TECHNICAL COMMENTARY

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Ziprasidone

Introduction

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

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

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

Method

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

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

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

Results

We found seven reviews that met our inclusion criteria[3-9].

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Ziprasidone

Compared to placebo

Efficacy: High quality evidence (consistent, precise, direct) suggests ziprasidone improves mental state more than placebo.

Adverse effects: Moderate quality evidence (imprecise) suggests ziprasidone causes more drowsiness and use of anti-parkinsonian medication than placebo.

Compared to first generation antipsychotic, haloperidol

Efficacy: High quality evidence (consistent, precise, direct) suggests ziprasidone results in better study retention than haloperidol.

Adverse effects: Moderate quality evidence (imprecise) suggests ziprasidone may be less likely to cause a movement disorder, but may increase the incidence of gastrointestinal symptoms more than haloperidol.

Compared to second generation antipsychotic amisulpride

Efficacy: Moderate to low quality evidence (imprecise, 1 small RCT) suggests ziprasidone had more participants leave the study early due to inefficacy than amisulpride.

Compared to second generation antipsychotic olanzapine

Efficacy: Moderate to high quality evidence (unable to assess precision) suggests olanzapine improved mental state more than ziprasidone. High quality evidence suggests more people leaving the study early for any reason, and more hospital readmissions with ziprasidone.

Adverse effects: Moderate quality evidence (inconsistent, unable to assess precision) suggests ziprasidone had less weight gain than olanzapine. High quality evidence suggests more extrapyramidal symptoms with ziprasiodone.

Compared to second generation antipsychotic quetiapine

Efficacy: Moderate quality evidence (consistent) suggests no difference in efficacy between quetiapine and ziprasidone for improving mental state.

Adverse effects: Moderate quality evidence (imprecise or unable to assess) suggests ziprasidone had more extrapyramidal effects and more prolactin increase, but less weight gain than quetiapine.

Compared to second generation antipsychotic risperidone

Efficacy: High quality evidence suggests ziprasidone has lower study retention than risperidone. Moderate quality evidence (some inconsistency, unable to assess precision) suggests ziprasidone should be less effective for symptoms than risperidone.

Adverse effects: High quality evidence suggests ziprasidone should produce less weight gain, and less movement disorders than risperidone. Moderate quality evidence (imprecise or unable to assess) suggests less prolactin increase and less extrapyramidal side effects, but greater cholesterol increase with ziprasidone than risperidone.

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Asenjo Lobos, C, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Leucht S. Clozapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 11: Art. No.: CD006633 DOI: 10.1002/14651858.CD006633.pub2.	
The review includes 27 blinded RCTs, N = 3099 – one compared clozapine with ziprasidone. No significant difference in mental states (PANSS total score) between ziprasidone and clozapine (1 RCT, N = 146, MD = 0.5, 95%CI -6.72 to 7.72, *p* = 0.89)	
Risks	Not reported
Consistency in results‡	Not applicable for 1 RCT.
Precision in results§	Unable to assess as standardised values are not reported.
Directness of results‖	Direct
Bagnall AM, Kleijnen J, Leitner M, Lewis R. Ziprasidone for schizophrenia and severe mental illness. Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD001945. DOI: 10.1002/14651858.CD001945	
This review includes 7 RCTs (N = not reported). 2 RCTs gave initial depot administration, then oral. Compared to placebo, ziprasidone had significantly greater improvement in mental state (N = 441, 2 RCTs, RR 0.83 CI 0.74-0.94, I^2 = 0%, *p* = 0.71). No differences in any other outcome. Compared to haloperidol there was no significant difference in mental state (N = 301, 1 RCT, RR 0.86 CI 0.77-1.00) but ziprasidone had better study retention (N = 438, 2 RCTs, RR 0.50, CI 0.35-0.72, I^2 = 0%, *p* = 0.85). No differences were found in any other outcome.	
Risks	Compared to placebo, ziprasidone was more likely to result in the use of anti-parkinsonian medication (N = 441, 2 RCTs, RR 1.67, CI 1.03 to 2.71, I^2 = 0%, p = 0.88).and drowsiness (N = 441, 2 RCTs, RR 2.40, CI 1.20 to 4.79 I^2 = 69%, p = 0.07). No other differences are reported. Compared to haloperidol, ziprasidone is less likely to cause movement disorders (N = 301, 1 RCT, RR 0.37 CI 0.24-0.56, I^2 = 0%, p = 0.54), but may cause more gastrointestinal symptoms (N = 301, 1 RCT, RR 2.14 CI 1.20-3.79). The injected form of the drug causes more pain at the injection site than haloperidol (N = 306, 1 RCT, RR 5.34 CI 1.28-22.26).
Consistency in results	Consistent where applicable (> 1 RCT).
Precision in results	Precise for all outcomes except use of anti-parkinsonian medication, drowsiness, nausea and pain at injection site.

Directness of results	Direct
Komossa K, Rummel-Kluge C, Hunger H, Schwarz S, Bhoopathi PS, Kissling W, Leucht S. Ziprasidone versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD006627. DOI: 10.1002/14651858.CD006627.pub2.	
The review currently includes 9 RCTs (N = 3361). Compared to amisulpride: ziprasidone resulted in more people leaving the study early due to inefficacy (1 RCT, N =123, RR 4.72 CI 1.06 to 20.98). Compared to olanzapine: ziprasidone resulted in more people leaving the study early for any reason (5 RCTs, N = 1937, RR 1.26 CI 1.18 to 1.35, I^2 = 0%, *p* = 0.51) or due to lack of efficiency (PANSS total score: 4 RCTs, N = 1291, MD 8.32 CI 5.64 to 10.99, I^2 = 0%, *p* = 0.88). Compared to risperidone: ziprasidone resulted in more people leaving the study early for any reason (3 RCTs, N = 1029, RR 1.11 CI 1.02 to 1.20, I^2 = 0%, *p* = 0.37) or due to lack of efficiency (PANSS total score: 3 RCTs, N = 1016, MD 3.91 CI 0.27 to 7.55, I^2 = 64%, *p* = 0.06).	
Risks	Compared to olanzapine: ziprasidone produced less weight gain (5 RCTs, N = 1659, MD -3.82 CI -4.69 to -2.96, I^2 = 59%, *p* = 0.04), and more extrapyramidal side effects (4 RCTs, N = 1732, RR 1.43 CI 1.03 to 1.99, I^2 = 15%, *p* = 0.43). Compared to quetiapine: ziprasidone produced less weight gain (2 RCTs, N = 754, RR 0.45 CI 0.28 to 0.74 I^2 = 0%, *p* = 0.95) and more prolactin increase (2 RCTs, N = 754, MD 4.77 CI 1.37 to 8.16, I^2 = 0%, *p* = 0.98). Compared to risperidone: ziprasidone produced less weight gain (3 RCTs, N = 1063, RR 0.49 CI 0.33 to 0.74, I^2 = 0%, *p* = 0.93), less movement disorders (2 RCTs, N = 822, RR 0.70 CI 0.51 to 0.97, I^2 = 0%, *p* = 0.59) and less prolactin increase (2 RCTs, N = 767, MD -21.97 CI -27.34 to -16.60, I^2 = 43%, *p* = 0.19).
Consistency in results	Consistent
Precision in results	Precise apart from leaving the study early in the comparison with amisulpride and weight gain in the comparison with quetiapine. Unable to assess MD.
Directness of results	Direct
Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Silveira da Mota Neto JI, Kissling W, Leucht S. Amisulpride versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD006624. DOI:	

10.1002/14651858.CD006624.pub2.	
This review includes 10 RCTs (N = 1549), compared amisulpride to olanzapine, risperidone or ziprasidone No significant difference was reported between any intervention for study attrition. Compared to ziprasidone, amisulpride was more effective (measured as leaving the study early due to inefficacy: N = 123, 1 RCT, RR 0.21, 95%CI 0.05 to 0.94, NNT 8 CI 5 to 50).	
Risks	There was no difference in cardiac effects compared to ziprasidone (akathisia: N = 123, 1 RCT, RR 0.63, CI 0.11 to 3.67).
Consistency in results	Not applicable; 1 RCT.
Precision in results	Imprecise
Directness of results	Direct
Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Duggan L, Kissling W, Leucht S. Olanzapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD006654 DOI: 10.1002/14651858.CD006654.pub2.	
The review includes 50 RCTs (N = 9476) of olanzapine compared to amisulpride, aripiprazole, clozapine, quetiapine, risperidone or ziprasidone. Olanzapine had greater improvement of general mental state (measured by PANSS) compared to ziprasidone (4 RCTs, N = 1291, WMD -8.32, 95%CI -10.99 to -5.64, I^2 = 0%, p = 0.88). Olanzapine had significantly fewer participants leave the study early due to inefficacy compared to ziprasidone (5 RCTs, N = 1937, RR 0.64, 95%CI 0.51 to 0.79, NNT 17, I^2 = 0%, p = 0.78). Olanzapine had fewer hospital re-admissions compared to ziprasidone (2 RCTs, N = 766, RR -0.06, 95%CI -0.11 to -0.01, NNT 17, I^2 = 0%, p = 0.77).	
Risks	Olanzapine induced more weight gain compared to ziprasidone (5 RCTs, N = 1659, WMD 3.82kg, 95%CI 2.96kg to 4.69kg, I^2 = 59%, p = 0.04). Related effects such as increases in glucose and cholesterol levels were also more frequent with olanzapine. Olanzapine was associated with less extrapyramidal side effects than ziprasidone (4 RCTs, N = 1732, RR 0.70, 95%CI 0.50 to 0.97, I^2 = 43%, p = 0.15).
Consistency in results	Consistent for all except weight gain.
Precision in results	Precise for dichotomous outcomes, unable to assess continuous measures.

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Directness of results	Direct
Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, Srisurapanont M, Kissling W, Leucht S. Quetiapine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD006625 DOI: 10.1002/14651858.CD006625.pub2.	
This review includes 21 RCTs (N = 4101) compared quetiapine with clozapine, olanzapine, risperidone or ziprasidone. No significant difference in study attrition was reported between the interventions, all had high numbers of participants leaving the study early. There were no significant differences in mental state when quetiapine was compared with ziprasidone (2 RCTs, N = 710, WMD -0.11, 95%CI -6.36 to 6.14, I^2 = 62%, *p* = 0.10).	
Risks	Compared with quetiapine, ziprasidone induced more extrapyramidal adverse effects (as measured by use of antiparkinson medication, 1 RCT, N = 522, RR 0.43, 95%CI 0.2 to 0.93) but led to less weight gain (2 RCTs, N = 754, RR 2.22, 95%CI 1.35 to 3.63, NNH 13, I^2 = 0%, *p* = 0.95).
Consistency in results	Consistent
Precision in results	Unable to assess continuous outcomes, imprecise for dichotomous outcomes.
Directness of results	Direct
Komossa K, Rummel-Kluge C, Schwarz S, Schmid F, Hunger H, Kissling W, Leucht S. Risperidone versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD006626. DOI: 10.1002/14651858.CD006626.pub2.	
Risperidone had less patients leaving the study early for any reason than ziprasidone (3 RCTs, N = 1209, RR 0.90, 95%CI 0.83 to 0.98, I^2 = 0%, *p* = 0.37), and was more effective for symptom severity (PANSS total score: 3 RCTs, N = 1016, MD -3.91, 95%CI -7.55 to -0.27, I^2 = 64%, *p* = 0.06).	
Risks	Risperidone produced more extrapyramidal side effects than ziprasidone (2 RCTs, N = 822, RR 1.42, 95%CI 1.03 to 1.96, I^2 = 0%) and had more cholesterol increase (2 RCTs, N = 767, MD 8.58, 95%CI 1.11 to 16.04, I^2 = 0%).
Consistency in results	Consistent
Precision in results	Precise for leaving the study early, imprecise for extrapyramidal side effects. Unable to assess MD.

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Directness of results	Direct

Explanation of acronyms

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

Explanation of technical terms

† Different effect measures are reported by different reviews.

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

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[10]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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

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

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

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§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either

direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[11].

‖ 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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References

1. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Komossa K, Rummel-Kluge C, Hunger H, Schwarz S, Bhoopathi PS, Kissling W*, et al.* (2009): Ziprasidone versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*: CD006627.
4. Komossa K, Rummel-Kluge C, Schwarz S, Schmid F, Hunger H, Kissling W*, et al.* (2011): Risperidone versus other atypical antipsychotics for schizophrenia. *Cochrane database of systematic reviews* 1: CD006626.
5. Bagnall A, Lewis RA, Leitner ML (2000): Ziprasidone for schizophrenia and severe mental illness. *Cochrane Database of Systematic Reviews*: CD001945.
6. Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Silveira da Mota Neto JI*, et al.* (2010): Amisulpride versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*: CD006624.
7. Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, Srisurapanont M*, et al.* (2010): Quetiapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*: CD006625.
8. Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Duggan L*, et al.* (2010): Olanzapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews* 3: CD006654.
9. Asenjo Lobos C, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S*, et al.* (2010): Clozapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*: Treatment.
10. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
11. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*