

Loxapine

Introduction

First generation 'typical' antipsychotics are an older class of antipsychotic than second generation 'atypical' antipsychotics. They are used primarily to treat positive symptoms including the experiences of perceptual abnormalities (hallucinations) and fixed, false, irrational beliefs (delusions).

First generation antipsychotics may cause side effects which can differ depending on which antipsychotic is being administered and on individual differences in reaction to the drug. Reactions may 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.

This table summarises overall group effectiveness of loxapine from information gained from randomised controlled trials (RCTs). 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 included only information reported in the abstracts of Cochrane systematic reviews¹. 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 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 risks². 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 one review that met our inclusion criteria³.

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Compared to placebo

Efficacy: Moderate quality evidence (imprecise) suggests loxapine results in greater improvement in global clinical state than placebo.

Adverse effects: Moderate to low quality evidence (imprecise, small sample) suggests loxapine may result in more adverse effects

Compared to first generation antipsychotics

Efficacy: High quality evidence (consistent, precise, direct) suggests no differences in global effect or mental state.

Adverse effects: High quality evidence (consistent, precise, direct) suggests no differences in any adverse event.

Compared to second generation antipsychotics

Efficacy: Moderate to high quality (some imprecision) evidence suggests no differences in global effect or mental state.

Adverse effects: Moderate quality evidence (imprecise) suggests loxapine may induce more extrapyramidal symptoms than second generation antipsychotics.

See below for detailed results from one review.

[Chakrabarti A, et al. Loxapine for schizophrenia. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD001943. DOI: 10.1002/14651858.CD001943.pub2.](#)

This review includes 41 RCTs (N = not reported). 3 RCTs (N = 145) included intramuscular administration of both loxapine and comparator drug.

Compared to placebo, loxapine had a significantly greater global clinical effect: N = 78, 2 RCTs, RR 0.30, CI 0.1 to 0.6, NNT 3, CI 3 to 5, $I^2 = 57%$, $p = 0.13$.

Compared to first generation antipsychotics, loxapine is as effective in the short term (4 -12 weeks). No significant difference was reported for global antipsychotic effect (N = 580, 13 RCTs, RR 0.86, CI 0.7 to 1.1, $I^2 = 0%$, $p = 0.59$), or for mental state (N = 915, 6 RCTs, RR 0.89, CI 0.8 to 1.1, $I^2 = 0%$, $p = 0.84$).

Compared to second generation antipsychotics, loxapine is as effective as risperidone or quetiapine for improving mental state; no significant difference was reported by 6 weeks (N = 468, 6 RCTs, RR 1.07, CI 0.8 to 1.5, $I^2 = 0%$, $p = 0.91$).

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| <p>Risks</p> | <p>Compared to placebo, in general more adverse effects were reported by the loxapine group (N = 67, 2 RCTs, RR 1.55, CI 1.04 to 2.17, I² = 0%, p = 0.95).</p> <p>Compared to first generation antipsychotics, no differences are reported for any adverse effect (N = 627, 14 RCTs, RR 0.96, CI 0.86 to 1.07, I² = 11%, p = 0.34). Authors state that very limited heterogeneous data suggest that, given intramuscularly (IM), loxapine may be at least as sedating as IM haloperidol and thiothixene.</p> <p>Compared to second generation antipsychotics, loxapine may cause more extrapyramidal adverse effects (N = 340, 4 RCTs, RR 2.18, CI 1.6 to 3.1, I² = 8%, p = 0.35).</p> |
| <p>Consistency in results[‡]</p> | <p>Consistent for all reported outcomes.</p> |
| <p>Precision in results[§]</p> | <p>Imprecise, except for first generation antipsychotics comparisons.</p> |
| <p>Directness of results</p> | <p>Direct</p> |

Explanation of acronyms

CI = Confidence Interval, I² = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, 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

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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 effect¹.

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 ⁴. InOR stands for logarithmic OR where a InOR 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 unforeseen 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. Unstandardized (*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. Standardized regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ 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 formula¹;

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

§ 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

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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 relaxed⁵.

|| 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

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3. Chakrabarti A, Bagnall A, Chue P, Fenton M, Palaniswamy V, Wong W, Xia J. Loxapine for schizophrenia. *Cochrane Database of Systematic Reviews*. 2007; (4): CD001943.
4. Rosenthal JA. Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research*. 1996; **21**(4): 37-59.
5. GRADEpro. [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*. 2008.