TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Second-generation antipsychotics

Introduction

Second-generation 'atypical' antipsychotics are a newer class of antipsychotic than first-generation 'typical' antipsychotics. Second-generation antipsychotics are effective for the positive symptoms of schizophrenia, including the experiences of perceptual abnormalities (hallucinations) and fixed, false, irrational beliefs (delusions). 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.

The table presents the current evidence on efficacy of particular second-generation antipsychotics. Please also see individual drug tables for Cochrane reviews on each drug.

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).

Results

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

- Moderate to high quality evidence suggests olanzapine is superior to aripiprazole, quetiapine, risperidone and ziprasidone for overall symptoms. Risperidone is superior to quetiapine and ziprasidone for overall symptoms, amisulpride is superior to risperidone for negative symptoms, and

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clozapine is superior to risperidone for less drop-outs due to inefficiency.

- Moderate quality evidence suggests amisulpride is superior to ziprasidone for less drop-outs due to inefficiency, and quetiapine is superior to clozapine for negative symptoms.
- Moderate to high quality evidence suggests a small effect of fewer hospitalisations with clozapine than with other second-generation antipsychotics combined. There were also less extrapyramidal side effects or anticholinergic use with clozapine, however, clozapine was associated with greater risk of cardiometabolic-related outcomes.
- For long-term psychopathology (over 6 months), moderate quality evidence finds aripiprazole was superior to quetiapine and ziprasidone. Clozapine was superior to quetiapine and risperidone. Lurasidone was superior to quetiapine. Olanzapine was superior to paliperidone and risperidone. Paliperidone was superior to aripiprazole and ziprasidone.
- For long-term side effects, clozapine, olanzapine, and risperidone were the best for reducing all-cause discontinuation, while quetiapine was the worst. Risperidone was the best for intolerability-related discontinuation, and clozapine was the worst. Olanzapine was the worst for weight gain, followed by risperidone. Risperidone and amisulpride were the worst for prolactin increase. Olanzapine was superior to risperidone for parkinsonism. Clozapine and quetiapine were the worst for sedation.

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Kishimoto T, Hagi K, Nitta M, Kane JM, Correll CU

Long-term effectiveness of oral second-generation antipsychotics in patients with schizophrenia and related disorders: A systematic review and meta-analysis of direct head-to-head comparisons

World Psychiatry 2019; 18: 208-24

View review abstract online

Comparison	**Long-term outcomes (≥6 months) of second generation vs. second generation antipsychotics for people with schizophrenia spectrum disorders.**
Summary of evidence	**Moderate quality evidence (mostly small to medium-sized samples, unable to assess consistency, mostly precise, direct) finds for long-term psychopathology (over 6 months), aripiprazole was superior to quetiapine and ziprasidone. Clozapine was superior to quetiapine and risperidone. Lurasidone was superior to quetiapine. Olanzapine was superior to paliperidone and risperidone. Paliperidone was superior to aripiprazole and ziprasidone.** **For long-term side effects, clozapine, olanzapine and risperidone were best for all-cause discontinuation, while quetiapine was the worst. Risperidone was best for intolerability-related discontinuation, and clozapine was the worst. Olanzapine was the worst for weight gain, followed by risperidone. Risperidone and amisulpride were the worst for prolactin increase. Olanzapine was superior to risperidone for parkinsonism. Clozapine and quetiapine were the worst for sedation.**

Overall symptoms

Aripiprazole was superior to;

Quetiapine: 2 RCTs, N = 488, SMD = -0.259, 95%CI -0.497 to -0.020, $p = 0.034$

Ziprasidone: 2 RCTs, N = 264, SMD = -0.309, 95%CI -0.552 to -0.066, $p = 0.013$

Clozapine was superior to;

Quetiapine: 1 RCT, N = 41, SMD = -0.900, 95%CI -1.696 to -0.103, $p = 0.027$

Risperidone: 3 RCTs, N = 121, SMD = -0.739, 95%CI -1.476 to -0.003, $p = 0.049$

Lurasidone was superior to;

Quetiapine: 1 RCT, N = 204, SMD = -0.401, 95%CI -0.691 to -0.111, *p* = 0.007 *Olanzapine was superior to;* Paliperidone: 1 RCT, N = 459, SMD = -0.200, 95%CI -0.384 to -0.017, *p* = 0.032 Risperidone: 9 RCTs, N = 1,144, SMD = -0.168, 95%CI -0.329 to -0.007, *p* = 0.041 *Paliperidone was superior to;* Aripiprazole: 1 RCT, N = 134, SMD = -1.108, 95%CI -0.743 to -1.472, *p* < 0.001 Ziprasidone: 1 RCT, N = 132, SMD = -1.331, 95%CI -1.709 to -0.954, *p* < 0.001 *There were no other significant differences between second-generation antipsychotics.*	
Risks	Clozapine, olanzapine, and risperidone were best for all-cause discontinuation, while quetiapine was the worst. Risperidone was best for intolerability-related discontinuation, and clozapine was the worst. Olanzapine was the worst for weight gain, followed by risperidone. Risperidone and amisulpride were the worst for prolactin increase. Olanzapine was superior to risperidone for parkinsonism. Clozapine and quetiapine were the worst for sedation.
Consistency in results‡	Not reported for symptoms
Precision in results§	Mostly precise
Directness of results‖	Direct

Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, Asenjo Lobos C, Schwarz S, Davis JM

A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia

American Journal of Psychiatry 2009; 166(2): 152-163

View review abstract online

Comparison	**Second-generation vs. second-generation antipsychotics for people with schizophrenia spectrum disorders.**

Summary of evidence	**Moderate to high quality evidence (large samples, mostly consistent, some imprecision, direct) suggests olanzapine may be superior to aripiprazole, quetiapine, risperidone and ziprasidone for overall symptoms. Risperidone may be superior to quetiapine and ziprasidone for overall symptoms, amisulpride may be superior to risperidone for negative symptoms, and clozapine may be superior to risperidone for less drop-outs due to inefficiency.** **Moderate quality evidence (small to medium samples) suggests amisulpride may be superior to ziprasidone for less drop-outs due to inefficiency, and quetiapine may be superior to clozapine for negative symptoms.** **Low quality evidence (1 RCT, small samples) is unable to determine the differences between clozapine and zotepine for overall symptoms.**

Overall symptoms

Amisulpride was superior to ziprasidone for less people dropping out of the study due to inefficiency;

1 RCT, N = 123, RR = 0.21, 95%CI 0.05 to 0.94, $p = 0.040$

Amisulpride was superior to risperidone for negative symptoms;

3 RCTs, N = 519, SMD = -0.18, 95%CI -0.36 to 0.01, $p = 0.037$

Note: this result was a trend effect when based on WMD ($p = 0.078$)

Clozapine was superior to zotepine for overall symptoms;

1 RCT, N = 59, WMD = -6.0, 95%CI -9.8 to -2.2, $p = 0.002$

Clozapine was superior to risperidone for less drop-outs due to inefficiency;

8 RCTs, N = 627, RR = 0.40, 95%CI 0.23 to 0.70, $p = 0.001$

Olanzapine was superior to aripiprazole for overall symptoms;

2 RCTs, N = 794, WMD = 5.0, 95%CI 1.9 to 8.1, $p = 0.002$

Olanzapine was superior to quetiapine for overall symptoms;

10 RCTs, N = 1,449, WMD = -3.7, 95%CI -5.4 to -1.9, $p < 0.001$

Olanzapine was superior to risperidone for overall symptoms;

15 RCTs, N = 2,404, WMD = -1.9, 95%CI -3.3 to -0.6, $p = 0.006$

Olanzapine was superior to ziprasidone for overall symptoms;

4 RCTs, N = 1,291, WMD = -8.3, 95%CI -11.0 to -5.6, $p < 0.001$

Quetiapine was superior to clozapine for negative symptoms;

2 RCTs, N = 142, WMD = -2.2, 95%CI -3.5 to -1.0, $p < 0.001$

Risperidone was superior to quetiapine for overall symptoms; 9 RCTs, N = 1,953, WMD = 3.2, 95%CI 1.1 to 5.4, *p* = 0.003 *Risperidone was superior to ziprasidone for overall symptoms;* 3 RCTs, N = 1,016, WMD = -4.6, 95%CI -7.6 to -1.7, *p* = 0.002 *No differences were found between;* Aripiprazole and risperidone for all symptoms Amisulpride and olanzapine for all symptoms Amisulpride and risperidone for positive symptoms Amisulpride and ziprasidone for all symptoms Clozapine and olanzapine for all symptoms Clozapine and quetiapine for positive symptoms alone Clozapine and risperidone for all symptoms Clozapine and ziprasidone for all symptoms Olanzapine and risperidone for positive symptoms alone Quetiapine and ziprasidone for all symptoms Risperidone and sertindole for all symptoms Note: meta-regressions and subgroup analyses found no differences in effects sizes due to differences in study duration, antipsychotic dosages or dose ratios, study quality, illness chronicity, study location, and study sponsorship (except clozapine vs. risperidone [*b* = 6.3, *p* = 0.015]).	
Risks	Not reported
Consistency in results	Consistent, apart from quetiapine vs. risperidone, and olanzapine vs. ziprasidone. Consistency is not reported for amisulpride vs. risperidone for negative symptoms (sensitivity analysis).
Precision in results	Precise for amisulpride vs. risperidone for negative symptoms. Imprecise for amisulpride vs. ziprasidone and clozapine vs. risperidone for drop-outs. Unable to assess WMD (not standardised).
Directness of results	Direct

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Masuda T, Misawa F, Takase M, Kane JM, Correll CU

Association with Hospitalization and All-Cause Discontinuation among Patients with Schizophrenia on Clozapine vs Other Oral Second-Generation Antipsychotics: A Systematic Review and Meta-analysis of Cohort Studies

JAMA Psychiatry 2019; 76: 1052-62

View review abstract online

Comparison	**Clozapine vs. any other second-generation antipsychotics for people with schizophrenia spectrum disorders.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests a small effect of fewer hospitalisations with clozapine than with other second-generation antipsychotics combined. There was also lower all-cause discontinuation with clozapine and less extrapyramidal side effects or anticholinergic use. However, clozapine was associated with greater risk of cardiometabolic-related outcomes, including increased body weight, BMI, triglycerides, glucose, insulin, insulin resistance, and type 2 diabetes.**
Hospitalisation	
A small effect showed clozapine was significantly associated with lower hospitalisation risk than other second-generation antipsychotics; 19 cohort studies, N = 49,453, RR = 0.817, 95%CI 0.725 to 0.920, $p = 0.001$, $I^2 = 67\%$ Authors report that patients on clozapine had significantly worse symptoms at baseline.	
Risks	There was lower all-cause discontinuation with clozapine. Clozapine reduced extrapyramidal side effects or anticholinergic use risk by 36%, but clozapine was associated with greater risk of cardiometabolic-related outcomes, including increased body weight, BMI, triglycerides, glucose, insulin, insulin resistance, and type 2 diabetes.
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct for antipsychotic class

Explanation of acronyms

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), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trials, SMD = standardised mean difference, vs. = versus, WMD = weighted mean difference

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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).

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.

Correlation coefficients (eg, *r*) indicate the strength of association or relationship

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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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