TECHNICAL COMMENTARY

Treatments for medication adherence

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Introduction

One-quarter to one-half of people with schizophrenia do not adhere to their medication. Non-adherence to maintenance treatments, for example antipsychotic medication, is a widespread issue that plagues clinical management for schizophrenia. It reduces the success of the treatment regimen and the ability to achieve remission from illness, but it also increases the burden for psychotic relapse treatments, emergency admissions and hospitalisation. Greater adherence to treatment can contribute not only to more successful disease management and better quality of life, but also to improved attitudes towards treatment and medication, as well as increasing insight and confidence. In controlled clinical trials, drop-out rates can be a proxy measure of the overall tolerability and efficacy of the medication.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

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 randomised controlled trials (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 or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found three systematic reviews that met inclusion criteria[3-5].

- High quality evidence shows a small to medium-sized effect of lower drop-out rates in trials of flexible dose, second-generation antipsychotics compared to flexible dose,

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first-generation antipsychotics, with no differences in drop-out rates in trials of fixed doses.

- Moderate to high quality evidence suggests olanzapine and risperidone showed similar treatment response rates, but olanzapine had lower dropout rates.
- Moderate quality evidence suggests drop-out rates may be higher in people receiving placebo or first-generation antipsychotics compared to second-generation antipsychotics. Drop-out rates may be increasing over time and may be increased by longer treatment duration.

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Martin JL, Pérez V, Sacristán M, Rodríguez-Artalejo F, Martínez C, Alvarez E

Meta-analysis of drop-out rates in randomised clinical trials, comparing typical and atypical antipsychotics in the treatment of schizophrenia.

European Psychiatry 2006; 21: 11-20

View review abstract online

Comparison	**Drop-out rates in fixed-dose and flexible-dose clinical trials of first- versus second-generation antipsychotic medications.**
Summary of evidence	**High quality evidence (large samples, precise, consistent, direct) shows a small to medium-sized effect suggesting lower drop-out rates in trials of flexible dose, second-generation antipsychotics compared to trials of flexible dose, first-generation antipsychotics, with no differences in trials of fixed doses.**

Patient dropout rates from clinical trial (proxy for treatment non-adherence)

Fixed-dose RCTs

No differences in short term (6 to 12 weeks) drop-out rates between first- and second-generation antipsychotics;

Dropout - any reason: 8 RCTs, N = 2,468, RR = 0.91, 95%CI 0.81 to 1.01, $p = 0.08$, $I^2 = 51.1\%$, $p = 0.05$

Dropout - adverse events: 7 RCTs, N = 2,209, RR = 0.77, 95%CI 0.57 to 1.05, $p = 0.10$, $I^2 = 51.2\%$, $p = 0.06$

Flexible-dose RCTs

A significant, small to medium-sized effect suggests lower drop-out rates in flexible-dose trials of second-generation antipsychotics in both the short (6 to 12 weeks) and long-term (> 12 weeks) compared to first-generation antipsychotics;

Short term dropout (any reason): 13 RCTs, N = 3,782, RR = 0.70, 95%CI 0.64 to 0.76, $p < 0.00001$, $I^2 = 37.2\%$, $p = 0.09$

Long term dropout (any reason): 6 RCTs, N = 1,504, RR = 0.72, 95%CI 0.65 to 0.80, $p < 0.00001$, $I^2 = 51.9\%$, $p = 0.06$

Short term dropout (adverse events): 12 RCTs, N = 3,514, RR = 0.54, 95%CI 0.41 to 0.72, $p < 0.00001$, $I^2 = 0\%$, $p = 0.46$

Long term dropout (adverse events): 6 RCTs, N = 1,504, RR = 0.73, 95%CI 0.56 to 0.95, $p = 0.02$, $I^2 = 38.1\%$, $p = 0.15$

Consistency in results‡	Consistent
Precision in results§	Precise
Directness of results‖	Direct

Santarlasci B, Messori A

Clinical trial response and dropout rates with olanzapine versus risperidone

The Annals of Pharmacotherapy 2003; 37:556-563

View review abstract online

Comparison	**Drop-out rates in clinical trials (6-12 week follow up) of olanzapine versus risperidone.**
Summary of evidence	**Moderate to high quality evidence (large samples, imprecise, consistent, direct) suggests olanzapine and risperidone showed similar response rates, but olanzapine had lower dropout rates.**

A medium-sized effect suggests significantly lower short-term (6 to 12 weeks) dropout rates in patients receiving olanzapine compared to risperidone;

4 RCTs, N = 838, OR = 1.50, 95%CI 1.12 to 2.01, $p = 0.006$, Q = 1.10, $p = 0.80$

No difference between risperidone and olanzapine in short-term rate of response;

2 RCTs, N = 716, OR = 1.03, 95%CI 0.76 to 1.39, $p = 0.78$, Q = 0.0003, $p > 0.90$

Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Wahlbeck K, Tuunainen A, Ahokas A, Leucht S

Dropout rates in randomised antipsychotic drug trials

Psychopharmacology 2001; 155: 230-233

View review abstract online

Comparison	**Drop-out rates in clinical trials (6-12 week follow up) of first- and second-generation antipsychotics.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests drop-out rates may be higher with placebo or first-generation antipsychotics compared to second-generation antipsychotics. Drop-out rates may be increasing over time and may be increased by longer treatment duration.**
Overall data from 163 trials (N = 18,585) showed similar drop-out rates in the active treatment (33.0%) and placebo groups (33.6%). However, specific medications had variable drop-out rates; Chlorpromazine: 18.6%, Haloperidol 44.3%, Clozapine 24.4%, Olanzapine 38.6%, Risperidone 27.6%. A linear ANOVA found that drop-out rates have been increasing over time (p = 0.0001), and were also higher in longer trials (p = 0.026). The drop-out rate was significantly higher in patients treated with first-generation compared to second-generation antipsychotics (p = 0.026), but this effect was lost when clozapine trials were excluded (p = 0.24). Second-generation antipsychotics also showed significantly lower drop-out rates relative to placebo (p = 0.004). Among second-generation antipsychotics, drop-out rates were lower in clozapine relative to olanzapine (p = 0.052, trend) and quetiapine (p = 0.015), but not risperidone (p = 0.756) or ziprasidone (p = 0.139).	
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Unable to assess, no measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

ANOVA = Analysis of Variance test, CI = confidence interval, d = Cohen's d standardised mean differences (see below for interpretation of effect size), g = Hedge's g standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic for the test of heterogeneity, RCT = randomised controlled trial, RR = relative risk, vs. = versus

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[6].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[6].

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. 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 can provide an indirect 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.

‡ 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[6];

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

§ 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 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[7].

‖ 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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