TECHNICAL COMMENTARY

Thioridazine

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 thioridazine 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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Thioridazine

Compared to placebo

Efficacy: High quality evidence (consistent, imprecise, direct) shows thioridazine improves global state and increases study retention in the short term when compared to placebo. Moderate quality evidence (inconsistent) suggests there may also be reduced relapse rates.

Adverse effects: Moderate quality evidence (imprecise) suggests thioridazine may cause dry mouth, constipation and vomiting. Moderate to low quality evidence (inconsistent, imprecise) suggests thioridazine may be sedating. There may also be increased tremor and increased use of antiparkinsonian drugs with thioridazine in the short term.

Compared to other first generation antipsychotics

Efficacy: High quality evidence (consistent, precise, direct) shows no differences in global state. Moderate quality evidence (either inconsistent or imprecise) suggests no differences in study retention for any reason, although there may be more people leaving the study early in the thioridazine group due to adverse events in the short term.

Adverse effects: Moderate quality evidence (either inconsistent or imprecise) suggests there may be less short term use of antiparkinsonian drugs for people allocated to thioridazine, with less rigidity in the medium term, however there may be increased risk of any cardiac adverse effects, dry mouth and short term vomiting and nausea.

Compared to second generation antipsychotics

Efficacy: High quality evidence (consistent, precise, direct) shows no differences in global state or study retention.

Adverse effects: Moderate to low quality evidence (limited data, small sample) suggests no differences in adverse effects.

See below for detailed results from two reviews.

Fenton M, Rathbone J, Reilly J. Thioridazine for schizophrenia. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD001944. DOI: 10.1002/14651858.CD001944.pub2.

This review includes 42 RCTs (N = 3498).

Compared to placebo, thioridazine may improve global state (by 6 months, N = 105, 3 RCTs, RR 0.32 CI 0.21 to 0.48, NNT of 2 CI 2 to 3, $I^2 = 0\%$, $p = 0.87$), reduce the rate of relapse (by 3 months, N = 261, 2 RCTs, RR 0.09 CI 0.03 to 0.27, $I^2 = 88\%$, $p = 0.004$), and reduce the number of participants leaving the study early ('any reason' by 3 months, N = 510, 9 RCTs, RR 0.42 CI 0.30 to 0.60, $I^2 = 0\%$, $p = 0.71$, 'due to relapse or worsening/no improvement' by 3 months, N = 396, 6 RCTs, RR 0.10 CI 0.05 to 0.24, $I^2 = 42\%$, $p = 0.12$).

Compared to other first generation antipsychotics, there were no differences in global state (< 3 months, N = 743, 11 RCTs, RR 0.98 CI 0.83 to 1.16, $I^2 = 32\%$, $p = 0.14$, > 3 months to 1 year, N =

142, 3 RCTs, RR 0.99, CI 0.62 to 1.59, I^2 = 0%, *p* = 0.59). There were no significant differences in the number of people leaving the study early 'for any reason' in the short term (< 3 months, N = 1587, 19 RCTs, RR 1.07 CI 0.85 to 1.34, I^2 = 36%, *p* = 0.09), however in the short term more participants left the thioridazine groups due to adverse events (< 3 months, N = 871, 8 RCTs, RR 2.24 CI 1.19 to 4.22, I^2 = 42%, *p* = 0.11). Compared to second generation antipsychotics remoxipride and sulpiride, there were no differences in short term global state (N = 203, 3 RCTs, RR 1.00 CI 0.81 to 1.25, I^2 = 0%, *p* = 0.53) or leaving the study early (< 3 months, N = 344, 6 RCTs, RR 0.86 CI 0.62 to 1.22, I^2 = 0%, *p* = 0.79).	
Risks	Compared with placebo, thioridazine is sedating (< 3 months, N = 324, 3 RCTs, RR 5.37 CI 3.18 to 9.08, NNH 4 CI 2 to 74, I^2 = 70%, *p* = 0.03, 3 months to 1 year, N = 162, 4 RCTs, RR 2.41 CI 1.28 to 4.52, I^2 = 3%, *p* = 0.38), may cause dry mouth (N = 324, 3 RCTs, RR 6.75 CI 3.05 to 14.94, I^2 = 0%, *p* = 0.76), short term constipation (< 3 months, N = 273, 2 RCTs, RR 2.47 CI 1.27 to 4.83, I^2 = 0%, *p* = 0.83) and vomiting (< 3 months, N = 236, 1 RCT, RR 12.01 CI 3.78 to 38.15). Generally, thioridazine did not cause more movement disorders than placebo, with the only difference being short term tremor (< 3 months, N = 279, 2 RCTs, RR 3.03 CI 1.24 to 7.30, I^2 = 0%, *p* = 0.72) and short term use of antiparkinsonian drugs (< 3 months, N = 236, 1 RCT, RR 2.53 CI 1.15 to 5.60). Compared to other first generation antipsychotics short term use of antiparkinsonian drugs was lower for those allocated to thioridazine (< 3 months, N = 1082, 7 RCTs, RR 0.45 CI 0.36 to 0.55, I^2 = 83%, *p* = 0.00001), with less rigidity in the medium term (3 months to 1 year, N = 509, 4 RCTs, RR 0.44 CI 0.22 to 0.86, I^2 = 0%, *p* = 0.70). Thioridazine may be associated with any cardiac adverse effects (N = 74, 1 RCT, RR 3.17 CI 1.43 to 7.02, NNH 3 CI 2 to 5) and electrocardiogram changes were significantly more frequent in the thioridazine group (N = 254, 2 RCTs, RR 2.38, CI 1.58 to 3.59, NNH 4 CI 3 to 10, I^2 = 51%, *p* = 0.15). Dry mouth was reported more often in the thioridazine group (< 3 months, N = 829, 5 RCTs, RR 1.47 CI 1.16 to 1.87, I^2 = 0%, *p* = 0.82) as was short term vomiting and nausea (< 3 months, N = 734, 3 RCTs, RR 1.82 CI 1.11 to 2.99, I^2 = 65%, *p* = 0.06). Compared to second generation antipsychotics, there were no differences from limited data in adverse events such as extrapyramidal symptoms (< 3 months, N = 81, 2 RCTs, RR 1.22 CI 0.54 to 2.76, I^2 = 0%, *p* = 0.51).
Consistency in results‡	For comparison with placebo, all outcomes are consistent where applicable (> 1 RCT) except relapse and sedation. For comparison with first generation antipsychotics, all outcomes are consistent where applicable (> 1 RCT) except use of parkinsonian

	medication. For comparison with second generation antipsychotics, all outcomes are consistent.
Precision in results[§]	For comparison with placebo, all effectiveness outcomes are precise and all adverse effects outcomes are imprecise. For comparison with first generation antipsychotics, all outcomes are imprecise except global state and use of antiparkinsonian drugs. For comparison with second generation antipsychotics, all outcomes are precise except global state.
Directness of results[‖]	Direct
Marriott RG, Neil W, Waddingham S. Antipsychotic medication for elderly people with schizophrenia. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD005580. DOI: 10.1002/14651858.CD005580	
This review includes 3 RCTs (N = 252 elderly people with schizophrenia). Compared to first generation antipsychotic, remoxipride, there were no differences in the number of people leaving the study early (N = 18, 1 RCT, RR 1.0 CI 0.07 to 13.6).	
Risks	Not reported
Consistency in results	Not applicable; 1 RCT
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

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

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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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