TECHNICAL COMMENTARY

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Zuclopenthixol

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

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Compared to placebo **Efficacy: Moderate to low quality evidence finds no difference in study retention.** **Adverse effects: Not reported.** **Compared to other first generation antipsychotics** **Efficacy: Moderate to low quality evidence finds fewer injections with zuclopenthixol acetate than with haloperidol, but no differences in the number of supplementary antipsychotics. Higher quality evidence (large samples) finds more people left the study early for any reason with zuclopenthixol compared to chlorpromazine.** **Adverse effects: Moderate to low quality evidence finds more extrapyramidal symptoms with zuclopenthixol than perphenazine.** **Compared to second generation antipsychotics** **Efficacy: Moderate quality evidence (small to medium-sized samples, imprecise) finds no differences in mental state or study retention compared to risperidone.** **Adverse effects: Moderate to low quality evidence (small sample, imprecise) finds zuclopenthixol is associated with more parkinsonian symptoms than risperidone.** **See below for detailed results from two reviews.**	
Gibson RC, Fenton M, da Silva Freire Coutinho E, Campbell C. Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD000525. DOI: 10.1002/14651858.CD000525.pub2.	
Compared to haloperidol, people given zuclopenthixol acetate were not given more supplementary antipsychotics (3 RCTs, N = 134, RR = 1.49, 95%CI 0.97 to 2.30, I^2 = 79%, *p* = 0.01). People given zuclopenthixol acetate had fewer injections over seven days compared with those allocated to haloperidol (1 RCT, N = 70, RR = 0.39, 95%CI 0.18 to 0.84, NNT 4). There was no difference between treatments for leaving the study early (8 RCTs, N = 522, RR = 0.85, 95%CI 0.31 to 2.31, I^2 = 0%, *p* = 0.53).	
Risks	Compared to haloperidol, there were no differences in the number adverse effects (1 RCT, N = 148, RR = 0.74, 95%CI 0.43 to 1.27), and no difference in dizziness (2 RCTs, N = 192, RR at 24 hours = 1.15, 95%CI 0.46 to 2.88, I^2 = 0%, *p* = 0.67). Zuclopenthixol acetate was no more sedating at two hours (1 RCT, N = 40, RR = 0.60, 95%CI 0.27 to 1.34). Compared with haloperidol or second generation clotiapine, there were no differences in use of parkinsonian medication for movement disorders (4 RCTs, N = 276, RR = 0.94, 95%CI 0.73 to 1.21, I^2 = 63%, *p* = 0.07), or blurred vision or dry mouth (2 RCTs, N = 192, RR

	= 0.90, 95%CI 0.48 to 1.70, I^2 = 0%, *p* = 0.47).
Consistency in results‡	Inconsistent for use of supplementary antipsychotics only.
Precision in results§	Imprecise for all outcomes.
Directness of results‖	Direct

Bryan EJ, Purcell MA, Kumar A. Zuclopenthixol dihydrochloride for schizophrenia. CochraneDatabase of SystematicReviews 2017, Issue 4. CD005474.

Compared to placebo, there was no difference in study retention (2 RCTs, N = 100, RR = 0.29, 95%CI 0.01 to 6.60, I^2 = not reported).

Compared to first generation antipsychotic chlorpromazine, there was no difference in global state (1 RCT, N = 60, MD = 0.00, 95%CI -0.49 to 0.49), but more people left the study early for any reason from the zuclopenthixol group (6 RCTs, N = 766, RR = 0.54, 95%CI 0.36 to 0.81, I^2 = 0%, *p* = 0.68).

Compared to first generation antipsychotic chlorprothixene, there was no difference in study retention (1 RCT, N = 20, RR = 1.00, 95%CI 0.34 to 2.93).

Compared to first generation antipsychotic haloperidol, there were no differences in global state (1 RCT, N = 49, MD = 0.13, 95%CI -0.30 to 0.55) or study retention (2 RCTs, N = 141, RR = 0.99, 95%CI 0.72 to 1.35, I^2 = 100%, *p* < 0.0001)

Compared to first generation antipsychotic perphenazine, there was no difference in study retention (2 RCTs, N = 104, RR = 0.63, 95%CI 0.27 to 1.47, I^2 = 0%, *p* = 0.58).

Compared to first generation antipsychotic sulpiride, there were no differences in global state (1 RCT, N = 61, RR = 1.18, 95%CI 0.49 to 2.85) or study retention (1 RCT, N = 61, RR = 2.07, 95% CI 0.97 to 4.40).

Compared to first generation antipsychotic thiothixene, there was no difference in global state (1 RCT, N = 20, RR = 0.50, 95%CI 0.17 to 1.46) or study retention (1 RCT, N = 20, RR = 0.57, 95%CI 0.24 to 1.35).

Compared to zuclopenthixol depot, there was no difference in study retention (1 RCT, N = 46, RR = 1.95, 95%CI 0.36 to 10.58).

Compared to second generation antipsychotic risperidone, there were no differences in study retention (3 RCTs, N = 154, RR = 1.30, 95%CI 0.84 to 2.02, I^2 = 0%, *p* = 1.00) or mental state (1 RCT, N = 25, MD = -3.20, 95% CI -7.71 to 1.31).

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Risks	Compared to perphenazine, those receiving zuclopenthixol were more likely to require medication in the short term for extrapyramidal symptoms (1 RCT, N = 50, RR = 1.90, 95%CI 1.12 to 3.22). Compared to chlorpromazine, there was no difference in movement disorders (3 RCTs, N = 199, RR = 0.94, 95%CI 0.61 to 1.45, I^2 = 0%, *p* = 0.82). Compared to sulpiride, there was no difference in requiring hypnotics/sedatives (1 RCT, N = 61, RR = 0.60, 95%CI 0.27 to 1.32). Compared to risperidone, those receiving zuclopenthixol were more likely to require medications for extrapyramidal symptoms (1 RCT, N = 98, RR = 1.92, 95% CI 1.12 to 3.28).
Consistency in results	Consistent where applicable, apart from comparison with haloperidol.
Precision in results	Imprecise
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.

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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 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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