TECHNICAL COMMENTARY

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Sertindole

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 sertindole 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

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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 two reviews that met our inclusion criteria[3, 4].

Sertindole	
Compared to placebo **Efficacy: Moderate quality evidence (imprecise) suggests sertindole may improve mental state and global state more than placebo.** **Adverse effects: Moderate quality evidence (imprecise) suggests no difference in movement disorders, but sertindole may result in more weight gain than placebo.** **Compared to first generation antipsychotic haloperidol** **Efficacy: Moderate quality evidence (imprecise) suggests sertindole may result in more study retention and medication compliance than haloperidol.** **Adverse effects: Moderate quality evidence (imprecise) suggests sertindole may result in fewer movement disorders and less sleepiness, but greater weight gain, rhinitis and cardiovascular effects than haloperidol.** **Compared to second generation antipsychotic risperidone** **Efficacy: Moderate quality evidence (imprecise or unable to assess) suggests no differences between sertindole and risperidone for mental state (PANSS change scores) or leaving the study early.** **Adverse effects: Moderate quality evidence (imprecise) suggests sertindole may result in fewer movement disorders, but greater weight gain, male sexual dysfunction and cardiovascular effects than risperidone.**	
Komossa K, Rummel-Kluge C, Hunger H, Schwarz S, Schmidt F, Lewis R, Kissling W, Leucht S. Sertindole versus other atypical antipsychotics for schizophrenia. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD006752. DOI: 10.1002/14651858.CD006752.pub2.	
This review includes 2 RCTs (N = 508) comparing sertindole with risperidone. There was no differences in PANSS total change from baseline scores (2 RCTs, N = 493, WMD = 1.98, 95%CI -8.24 to 12.20, $p > 0.05$) or leaving the study early (2 RCTs, N = 504, RR = 1.23, 95%CI 0.94 to 1.60, $p > 0.05$).	
Risks	Compared with relatively high doses of risperidone, (4 to 12 mg/day), sertindole produced significantly less akathisia and parkinsonism (1 RCT, N = 321, RR 0.24, 95%CI 0.09 to 0.69, $p < 0.05$), although sertindole produced more QTc prolongation (2 RCTs, N = 508, RR 4.86, 95% CI 1.94 to 12.18, $p < 0.05$), weight change (2 RCTs, N = 328, WMD 0.99, 95%CI 0.12 to 1.86, $p < 0.05$) and male sexual dysfunction (2 RCTs, N = 437, RR 2.90, CI 1.32 to 6.35, $p < 0.05$)
Consistency in results‡	Consistent

Precision in results[§]	Unable to assess WMD, RR CIs are imprecise.
Directness of results[‖]	Direct
Lewis R, Bagnall AM, Leitner M. Sertindole for schizophrenia. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD001715 DOI: 10.1002/14651858.CD001715.pub2	
This review includes 3 RCTs (N = 1104). Compared to placebo, higher doses of sertindole improved mental state (1 RCT, N = 78, MD = 6.2, CI -11.8 to -0.6) and global state (1 RCT, N = 78, MD -0.9, CI -1.6 to -0.2), but not doses lower than 20mg. Compared to haloperidol, sertindole had higher study retention at 12 months, (1 RCT, N = 282, RR = 0.6, CI 0.4 to 1.0, NNH 8.8, CI 4.7 to 74.0) and lower non-compliance (1 RCT, N = 282, RR = 0.2, CI 0.0 to 0.7, NNH 12.8, CI 7.7 to 37.8).	
Risks	Compared to placebo, no difference was reported for extrapyramidal events, or other movement disorders including akathisia, cogwheel rigidity, hypertonia and tremor or somnolence. Significant weight gain was reported for higher doses of sertindole, mean weight gain of 3.3 kg) as compared to placebo (mean weight gain of 0.8 kg; p <0.05). Compared to haloperidol, sertindole had reduced risk of extrapyramidal symptoms, (8mg: 1 RCT, N = 245, RR 0.1, CI 0.0 to 0.7, NNH 11.4, CI 7.1 to 29.8; 16mg: 1 RCT, N = 252, RR 0.3, CI 0.1 to 1.0, NNH 15.5, CI 8.0 to 217.9; 20mg: 1 RCT, N = 253, RR 0.2, CI 0.1 to 0.8, NNH 13.7, CI 7.7 to 68.3; 24mg: 2 RCTs, N = 524, RR 0.6, CI 0.4 to 0.8, NNH 8.7, CI 5.4 to 23.0, I^2 = 0%, p = 0.32), and other movement disorders including akathisia (8mg: 1 RCT, N = 245, RR 0.2, CI 0.1 to 0.5, NNH 6.0, CI 4.1 to 11.2; 16mg: 1 RCT, N = 252, RR 0.1, CI 0.0 to 0.3, NNH 5.4, CI 3.9 9.0; 20mg: 1 RCT, N = 253, RR 0.3, CI 0.2 to 0.7, NNH 7.3, CI 4.6 to 17.9; 24mg: 2 RCTs, N = 524, RR 0.5, CI 0.3 to 0.7, NNH 8.6, CI 5.6 to 18.3, I^2 = 11%, p = 0.29), and tremor (8mg: 1 RCT, N = 245, RR 0.3, CI 0.1 to 0.7, NNH 8.5, CI 5.2 to 24.0; 16mg: 1 RCT, N = 252, RR 0.2, CI 0.1 to 0.5, NNH 7.3, 4.8 to 15.6; 20mg: 1 RCT, N = 253, RR 0.2, CI 0.1 to 0.6, NNH 7.8, CI 4.9 to 18.1; 24mg: 2 RCTs, N = 524, RR 0.4, CI 0.2 to 0.6, NNH 8.2, CI 5.6 to 15.3, I^2 = 0%, p = 0.35) and hypertonia (2 RCTs, N = 524, RR 0.5, CI 0.3 to 0.8, NNH 12.4, CI 7.5 to 35.0, I^2 = 0%, p = 0.85). Sertindole was associated with significant increase in mean QTc interval compared to haloperidol at 6 weeks. This effect continued in the long term (1 RCT, N = 282, RR 23.0, CI 1.4 to 386.6, NNH 12.8, CI 8.2 to 29.6). Sertindole had reduced incidence of sleepiness at six weeks compared to haloperidol (8mg: 1 RCT, N = 245, RR 0.1, CI 0.0 to 0.7, NNH 11.4, CI 7.1 to 29.8; 24mg: 2 RCTs, N = 524, RR 0.6, CI 0.4 to 1.0, NNH 14.8, CI 7.7 to 205.2), but higher

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	incidence of rhinitis (16mg: 1 RCT, N = 252, RR 10.8, CI 1.4 to 82.6, NNH 12.7, CI 7.7 to 36.7; 24mg: 2 RCTs, N = 524, RR 2.1, CI 1.4 to 3.1, NNH 8.7, CI 5.6 to 18.6) and greater weight gain compared to haloperidol (1 RCT, N = 282, RR 6.3, CI 1.9 to 20.9, NNH 8.8, CI 5.7 to 19.1).
Consistency in results	Not applicable for most outcomes, 1 RCT only.
Precision in results	Unable to assess continuous outcomes. Imprecise for dichotomous outcomes.
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, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, RR = relative risk, vs = versus, WMD = weighted mean difference

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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[5]. 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

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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[6].

‖ 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, Schmidt F, Lewis R, *et al.* (2009): Sertindole versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews*: CD006752.
4. Lewis R, Bagnall AM, Leitner M (2005): Sertindole for schizophrenia.[update of Cochrane Database Syst Rev. 2000;(2):CD001715; PMID: 10796657]. *Cochrane Database of Systematic Reviews*: CD001715.
5. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
6. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*