TECHNICAL COMMENTARY

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Aripiprazole

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 aripiprazole 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

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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 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 five reviews that met our inclusion criteria[3-7].

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Aripiprazole

Aripiprazole

Compared to placebo

Efficacy: High quality evidence (consistent, precise, direct) suggests aripiprazole reduces psychotic relapse and increases compliance with study protocols. Moderate quality evidence (inconsistent) suggests aripiprazole may also increase study retention rates.

Adverse effects: Moderate to low quality evidence (imprecise, unable to assess consistency, 1 RCT) suggests no differences in any adverse effect apart from possible reduced prolactin levels with aripiprazole.

Compared to first generation antipsychotics

Efficacy: High quality evidence (large samples, consistent, precise, direct) from the most recent review suggests aripiprazole should retain more patients in treatment. Moderate quality evidence (some inconsistency and imprecision) suggests no differences in global state, mental state or quality of life.

Adverse effects: Moderate quality evidence (some inconsistency and imprecision) suggests aripiprazole may be associated with a lower risk of akathisia and other extrapyramidal symptoms, hyperprolactinaemia, blurred vision, sinus tachycardia, dizziness and nausea, than first generation antipsychotics.

Compared to other second generation antipsychotics, olanzapine and risperidone

Efficacy: Moderate to high quality evidence (large samples, imprecise) suggests no differences in global state or leaving the study early between aripiprazole and olanzapine or risperidone, although aripiprazole may be less effective than olanzapine for mental state.

Adverse effects: Moderate to high quality evidence (mostly precise) suggests aripiprazole may be associated with less cholesterol and less prolactin increases, with no differences in extrapyramidal side effects or glucose levels, compared to olanzapine or risperidone. Compared to olanzapine, aripiprazole may be associated with less weight gain and less sedation. When compared to risperidone, patients on aripiprazole reported less cardiac side effects, but higher incidence of tremor. There were no differences in weight gain between risperidone and aripiprazole.

See below for detailed results from five reviews.

Bhattacharjee J, El-Sayeh HG. Aripiprazole versus typical antipsychotic drugs for schizophrenia. Cochrane Database of Systematic Reviews 2008, Issue 3. CD006617.

Aripiprazole

Compared to first generation antipsychotics, significantly more participants in the aripiprazole group completed the study in the long term, (1 RCT, N = 1,294, RR = 0.81, 95%CI 0.8 to 0.9, NNT 8). No significant differences were found for mental state or global state.	
Risks	Compared to first generation antipsychotics, aripiprazole provided fewer occurrences of extra-pyramidal symptoms (3 RCTs, N = 968, RR = 0.46, 95%CI 0.3 to 0.9, NNT 13, I^2 = 69%, *p* = 0.04), particularly akathisia (3 RCTs, N = 897, RR = 0.39, 95%CI 0.3 to 0.6, NNT 11, I^2 = 0%, *p* = 0.54). Fewer participants given aripiprazole developed hyperprolactinaemia (1 RCT, N = 300, RR = 0.07, 95%CI 0.03 to 0.2, NNT 2). Aripiprazole presented a lesser risk of sinus tachycardia (1 RCT, N = 289, RR = 0.09, 95%CI 0.01 to 0.8, NNT 22) and blurred vision (1 RCT, N = 308, RR = 0.19, 95%CI 0.1 to 0.7, NNT 14); but increased risk of dizziness (3 RCTs, N = 957, RR = 1.88, 95%CI 1.1 to 3.2, NNH 20, I^2 = 0%, *p* = 0.64) and nausea (3 RCTs, N = 957, RR = 3.03, 95%CI 1.5 to 6.1, NNH 17, I^2 = 0%, *p* = 0.68).
Consistency in results‡	Consistent for all outcomes except mental state and extra-pyramidal symptoms.
Precision in results§	Precise for attrition and akathisia. Imprecise for all other outcomes.
Directness of results‖	Direct
El-Sayeh HG, Morganti C. Aripiprazole for schizophrenia. Cochrane Database of Systematic Reviews 2006, Issue 2. CD004578. **Belgamwar RB, El-Sayeh HG. Aripiprazole versus placebo for schizophrenia. Cochrane Database of Systematic Reviews 2011, Issue 8. CD006622.**	
Compared to placebo, fewer people left the aripiprazole group early (9 RCTs, N = 2,585, RR = 0.73, 95%CI 0.60 to 0.87, I^2 = 70%, *p* = 0.00088). Aripiprazole significantly decreased psychotic relapse in both the short and medium term (medium term: 1 RCT, N = 310, RR = 0.66, 95%CI 0.5 to 0.8, I^2 = 0%, *p* = 0.53). It also produced better compliance with study protocol (8 RCTs, N = 2,275, RR = 0.74, 95%CI 0.59 to 0.93, I^2 = 35%, *p* = 0.15). Compared to first generation antipsychotics, there were no significant benefits for aripiprazole with regards to global state (deterioration; 7 RCTs, N = 2,868, RR = 1.15, 95%CI 0.95 to 1.38, I^2 = 0%, *p* = 0.93), mental state (1 RCT, N = 310, RR = 1.23, 95%CI 0.81 to 1.87) quality of life (1 RCT, N = 300, RR = 0.88, 95%CI = 0.78 to 1.00) or leaving the study early (7 RCTs, N = 2,868, RR = 0.86, 95%CI = 0.71 to 1.06, I^2 = 53%, *p* = 0.05). Compared to second generation antipsychotics olanzapine and risperidone, aripiprazole was no better or worse on outcomes of global state (2 RCTs, N = 618, RR = 1.76, 95%CI = 0.87 to 3.54, I^2 = 69%, *p* = 0.07) and leaving the study early (3 RCTs, N = 832, RR = 1.08, 95%CI 0.96 to 1.21, I^2 =	

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0%, p = 0.46). Compared to standard care (receiving first or second generation antipsychotics) one aripiprazole study found fewer people not responding to treatment (RR = 0.70, N = 1,599, 95%CI 0.7 to 0.8, NNT 5), not satisfied with care (N = 1,599, RR = 0.62, 95%CI 0.6 to 0.7, NNT 4), and leaving the study early (N = 1,599, RR = 0.81, 95%CI 0.7 to 0.9, NNT 13).	
Risks	Compared to placebo, aripiprazole may decrease prolactin levels (2 RCTs, N = 725, RR = 0.21, 95%CI 0.11 to 0.37, I^2 = 40%, p = 0.20). Compared to first generation antipsychotics, there were no differences in adverse effects, with the exception of less akathisia (N = 955, RR = 0.31, 95%CI 0.2 to 0.6, NNT 20, I^2 = 0%, p = 0.56) and less need for antiparkinson medication (4 RCTs, N = 1,854, RR = 0.45, 95%CI 0.3 to 0.6, NNT 4, I^2 = 59%, p = 0.06) which were both lower in those receiving aripiprazole. Compared to second generation antipsychotics, the rates of adverse effects were also similar, with the exception of less elevation of prolactin (1 RCT, N = 301, RR = 0.04, 95%CI 0.02 to 0.1, NNT 2) and less prolongation of the average QTc interval (30 mg/day) (1 RCT, N = 200, WMD = -10.0, 95%CI -16.99 to -3.0) compared with risperidone. Note; see Komossa 2009 for more up to date information on adverse effects compared to other second generation antipsychotics.
Consistency in results	Inconsistent for aripiprazole vs. placebo – leaving early; aripiprazole vs. first generation antipsychotics – adverse effects and leaving early; aripiprazole vs. second generation antipsychotics – most adverse effects. Consistent for all other outcomes.
Precision in results	Precise for all outcomes except prolactin levels compared to placebo, unable to assess cardiac effects (standardised measure not reported).
Directness of results	Direct
Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, El-Sayeh HGG, Kissling W, Leucht S. Aripiprazole versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: DOI: 10.1002/14651858.CD006569.pub3.	
Compared to second generation antipsychotics, olanzapine and risperidone, no significant difference was reported with either comparison group for study retention. Compared to olanzapine, aripiprazole was less effective for improving mental state (2 RCTs, N = 794, MD = 4.96 CI 1.85 to 8.06, I^2 = 0%, p = 0.66). Compared to risperidone, no significant difference in efficacy was reported.	

Risks	Compared to olanzapine, aripiprazole was associated with less cholesterol (1 RCT, N = 223, RR = 0.32, 95%CI 0.19 to 0.54), less weight gain (1 RCT, N = 317, RR = 0.37, 95%CI 0.24 to 0.58), less sedation (1 RCT, N = 317, RR = 0.33, 95%CI 0.18 to 0.62) and less prolactin (1 RCT, N = 317, RR = 0.27, 95%CI 0.12 to 0.60). No differences in extrapyramidal side effects or glucose levels. Compared to risperidone, patients on aripiprazole had less cardiac effects (QTc abnormalities) (2 RCTs, N = 383, MD = -7.19, 95%CI -12.19 to -2.19, I^2 = 0%, *p* = 0.81), less cholesterol (1 RCT, N = 83, MD = -22.30, 95%CI -39.69 to -4.91), less prolactin (1 RCT, N = 383, MD = -54.71, 95%CI -60.06 to -49.36) but had a higher incidence of tremor (1 RCT, N = 301, RR = 4.66, 95%CI 1.11 to 19.59). No differences in other adverse effects such as weight gain, extrapyramidal side effects or glucose levels.
Consistency in results	Consistent.
Precision in results	Unable to assess precision, standardised values not reported.
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.

Olanzapine had greater improvement of general mental state (measured by PANSS) compared to aripiprazole, (2 RCTs, N = 794, WMD = -4.96, 95%CI -8.06 to -1.85, I^2 = 0%, *p* = 0.66).

Risks	Olanzapine induced more weight gain compared to aripiprazole (1 RCT, N = 90, WMD = 5.60kg, 95%CI 2.15kg to 9.05kg). Related effects such as increases in glucose and cholesterol levels were also more frequent with olanzapine. Olanzapine also increased prolactin more than aripiprazole (1 RCT, N = 317, RR = 3.74, 95%CI 1.68 to 8.33).
Consistency in results	Consistent
Precision in results	Unable to assess continuous measures
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[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[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[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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