TECHNICAL COMMENTARY

Amisulpride

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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 amisulpride 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. We have included only Cochrane reviews that have been published from the year 2000 to date to ensure the latest available evidence is presented. When multiple copies of reviews were found and/or when findings conflict, we present the most recent version and the most recent conclusions.

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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are 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 three reviews that met our inclusion criteria[3-5].

Amisulpride

Compared to placebo

Efficacy: High quality evidence (large samples, consistent, precise, direct) suggests low dose amisulpride may retain more patients in treatment and be more effective for global state and negative symptoms.

Adverse effects: Moderate quality evidence (imprecise) suggests amisulpride may cause more extrapyramidal symptoms than placebo.

Compared to first generation antipsychotics

Efficacy: High quality evidence (large samples, consistent, precise, direct) suggests amisulpride may retain more patients in treatment, and be more effective for global state, mental state and negative symptoms, but not positive symptoms.

Adverse effects: High quality evidence suggests amisulpride may be less likely to cause at least one adverse event or extrapyramidal symptom.

Compared to other second generation antipsychotics

Efficacy: Overall, moderate quality evidence (imprecise) suggests no differences between amisulpride and other second generation antipsychotics for any outcome. Moderate to low quality evidence (small sample) suggests fewer participants leaving the study early due to inefficacy with amisulpride than with ziprasidone.

Adverse effects: Moderate to high quality evidence (large samples) suggests amisulpride was associated with less weight gain than risperidone or olanzapine. Moderate quality evidence (imprecise) suggests agitation may be reported more often by patients receiving amisulpride. There were no differences in extrapyramidal symptoms between amisulpride and risperidone, olanzapine or ziprasidone.

See below for detailed results from three reviews.

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.

No significant difference was reported between any intervention for study attrition.

Compared to ziprasidone there were fewer people leaving the study early due to inefficacy with amisulpride (1 RCT, N = 123, RR = 0.21, 95%CI 0.05 to 0.94, NNT 8). No significant differences in

efficacy were reported compared to olanzapine and risperidone.	
Risks	Compared to risperidone, amisulpride induced less weight gain (3 RCTs, N = 585, MD = -0.99, 95%CI -1.61 to -0.37, I^2 = 0%, *p* = 0.80). There was no difference in akathisia compared to risperidone (3 RCTs, N = 586, RR = 0.80, 95%CI 0.58 to 1.11, I^2 = 0%, *p* = 0.64). Compared to olanzapine, amisulpride also induced less weight gain (3 RCTs, N = 671, MD = -2.11, 95%CI -2.94 to -1.29, I^2 = 0%, *p* = 0.58). Olanzapine was also associated with a higher increase of glucose (2 RCTs, N = 406, MD = -7.30, 95%CI -7.62 to -6.99, I^2 = 0%, *p* = 0.52).There was no difference in akathisia (2 RCTs, N = 587, RR = 0.66, 95%CI 0.36 to 1.21, I^2 = 0%, *p* = 0.51). Compared to ziprasidone, there was no difference in akathisia (1 RCT, N = 123, RR = 0.63, 95%CI 0.11 to 3.67).
Consistency in results‡	Consistent, no significant heterogeneity in reported outcomes.
Precision in results§	Imprecise for binary data, unable to assess continuous measures.
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.	
There was no difference in general mental state (measured by PANSS) between olanzapine and amisulpride.	
Risks	Olanzapine induced more weight gain than amisulpride (3 RCTs, N = 671, WMD = 2.11kg, 95%CI 1.29kg to 2.94kg, I^2 = 0%, *p* = 0.58). Related effects such as increases in glucose and cholesterol levels were also more frequent with olanzapine.
Consistency in results	Consistent
Precision in results	Unable to assess continuous measures (WMD).
Directness of results	Direct
Mota Neto JS, Lima MS, Soares BG. Amisulpride for schizophrenia. Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD001357 DOI: 10.1002/14651858.CD001357	
Compared to placebo, low-dose (up to 300mg/day) amisulpride retained more patients in treatment	

(4 RCTs, N = 514, RR = 0.6, 95%CI 0.5 to 0.8, NNT 3, I^2 = 21%, *p* = 0.28). There were also greater improvements in global state (1 RCT, N = 242, RR = 0.6, 95%CI 0.5 to 0.8, NNT 3) and negative symptoms (2 RCTs, N = 177, WMD = -10.1, 95%CI -16.6 to -3.5, I^2 = 0%, *p* = 0.39). Compared to first generation antipsychotics, amisulpride retained more people in treatment (14 RCTs, N = 1512, RR = 0.8, 95%CI 0.7 to 0.9, NNT 16, I^2 = 0%, *p* = 0.53). Authors state that this result might have been overestimated due to possible publication bias. Amisulpride was also more effective than first generation antipsychotics in improving global state (4 RCTs, N = 651 RR = 0.7, 95%CI 0.5 to 0.9, NNT 6, I^2 = 42%, *p* = 0.16), general mental state (5 RCTs, N = 695, WMD = -4.2, 95% -6.5 to -1.9, I^2 = 0%, *p* = 0.69) and negative symptoms (3 RCTs, N = 506, WMD = -2.8, 95%CI -4.3 to -1.3) but there were no differences in positive symptoms. Compared to other second generation antipsychotics, no significant differences were reported in any outcome from 1 RCT.	
Risks	Compared to placebo, amisulpride was more likely to cause extra-pyramidal symptoms (2 RCTs, N = 269, RR = 2.2, 95%CI 1.2 to 4.2, I^2 = 0%). No differences in any other adverse outcome. Compared to first generation antipsychotics, amisulpride was less likely to cause at least one general adverse event (6 RCTs, N = 751, RR = 0.87, 95%CI 0.78 to 0.97, NNH 9, I^2 = 48%, *p* = 0.08), cause at least one extrapyramidal symptom (7 RCTs, N = 771, RR = 0.7, 95%CI 0.6 to 0.9, NNH 5, I^2 = 49%, *p* = 0.07) or to require the use of antiparkinson medication (9 RCTs, N = 851, RR = 0.6, 95%CI 0.5 to 0.8, NNH 4, I^2 = 41%, *p* = 0.10). Compared to other second generation antipsychotics agitation was more frequent with amisulpride (1 RCT, N = 228, RR = 3.4, 95%CI 1.2 to 10.1, NNH 11).
Consistency in results	Consistent.
Precision in results	Precise for dichotomous outcomes, unable to assess continuous outcomes (standardised values not reported).
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), 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[6]. 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[7].

‖ 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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