TECHNICAL COMMENTARY

Zotepine

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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 zotepine 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[3]. 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

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dose dependent response or if results are reasonably consistent, precise and direct with low associated risks[4]. 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 three reviews that met our inclusion criteria [5-7].

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Zotepine	
Compared to placebo **Efficacy: High quality evidence (consistent, precise, direct) suggests zotepine results in greater study retention than placebo. Moderate to low quality evidence (imprecise, 1 medium-sized RCT) suggests a greater clinical response with zotepine than placebo.** **Adverse effects: Moderate to low quality evidence (imprecise, 1 medium-sized RCT) suggests zotepine may result in more sleep problems than placebo.** **Compared to first generation antipsychotics** **Efficacy: High quality evidence (consistent, precise, direct) suggests zotepine is associated with a greater clinical response, with improved global and mental state than first generation antipsychotics in general.** **Adverse effects: High quality evidence (consistent, precise, direct) suggests zotepine causes less akathisia than first generation antipsychotics. Moderate quality evidence (imprecise, medium to large samples) suggests zotepine may also cause less akathisia and dystonia.** **Compared to second generation antipsychotics** **Efficacy: Low quality evidence (inconsistent, imprecise, small samples) is unable to determine any differences in mental state between zotepine and clozapine, risperidone or remoxipride.** **Adverse effects: Moderate to low quality evidence (medium-sized sample, consistent, direct, very imprecise) suggests zotepine may result in higher levels of extrapyramidal symptoms than clozapine. Low quality evidence (small samples) is unable to determine any differences in adverse effects between zotepine and risperidone or remoxipride.** **See below for detailed results from three reviews.**	
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. Clozapine participants had greater improvement in mental state (BPRS total score) compared to the zotepine group (1 RCT, N = 59, MD = -6 95%CI -9.83 to -2.17, p = 0.0021).	
Risks	Clozapine produces fewer extrapyramidal side-effects than zotepine (1 RCT, N = 59, RR = 0.05, 95%CI 0.00 to 0.86, p = 0.039, NNT 3 95%CI 2 to 5), and zotepine altered prolactin levels (p < 0.005) compared to clozapine.
Consistency in results‡	Not applicable; 1 RCT.

Precision in results§	Imprecise for all other measures. Unable to assess for mental states.
Directness of results‖	Direct
DeSilva P, FentonM, Rathbone J. Zotepine for schizophrenia. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD001948. DOI: 10.1002/14651858.CD001948.pub2	
This review includes 11 studies (N = 966). Compared to placebo, zotepine was associated with greater clinical response (N = 106, 1 RCT, RR 0.44 CI 0.27 to 0.72, NNT 3, CI 2 to 6) and more study retention (N = 312, 3 RCTs, RR 0.78 CI 0.63 to 0.96, NNT 3, CI 2 to 6, I^2 = 0%, p = 0.88). Compared to first generation antipsychotics in general, zotepine was associated with greater clinical response (N = 356, 4 RCTs, RR 0.77 CI 0.65 to 0.92, NNT 7 CI 4 to 22, I^2 = 58%, p = 0.07), improved global state (N = 135, 2 RCTs, MD - 0.61 CI -1.01 to -0.21, I^2 = 0%, p = 0.59) and improved mental state (N = 234, 4 RCTs, MD – 6.92 CI -11.02 to -2.83, I^2 = 34%, p = 0.21).	
Risks	Compared to placebo, zotepine may decrease drowsiness (N = 106, 1 RCT, RR 1.48 CI 1.06 to 2.07) and increase insomnia (N = 106, 1 RCT, RR 0.68 CI 0.45 to 1.01). Compared to first generation antipsychotics in general, zotepine was associated with fewer cognitive problems (N = 65, 1 RCT, RR 0.32 CI 0.13 to 0.80), less akathisia (N = 396, 5 RCTs, RR 0.73 CI 0.58 to 0.93, I^2 = 0%, p = 0.62) and dystonia (N = 70, 2 RCTs, RR 0.47 CI 0.24 to 0.93, I^2 = 0%, p = 0.46). No other differences were reported.
Consistency in results	Consistent where applicable (> 1 RCT).
Precision in results	Precise for reported outcomes except mental state and sleep problems for comparison with placebo and cognition and dystonia for comparison with first generation antipsychotics. Unable to assess continuous outcomes (standardized measure not reported).
Directness of results	Direct
Subramanian S, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Kissling W, Leucht S, Komossa K. Zotepine versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD006628. DOI: 10.1002/14651858.CD006628.pub3.	
This review includes 3 RCTs (N = 289). No significant difference in study retention was reported. Compared to clozapine, zotepine had less clinically significant response (N = 59, 1 RCT, RR 8.23,	

95%CI 1.14 to 59.17, *p* = 0.036, NNH 3 CI 2 to 8) and less reduction in symptom severity (BPRS; N = 59, 1 RCT, MD 6.00, 95%CI 2.17 to 9.83, *p* < 0.01). There were no differences in symptom severity between zotepine and risperidone (BPRS, vs 4 mg: N = 40, 1 RCT, MD 1.40, 95%CI -9.82 to 12.62, *p* = 0.81; vs. 8 mg N = 40, 1 RCT, MD -1.30, 95%CI -12.95 to10.35, p = 0.83) or between zotepine and remoxipride (BPRS, N = 58, 1 RCT, MD 5.70, 95%CI -4.13 to 15.53, *p* = 0.26).	
Risks	Zotepine had higher levels of extrapyramidal symptoms than clozapine, measured as use of antiparkinson medication (N = 116, 2 RCTs, RR 20.96, 95%CI 2.89 to 151.90, *p* < 0.01, I^2 = 0%, *p* = 0.91) and higher prolactin levels (N = 59, 1 RCT, MD 33.40, 95%CI 14.87 to 51.93, *p* < 0.01). No significant difference between zotepine and risperisone in extrapyramidal symptoms, measured as use of antiparkinson medication (vs 4 mg: N = 40, 1 RCT, MD 1.80, 95%CI -0.64 to 4.24, *p* = 0.15; vs 8 mg: N = 40, 1 RCT, MD 2.50 95%CI -0.05 to 5.05, *p* = 0.055). No significant difference between the zotepine and remoxipride in extrapyramidal symptoms measured as use of antiparkinson medication (N = 49, 1 RCT, RR 0.97, 95%CI 0.41 to 2.29, *p* = 0.94).
Consistency in results	Inconsistent for clozapine use of antiparkinson medication, unable to assess for 1 RCT.
Precision in results	Imprecise
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, 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), RCT = randomised control trial, RR = relative risk, vs = versus

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[3].

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 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[3];

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

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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

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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.

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