placebo for;

Paliperidione: 1 RCT, N = 147, OR = 29.33, 95%CI 1.74 to 495.11, $p = 0.02$

Ziprasidone: 1 RCT, N = 283, OR = 11.45, 95%CI 1.52 to 86.34, $p = 0.01$

Risperidone: 2 RCTs, N = 417, OR = 4.32, 95%CI 2.31 to 8.06, $p < 0.00001$, $I^2 = 0\%$

Aripiprazole: 1 RCT, N = 302, OR = 3.98, 95%CI 1.51 to 10.51, $p = 0.005$

No differences in extrapyramidal symptoms were found between placebo and quetiapine, asenapine or olanzapine.

For akathasia in particular, no effects were found in direct comparisons between any antipsychotic and placebo, apart from risperidone which showed a large effect of more frequent akathasia. Indirect network meta-analyses also showed more akathisia with aripiprazole, olanzapine, and

paliperidone than with placebo. Authors state that risk of bias across trials was generally low.	
Consistency in results	Consistent where applicable (risperidone [>1 RCT]).
Precision in results	Imprecise
Directness of results	Direct, apart from network analyses.
Comparison 2	**Antipsychotics vs. antipsychotics in children and adolescents (8 to 19 years) with schizophrenia spectrum disorders.**
Summary of evidence	**Moderate to low quality evidence (small sample, imprecise, direct) suggests a large effect of less extrapyramidal side effects with olanzapine when compared to molindone in children and adolescents with schizophrenia.**
Extrapyramidal symptoms	
A significant, large effect of fewer extrapyramidal side effects with olanzapine compared to molindone; 1 RCT, N = 75, OR = 4.91, 95%CI 1.58 to 15.25, *p* = 0.006 Indirect network meta-analysis showed a small effect of more extrapyramidal symptoms with molindone when compared to asenapine.	
Consistency in results	Not applicable (1 RCT).
Precision in results	Imprecise
Directness of results	Direct, apart from network analyses.

Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Kissling W, Davis JM, Leucht S

Second-Generation Antipsychotic Drugs and Extrapyramidal Side Effects: A Systematic Review and Meta-analysis of Head-to-Head Comparisons

Schizophrenia Bulletin 2012; 38(1): 167-177

View review abstract online

Comparison	**Second generation antipsychotics for schizophrenia.**

Summary of evidence	**Moderate to high quality evidence (large samples, imprecise, consistent, direct) suggests risperidone may be associated with more use of antiparkinson medication than clozapine (medium effect), olanzapine, quetiapine, and ziprasidone (small effects).** **Ziprasidone may be associated with more use of antiparkinson medication than olanzapine (small effect) and quetiapine (medium effect).** **Olanzapine may be associated with more use of antiparkinson medication than quetiapine (medium effect), and aripiprazole may be associated with more use of antiparkinson medication than olanzapine (small effect).** **Low quality evidence (1 small RCT, very imprecise data) is unable to determine differences between zotepine and clozapine.**
Use of antiparkinson medication	
Risperidone showed a medium effect of more use of antiparkinson medication than clozapine; 6 RCTs, N = 304, RR = 2.57, 95%CI 1.47 to 4.48, *p* = 0.0009 *Risperidone showed a small effect of more use of antiparkinson medication than olanzapine;* 13 RCTs, N = 2599, RR = 1.28, 95%CI 1.06 to 1.55, *p* = 0.01 *Risperidone showed a small effect of more use of antiparkinson medication than quetiapine;* 6 RCTs, N = 1715, RR = 1.98, 95%CI 1.16 to 3.39, *p* = 0.01 *Risperidone showed a small effect of more use of antiparkinson medication than ziprasidone;* 2 RCTs, N = 822, RR = 1.42, 95%CI 1.03 to 1.96, *p* = 0.03 *Olanzapine showed a medium effect of more use of antiparkinson medication than quetiapine;* 6 RCTs, N = 1090, RR = 2.05, 95%CI 1.26 to 3.32, *p* = 0.004 *Ziprasidone showed a medium effect of more use of antiparkinson medication than quetiapine;* 1 RCT, N = 522, RR = 2.32, 95%CI 1.07 to 5.00, *p* = 0.03 *Ziprasidone showed a small effect of more use of antiparkinson medication than olanzapine;* 4 RCTs, N = 1732, RR = 1.43, 95%CI 1.03 to 1.99, *p* = 0.03 *Aripiprazole showed a small effect of more use of antiparkinson medication than olanzapine;* 1 RCT, N = 703, RR = 1.80, 95%CI 1.19 to 2.72, *p* = 0.005 *Zotepine showed a large effect of more use of antiparkinson medication than clozapine;* 1 RCT, N = 59, RR = 18.75, 95%CI 1.17 to 301.08, *p* = 0.04 There were no significant differences found between amisulpride and olanzapine, risperidone, or	

ziprasidone. No differences were found between aripiprazole and risperidone, or between clozapine and olanzapine or ziprasidone. Subgroup analyses and meta-regressions showed washout period was significant for the comparison of olanzapine vs. ziprasidone only (the longer the washout period the higher the superiority of olanzapine relative to the use of antiparkinson medication). Excluding studies with risperidone mean daily doses over 6 mg showed that the results of the primary outcome remained the same apart from the differences between risperidone and olanzapine were no longer statistically significant. Excluding studies with olanzapine mean daily doses over 20 mg showed that the results remained the same apart from the difference between olanzapine and quetiapine was no longer statistically significant. Excluding studies with mean daily risperidone doses lower than 4 mg showed that the results remained the same apart from the comparisons of quetiapine and risperidone where results were no longer significant. Excluding studies with ziprasidone mean daily doses lower than 120 mg showed that the comparison between olanzapine and ziprasidone was no longer significant. There were no effects of study sponsorship.	
Consistency in results	Authors report consistency in results.
Precision in results	Imprecise
Directness of results	Direct

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, direct, inconsistent) suggests less extrapyramidal side effects and akathisia with second generation antipsychotics, in particular olanzapine and risperidone when compared to haloperidol, and clozapine when compared to chlorpromazine.**
Extrapyramidal symptoms	

Extrapyramidal side effects

Overall, second generation antipsychotics was associated with fewer extrapyramidal symptoms and akathisia than first generation antipsychotics; Extrapyramidal symptoms: 9 RCTs, N = 1338, *g* = -0.43, 95%CI -0.64 to -0.22, *p* < 0.01 Akathisia: 7 RCTs, N = 998, *g* = -0.48, 95%CI -0.62 to -0.34, *p* < 0.01 *The only significant individual drug analyses were;* Olanzapine vs. haloperidol extrapyramidal: 4 RCTs, N = 609, *g* = -0.69, 95%CI -1.02 to -0.35, *p* < 0.01 Olanzapine vs. haloperidol akathisia: 4 RCTs, N = 611, *g* = -0.61, 95%CI -0.79 to -0.42, *p* < 0.01 Risperidone vs. haloperidol extrapyramidal: 3 RCTs, N = 588, *g* = -0.33, 95%CI -0.51 to -0.16, *p* < 0.01 Risperidone vs. haloperidol akathisia: 2 RCTs, N = 406, *g* = -0.29, 95%CI -0.52 to -0.06, *p* < 0.05 Clozapine vs. chlorpromazine extrapyramidal: 1 RCT, N = 160, *g* = -0.72, 95%CI -1.04 to -0.41, *p* < 0.01 Meta-regressions showed that more recent studies had smaller effect sizes (*b* = 0.04, *p* = 0.02), and higher patient age was associated with larger effect sizes (*b* = -0.04, *p* = 0.006).

Consistency in results	Authors report inconsistency in results.
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

b = coefficient, CI = confidence interval, CrI = credible interval, *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect size), I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), mg = milligram, N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result (*p* < 0.05 generally regarded as significant), RCT = randomised controlled trial, RR = relative risk, SMD = standardised mean difference, vs. = versus

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[13].

† 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[13].

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[14]. 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[13];

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

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data 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[15].

‖ 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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