# TECHNICAL COMMENTARY

## Fluphenazine

## 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 fluphenazine 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 three reviews that met our inclusion criteria[3-5].



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### Fluphenazine

**Compared to placebo**

**Efficacy: Moderate quality evidence (inconsistent) suggests less risk of relapse with oral fluphenazine. Low quality evidence (imprecise, small sample size, 1 RCT) is uncertain of the effectiveness of fluphenazine decanoate. There is no data for fluphenazine enanthate.**

**Adverse effects: Moderate quality evidence (imprecise) suggests oral fluphenazine may increase drowsiness, akathisia and rigidity. Low quality evidence (imprecise, small sample size, 1 RCT) is uncertain of the adverse effects of fluphenazine decanoate and fluphenazine enanthate.**

**Compared to other first or second generation antipsychotics**

**Efficacy: Moderate to high quality evidence (large samples, consistent, some imprecision) suggests no differences between oral fluphenazine and low-potency first generation antipsychotics in acceptability and response to treatment. Moderate to low quality evidence (inconsistent and imprecise) suggests no differences between fluphenazine decanoate and other antipsychotics in relapse rates.**

**Adverse effects: Moderate quality evidence (imprecise) suggests less risk of movement disorders with fluphenazine decanoate than with pimozide or fluphenazine hydrochloride. There were no differences in adverse effects when enanthate was compared to other depot antipsychotics. Moderate quality evidence (mostly imprecise) suggests oral fluphenazine may result in more akathisia, dystonia, loss of associated movement, rigor, and tremor than low-potency first generation antipsychotics. Conversely, there is greater risk of dizziness, drowsiness, sedation, dry mouth, nausea, and vomiting with low-potency first generation antipsychotics.**

**See below for detailed results from three reviews.**

**Maayan N, Quraishi SN, David A, Jayaswal A, Eisenbruch M, Rathbone J, Asher R, Adams CE. Fluphenazine de-canoate (depot) and enanthate for schizophrenia. Cochrane Database of Systematic Reviews 2015, Issue 2. CD000307.**

Fluphenazine decanoate

Compared to placebo, relapse was significantly reduced with fluphenazine decanoate by 2 years (N = 54, 1 RCT, RR 0.35, CI 0.20 to 0.60, $p < 0.05$). There were no differences in other measures of mental state.

Compared to placebo, less people left the study with fluphenazine decanoate by 2 years (N = 54, 1 RCT, RR 0.47, CI 0.23 to 0.96, $p < 0.05$).

Compared to first or second generation oral or depot antipsychotics, there were no differences in relapse rates (oral; N = 419, 6 RCTs, RR relapse 26 to 52 weeks 1.46 CI 0.8 to 2.8, $I^2 = 76\%$, $p = 0.001$, depot; N = 581, 11 RCTs, RR relapse 26-52 weeks 0.82 CI 0.6 to 1.2, $I^2 = 0\%$, $p = 0.57$).

Comparing standard dose to low dose fluphenazine decanoate, there were no differences in relapse



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| rates over 6 months to 1 year (N = 523, 4 RCTs, RR 2.09 CI 0.6 to 7.1, $I^2$ = 89%, *p* = 0.00001).<br><br>Fluphenazine enanthate<br><br>Compared to first or second generation oral or depot antipsychotics, there were no differences in global change (0 to 5 weeks, N = 31, 1 RCT, RR 0.67 CI 0.3 to 1.7). | |
| Risks | Compared to placebo, toxicity was experienced more often in the fluphenazine decanoate group than with placebo (N = 45, 1 RCT, RR 7.65 CI 1.04 to 56.26).<br><br>Compared to pimozide (2 RCTs) and fluphenazine hydrochloride (1 RCT), movement disorders were significantly less with fluphenazine decanoate (N = 259, 3 RCTs, RR 0.47 CI 0.2 to 0.9, NNT 14, CI 10 to 82, $I^2$ = 0%, *p* = 0.57).<br><br>Movement disorders, tardive dyskinesia, tremor, blurred vision and dry mouth were equally prevalent when enanthate was compared with other depot antipsychotics. |
| Consistency in results‡ | Inconsistent for relapse rates compared to other antipsychotics and dosage comparison. |
| Precision in results§ | Imprecise. |
| Directness of results‖ | Direct. |
| **Matar HE, Almerie MQ, Sampson S. Fluphenazine (oral) versus placebo for schizophrenia. Cochrane Database of Systematic Reviews 2018, Issue 6. CD006352.** | |
| Compared to placebo, there was less risk of relapse with fluphenazine (N = 124, 3 RCTs, RR 0.44 CI 0.30 to 0.67, $I^2$ = 88%, *p* = 0.00023). There were no differences found in global state (N = 75, 2 RCTs, RR 0.71 CI 0.45 to 1.12, $I^2$ = 0%, *p* = 0.55) or leaving the study early (N = 227, 2 RCTs, RR 0.70 CI 0.44 to 1.10, $I^2$ = 0%, *p* = 0.99). | |
| Risks | Compared to placebo, fluphenazine in the short term could increase drowsiness (N = 190, 1 RCT, RR 3.91 CI 1.98 to 7.71) and the risk of extrapyramidal effects such as akathisia (N = 227, 2 RCTs, RR 3.43 CI 1.23 to 9.56, NNH 13 CI 4 to 128 , $I^2$ = 0%, *p* = 0.56) and rigidity (N = 227, 2 RCTs, RR 3.54 CI 1.76 to 7.14, NNH 6 CI 3 to 17, $I^2$ = 0%, *p* = 0.32). |
| Consistency in results | Inconsistent for relapse only. |
| Precision in results | Precise for relapse only. |
| Directness of results | Direct. |



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| Tardy M, Huhn M, Engel RR, Leucht S. Fluphenazine versus low-potency first-generation antipsychotic drugs for schizophrenia. Cochrane Database of Systematic Reviews 2014, Issue 8. CD009230. | |
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| Compared to low-potency first generation antipsychotics, there were no differences in response to treatment (2 RCTs, N = 105, RR 1.06, CI 0.75 to 1.50, $I^2$ 0%, $p$ = 0.84), or acceptability of treatment (leaving the study early; 6 RCTs, N = 1532, RR 1.00, CI 0.88 to 1.14, $I^2$ 0%, $p$ = 0.60).<br>All studies assessed oral fluphenazine. | |
| Risks | Compared to low-potency first generation antipsychotics, fluphenazine may result in more akathisia (5 RCTs, N = 1209, RR 2.28, CI 1.58 to 3.28, $I^2$ 0%, $p$ = 0.42), dystonia (4 RCTs, N = 1309, RR 2.66, CI 1.25 to 5.64, $I^2$ 0%, $p$ = 0.55), loss of associated movement (1 RCT, N = 338, RR 11.15, CI 3.95 to 31.47), rigor (2 RCTs, N = 403, RR 2.18, CI 1.20 to 3.97, $I^2$ 49%, $p$ = 0.16), and tremor (2 RCTs, N = 403, RR 2.53, CI 1.37 to 4.68, $I^2$ 0%, $p$ = 0.77).<br>Conversely, dizziness (4 RCTs, N = 1051, RR 0.49, CI 0.32 to 0.73, $I^2$ 0%, $p$ = 0.56), drowsiness (3 RCTs, N = 986, RR 0.67, CI 0.53 to 0.86, $I^2$ 0%, $p$ = 0.50), sedation (1 RCT, N = 65, RR 0.31, CI 0.13 to 0.77), dry mouth (4 RCTs, N = 1051, RR 0.63, CI 0.45 to 0.89, $I^2$ 0%, $p$ = 0.52), nausea (3 RCTs, N = 986, RR 0.25, CI 0.14 to 0.45, $I^2$ 0%, $p$ = 0.46), and vomiting (3 RCTs, N = 986, RR 0.36, CI 0.18 to 0.72, $I^2$ 0%, $p$ = 0.98) occur more frequently with low-potency first generation antipsychotics. |
| Consistency in results | Consistent |
| Precision in results | Precise for leaving the study early, dizziness, drowsiness, and nausea only. |
| 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), RCT = randomised controlled trial, 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 randomized trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardized 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 moderate 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 large effect is considered if RR > 2 or < 0.5 and a very large effect if RR > 5 or < 0.2[6]. 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. 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.

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‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) which 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.

## References

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