TECHNICAL COMMENTARY

Treatment non-adherence

Introduction

Non-adherence to treatments is a widespread issue that hampers clinical management of many mental disorders. It reduces the success of the treatment regimen and the ability to achieve remission from illness, but it also increases the burden for relapse treatments, emergency admissions and hospitalisation. Greater adherence to treatment can contribute not only to more successful disorder management and better quality of life, but also to improved attitudes towards treatment and medication, as well as increasing insight and confidence.

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 2010 that report results separately for people with bipolar or related disorders. We have prioritised reviews with pooled data for inclusion. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, only the most recent and/or comprehensive version was included.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with 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].

- Moderate to high quality evidence found around 44% of people with bipolar disorder were non-adherent to psychotropic medications.
- Moderate to low quality evidence found factors associated with antipsychotic non-adherence included poor insight, substance use, negative attitudes toward medication, medication side effects, and to a lesser extent, cognitive impairments.
- In children and adolescents, moderate to high quality evidence found factors associated with medication non-adherence

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included greater illness severity, medication side effects, and having a comorbid substance use disorder or ADHD. Moderate quality evidence found factors associated with medication adherence included having positive patient and family attitudes toward care, a positive clinician-patient relationship, adherence to psychotherapy, patient insight, and a comorbid medical illness.

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Edgcomb JB, Zima B

Medication Adherence Among Children and Adolescents with Severe Mental Illness: A Systematic Review and Meta-Analysis

Journal of Child & Adolescent Psychopharmacology 2018; 28: 508-20

View review abstract online

Comparison	**Prevalence and factors associated with medication adherence in children and adolescents with a severe mental illness.** **The sample included people with psychotic disorders, bipolar disorder, depression, or mixed diagnoses.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, precise, direct) found factors associated with medication non-adherence include greater illness severity, medication side effects, and having a comorbid substance use disorder or ADHD. Moderate quality evidence (imprecise) finds factors associated with medication adherence include having positive patient and family attitudes toward care, a positive clinician-patient relationship, adherence to psychotherapy, patient insight, and a comorbid medical illness.**

Assessment methods

28 studies, N = 180,870; 65.9% were medication adherent.

Medication adherence was associated with;

Positive patient attitudes toward care: 8 studies, N = 474, OR = 3.41, 95%CI 1.50 to 7.77, p = 0.001, I^2 = 78%

Positive family attitudes toward care: 6 studies, N = 3884, OR = 2.82, 95%CI 1.79 to 4.45, p = 0.001, I^2 = 80%

Positive clinician-patient relationship: 3 studies, N = 1,742, OR = 5.92, 95%CI 1.73 to 18.55, p = 0.002, I^2 = 54%

Adherence to psychotherapy: 6 studies, N = 752, OR = 5.70, 95%CI 2.51 to 12.95, $p < 0.001$, I^2 = 83%

Patient insight: 3 studies, N = 3,784, OR = 3.60, 95%CI 1.42 to 9.10, p = 0.003, I^2 = 88%

Comorbid medical illness: 3 studies, N = 1,786, OR = 1.82, 95%CI 0.96 to 3.46, p = 0.033, I^2 = 33%

Medication non-adherence was associated with;

Illness severity: 11 studies, N = 2,911, OR = 0.44, 95%CI 0.32 to 0.62, $p < 0.001$, I^2 = 51%

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Medication side effects: 8 studies, N = 4,036, OR = 0.52, 95%CI 0.26 to 1.02, p = 0.029, I^2 = 76%
Comorbid alcohol use: 4 studies, N = 3,889, OR = 0.82, 95%CI 0.70 to 0.96, p = 0.008, I^2 = 0%
Comorbid substance use: 7 studies, N = 5,681, OR = 0.66, 95%CI 0.45 to 0.98, p = 0.020, I^2 = 40%
Comorbid ADHD: 5 studies, N = 1,920, OR = 0.61, 95%CI 0.41 to 0.91, p = 0.008, I^2 = 18%

Consistency in results‡	Mostly inconsistent
Precision in results§	Imprecise for medication adherence, precise for medication non-adherence.
Directness of results‖	Direct

Semahegn A, Torpey K, Manu A, Assefa N, Tesfaye G, Ankomah A

Psychotropic medication non-adherence and its associated factors among patients with major psychiatric disorders: a systematic review and meta-analysis

Systematic reviews 2020; 9: 17

View review abstract online

Comparison	**Prevalence of medication non-adherence in people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) found around 44% of people with bipolar disorder were non-adherent to medication.**

Prevalence
Nearly half of patients with bipolar disorder were non-adherent;
10 studies, N = 73,250, medication non-adherence was 44%, 95%CI 43% to 45%, I^2 = 100%
Authors suggest individual patient's behaviours, lack of social support, clinical, treatment, illness-related and health system factors influenced non-adherence,

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Velligan DI, Sajatovic M, Hatch A, Kramata P, Docherty JP

Why do psychiatric patients stop antipsychotic medication? A systematic review of reasons for non-adherence to medication in patients with serious mental illness

Patient Preference and Adherence 2017; 11: 449-68

View review abstract online

Comparison	**Risk factors for antipsychotic non-adherence.** **The sample included people with bipolar disorder or schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (large number of studies, appears inconsistent, unable to assess precision, direct) suggests risk factors of antipsychotic non-adherence include poor insight, substance use, negative attitudes toward medication, medication side effects, and to a lesser extent, cognitive impairments.**

Assessment methods

Factors associated with poor adherence;

Poor insight in 55.6% (20/36) of studies

Substance abuse in 36.1% (13/36) of studies

Negative attitude toward medication in 30.5% (11/36) of studies

Medication side effects in 27.8% (10/36) of studies

Cognitive impairments in 13.4% (7/36) of studies

Authors report that substance abuse was the only reason consistently associated with unintentional non-adherence.

Consistency in results	Appears inconsistent
Precision in results	Unable to assess; no CIs are reported
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, I^2 = proportion of heterogeneity across study results, N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), vs. = versus

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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) that 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[7]. 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.

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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[8].

‖ 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 that 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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