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Chlorpromazine

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 chlorpromazine 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 nine reviews that met our inclusion criteria[3-11].

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Chlorpromazine

Compared to placebo

Efficacy: High quality evidence (large samples, consistent, precise, direct) shows fewer people allocated to chlorpromazine left the study early. Moderate quality evidence (inconsistent) suggests chlorpromazine reduces relapse and improves symptoms and functioning.

Adverse effects: Moderate quality evidence (imprecise) suggests chlorpromazine is sedating, causes a lowering of blood pressure and more weight gain than placebo.

Compared to first generation antipsychotics

Efficacy: Moderate quality evidence (large samples, inconsistent or imprecise, direct) suggests less people left the study early if they were taking haloperidol. Moderate to low quality evidence (smaller samples) finds some benefit of chlorpromazine over haloperidol for sedation but less benefit for any global improvement. There were no differences between chlorpromazine and piperacetazine in global state, mental state or leaving the study early, no differences between chlorpromazine and penfluridol in leaving the study early, and no differences between chlorpromazine and metiapine in clinical improvement.

Adverse effects: Moderate quality evidence (either inconsistent or imprecise) suggests movement disorders may be more frequent with haloperidol, while chlorpromazine was associated with more hypotension. Moderate to low quality evidence (small sample) finds the risk of needing additional antiparkinsonian medication was less with chlorpromazine than with penfluridol, and there was an increased risk of drowsiness with chlorpromazine than with haloperidol. There were no differences between chlorpromazine and piperacetazine in the number of adverse events and no differences between chlorpromazine and metiapine in rates of parkinsonism.

Compared to second generation antipsychotics

Efficacy: Moderate to low quality evidence (small sample, imprecise or unable to assess, direct) finds no differences between chlorpromazine and clotiapine for leaving the study early. Lower quality evidence (very small samples) is unable to determine any differences in symptoms.

Adverse effects: Low quality evidence (very small sample) finds was no difference in rates of dyskinesia.

Chlorpromazine dosage differences

Efficacy: Moderate quality evidence (medium to large sample, precise, direct) suggests global state is better with high-dose chlorpromazine (2gms/day) than low-dose chlorpromazine (≤400mg/day).

Adverse effects: Moderate to low quality evidence (some imprecision) suggests more people left the study early in the high-dose group due to adverse effects, with less dystonia and extrapyramidal effects in the low-dose group.

Adams CE, Awad G, Rathbone J, Thornley B. Chlorpromazine versus placebo for schizophrenia.

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Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD000284. DOI: 10.1002/14651858.CD000284.pub2.	
Compared to placebo, fewer people allocated to chlorpromazine left the study early (26 RCTs, N = 1,780, RR = 0.65, 95%CI 0.53 to 0.79, NNT 15, I^2 = 24%, *p* = 0.16). Chlorpromazine reduces relapse over the short (< 8 weeks, 2 RCTs, N = 74, RR = 0.29, 95%CI 0.11 to 0.75, I^2 = 78%, *p* = 0.03), medium (9 weeks to 6 months, 4 RCTs, N = 809, RR = 0.49, 95%CI 0.41 to 0.60, I^2 = 96%, *p* = 0.00001) and longer term (6 months to 2 years, 3 RCTs, N = 512, RR = 0.57, 95%CI 0.48 to 0.67, NNT 4, I^2 = 72%, *p* = 0.03, 5 years, 2 RCTs, N = 394, RR = 0.65, 95%CI 0.56 to 0.75, I^2 = 84%, *p* = 0.01). Chlorpromazine provided a global improvement in a person's symptoms and functioning (13 RCTs, N = 1,121, RR = 0.80, 95%CI 0.75 to 0.85, NNT 6, I^2 = 51%, *p* = 0.02).	
Risks	Compared to placebo, chlorpromazine is sedating (19 RCTs, N = 1,404, RR = 2.63, 95%CI 2.10 to 3.28, NNH 5, I^2 = 36%, *p* = 0.07), and increases the risk of an acute movement disorder (dystonia) (5 RCTs, N = 942, RR = 3.47, 95%CI 1.50 to 8.03, NNH 32, I^2 = 0%, *p* = 0.86) and parkinsonism (12 RCTs, N = 1,265, RR = 2.01, 95%CI 1.50 to 2.70, NNH 14, I^2 = 59%, *p* = 0.01). Akathisia did not occur more often in the chlorpromazine group than placebo (9 RCTs, N = 1,164, RR = 0.78, 95%CI 0.54 to 1.11, I^2 = 22%, *p* = 0.26). Chlorpromazine causes a lowering of blood pressure with accompanying dizziness (16 RCTs, N = 1,394, RR = 2.37, 95%CI 1.73 to 3.24, NNH 11, I^2 = 0%, *p* = 0.46) and more weight gain (5 RCTs, N = 165, RR = 4.92, 95%CI 2.32 to 10.43, NNH 2, I^2 = 0%, *p* = 0.89).
Consistency in results‡	Inconsistent for relapse rates, symptoms and functioning, and parkinsonism. Consistent for all other outcomes
Precision in results§	Imprecise for short-term relapse rates and all adverse effects. Precise for all other outcomes
Directness of results‖	Direct
Alkhateeb H, Essali A, Matar HED, Rezk E, Almerie MQ. Cessation of medication for people with schizophrenia already stable on chlorpromazine. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD006329. DOI: 10.1002/14651858.CD006329.	
Compared to replacement placebo, those who remained on chlorpromazine were less likely to relapse in the short term (< 8 weeks, 3 RCTs, N = 376, RR = 6.76, 95%CI 3.37 to 13.54, NNH 4, I^2 = 0%, *p* = 0.72), medium term (9 weeks to 6 months, 6 RCTs, N = 850, RR = 4.04, 95%CI 2.81 to 5.8, NNH 4, I^2 = 40%, *p* = 0.14) and long term (6 months to 2 years, 3 RCTs, N = 510, RR = 1.70, 95%CI 1.44 to 2.01, NNH = 4, I^2 = 0%, *p* = 0.74).	
Risks	None reported

Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct
Dudley K, Liu X, De Haan S. Chlorpromazine dose for people with schizophrenia. Cochrane Database of Systematic Reviews 2017, 4: CD007778.	
This review includes 5 RCTs (N = 1,132) which authors state are all at least of moderate quality. Comparing low dose (≤400mg/day) with medium dose (401-800mg/day), no significant differences in efficacy are reported. When low dose (≤400mg/day) was compared with high dose (1 study - 2gms chlorpromazine/day), global state favoured the high dose group (1 RCT, N = 416, RR = 1.12, 95%CI 1.01 to 1.23).	
Risks	Comparing low dose (≤400mg/day) with medium dose (401-800 mg/day), in the short term, the risk of dystonia was lower in the low dose group (<12 weeks, 2 RCTs, N = 70, RR = 0.20, 95%CI 0.04 to 0.97, I^2 = 16%, *p* = 0.28). When low dose (≤400mg/day) was compared with high dose (1 study - 2gms chlorpromazine/day), more people left the study early in the high dose group due to adverse effects (1 RCT, N = 416, RR = 0.10, 95%CI 0.04 to 0.27). There was less dystonia (1 RCT, N = 416, RR = 0.11, 95%CI 0.02 to 0.45) and unspecified extrapyramidal adverse effects in the low dose group (1 RCT, N = 416, RR = 0.43, 95%CI 0.32 to 0.59).
Consistency in results	Consistent where applicable (>1 RCT).
Precision in results	Imprecise for dystonia outcomes only.
Directness of results	Direct
Eslami Shahrbabaki M, Dehnavieh R, Vali L, Sharafkhani R. Chlorpromazine versus piperacetazine for schizophrenia. Cochrane Database of Systematic Reviews 2018, Art. No.: CD011709. doi: 10.1002/14651858.CD011709.pub2.	
There were no significant differences between chlorpromazine and first generation piperacetazine in global state (2 RCTs, N = 208, RR = 0.90, 95%CI 0.80 to 1.02, I^2 = 71%, *p* = 0.06), mental state (1 RCT, N = 182, MD = -0.40, 95%CI -1.41 to 0.61, I^2 = 0%, *p* = 0.38) or leaving the study early (4 RCTs, N = 256, RR = 0.50, 95%CI 0.10 to 2.56, I^2 = 0%, *p* = 0.55).	
Risks	There were no differences in the number of adverse effects (3 RCTs, N = 74, RR = 1.00, 95%CI 0.75 to 1.33, I^2 = 80%, *p* = 0.02).
Consistency in results	Inconsistent, apart from leaving the study early.

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Precision in results	Precise for global state, imprecise for leaving the study early and adverse effects.
Directness of results	Direct
Leucht C, Kitzmantel M, Kane J, Leucht S, Chua WL. Haloperidol versus chlorpromazine for schizophrenia. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD004278. DOI: 10.1002/14651858.CD004278.pub2.	
Compared to first-generation antipsychotic haloperidol, less people left the study early if they were taking haloperidol (13 RCTs, N = 476, RR = 0.26, 95%CI 0.08 to 0.82, I^2 = 0%, *p* = 0.88). There were no significant differences in clinical improvement (9 RCTs, N = 400, RR = 0.81, 95%CI 0.64 to 1.04, I^2 = 59%, *p* = 0.01). Authors state that similar trends were found when studies comparing intramuscular formulations and studies comparing oral formulations were analysed separately.	
Risks	Compared to first generation antipsychotic haloperidol, movement disorders were more frequent in the haloperidol groups (6 RCTs, N = 212, RR = 2.2, 95%CI 1.11 to 4.40, NNH = 5, I^2 = 43%, *p* = 0.14), while chlorpromazine was associated with more hypotension (5 RCTs, N = 175, RR = 0.31, 95%CI 0.11 to 0.88, NNH = 7, I^2 = 0%, *p* = 0.73). Authors state that similar trends were found when studies comparing depot formulations and studies comparing oral formulations were analysed separately.
Consistency in results	Consistent for all outcomes except clinical improvement.
Precision in results	Imprecise for all outcomes except clinical improvement.
Directness of results	Direct
Mazhari S, Esmailian S, Shah-Esmaeili A, Goughari AS, Bazrafshan A, Zare M. Chlorpromazine versus clotiapine for schizophrenia. Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD011810. DOI: 10.1002/14651858.CD011810.pub2.	
There was less improvement in total symptoms with chlorpromazine than with second-generation clotiapine (1 RCT, N = 31, MD = 11.50, 95%CI 9.42 to 13.58). There were no differences in negative symptoms (1 RCT, N = 21, MD = -0.97, 95%CI -2.76 to 0.82) or study retention (3 RCTs, N = 158, RR = 0.68, 95%CI 0.24 to 1.88).	
Risks	There was no difference in incidence of dyskinesia (1 RCT, N = 68, RR = 3.00, 95%CI 0.13 to 71.15).
Consistency in results	Not applicable; 1 RCT
Precision in results	Imprecise or unable to assess MDs (not standardised).

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Directness of results	Direct
Nikvarz N, Vahedian M, Khalili N. Chlorpromazine versus penfluridol for schizophrenia. Cochrane Database of Systematic Reviews 2017, 9: CD011831.	
There were no differences between chlorpromazine and penfluridol in rates of hospital admissions (1 RCT, N = 29, RR = 0.19, 95%CI 0.01 to 3.60) or leaving the study early (3 RCTs, N = 130, RR = 1.21, 95%CI 0.83 to 1.77, I^2 = 0%, *p* = 0.44).	
Risks	The risk of needing additional antiparkinsonian medication was less in the chlorpromazine group (2 RCTs, N = 74, RR = 0.70, 95%CI 0.51 to 0.95, I^2 = 0%, *p* = 0.45) and there were no differences in rates of akathisia (2 RCTs, N = 85, RR = 0.19, 95%CI 0.04 to 1.06, I^2 = 0%, *p* = 0.56).
Consistency in results	Consistent where applicable.
Precision in results	Imprecise
Directness of results	Direct
Ostinelli EG, Brooke-Powney MJ, Li X, Adams CE. Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation). Cochrane Database of Systematic Reviews 2017, 7: CD009377.	
There was a small to medium-sized benefit of chlorpromazine over first-generation haloperidol for sedation (1 RCT, N = 39, RR = 1.93, 95%CI 1.04 to 3.60, *p* = 0.039), and a large benefit of haloperidol over chlorpromazine for any global improvement (2 RCTs, N = 89, RR = 0.15, 95%CI 0.05 to 0.49, *p* = 0.0017, Q= 0.09, *p* = 0.76, I^2 = 0%) and leaving the study early for any reason (4 RCTs, N = 153, RR = 0.21, 95%CI 0.07 to 0.71, *p* = 0.011, Q= 0.87, *p* = 0.35, I^2 = 0%). There was no significant difference between groups for need for urgent additional injection (1 RCT, N = 30, RR = 1.07, 95%CI 0.89 to 4.26, *p* = 0.45).	
Risks	There was an increased risk of drowsiness with chlorpromazine than haloperidol (1 RCT, N = 39, RR = 0.06, 95%CI 0.01-0.42, *p* = 0.0049). There were no significant differences in other adverse events.
Consistency in results	Consistent where applicable.
Precision in results	Precise apart from sedation, need for urgent injection and adverse effects.
Directness of results	Direct

Chlorpromazine

Zare M, Bazrafshan A. Chlorpromazine versus metiapine for schizophrenia. Cochrane Database of Systematic Reviews 2017, 3: CD011655.	
There was no difference between chlorpromazine and metiapine in clinically important improvement (2 RCTs, N = 120, RR = 1.11, 95%CI 0.84 to 1.47, I^2 = 8%, *p* = 0.30).	
Risks	There were no differences in rates of parkinsonism (2 RCTs, n = 70, RR = 0.97, 95%CI 0.46 to 2.03, I^2 = 53%, *p* = 0.14).
Consistency in results	Consistent
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), 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, RCT = randomised controlled trial, RR = relative risk

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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 randomized 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[12]. 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[13].

‖ 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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