TECHNICAL COMMENTARY

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Psychosocial treatments for treatment non-adherence

Introduction

Non-adherence to treatment is a widespread issue that can make the clinical management of schizophrenia problematic. Non-adherence to treatment reduces the likelihood of symptom improvement and increases the likelihood of relapse and hospitalisation. Greater treatment adherence generally improves quality of life, fosters positive attitudes towards treatment, and results in greater insight into the disorder.

Strategies have been investigated for improving adherence to both medications and clinical appointments. These have included behavioural therapies, which are focused on reinforcing or reshaping target behaviours. Particular strategies used for behavioural interventions for treatment adherence include skill building, practice activities, altered medication packaging and dosage modifications[1]. Other strategies for improving adherence include cognitive-based compliance therapy, psychotherapy, family interventions, education programs, telephone prompts, community services and social policies[2, 3].

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 that describes a preferred way to present a meta-analysis[4]. 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, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[5]. The resulting table represents an objective summary of the available evidence, although the conclusions

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found four systematic reviews that met our inclusion criteria[1, 3, 6, 7].

- Moderate quality evidence suggests behavioural therapies alone or in combination with educational or affective interventions may improve treatment adherence compared to standard care.
- Moderate to low quality evidence suggests family therapies or educational therapies may improve treatment adherence, but there was no clear benefit of manual-directed compliance therapy over non-specific counselling.
- Moderate quality evidence finds no benefit of adherence therapy (motivational interviewing plus CBT) for treatment adherence over standard care, although there is some benefit for improving symptoms.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Dolder CR, Lacro JP, Leckband S, Jeste DV

Interventions to improve antipsychotic medication adherence: review of recent literature

Journal of Clinical Psychopharmacology 2003; 23(4): 389-399

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Comparison	**Behavioural interventions for treatment adherence (involving skill building and practice activities, behavioural modelling and contracting, medication packaging, and dosage modifications) vs. standard care.**
Summary of evidence	**Moderate quality evidence (medium to large samples, unable to assess precision or consistency, direct) finds behavioural therapies alone or in combination with educational or affective interventions improves treatment adherence in chronically ill patients.**

Treatment adherence

Measured indirectly by pill counting or family/patient/therapist reports; or directly by blood or urine sampling

12 included studies containing chronically ill schizophrenia patients (both in and out of hospital);

Mean baseline treatment adherence rates for 10 of the included studies (6 were RCTs) was 41.0%. Two controlled studies (N = 196) reported behavioural interventions alone and both reported improvement in adherence ranging from 15-26% improvement.

A further 10 RCT (N = 1,519) reported behavioural therapies in combination with educational or affective interventions, and 8 of these reported improvements in treatment adherence.

Consistency in results‡	No measure of consistency is reported.
Precision in results§	No measure of precision is reported.
Directness of results‖	Direct

Gray R, Bressington D, Ivanecka A, Hardy S, Jones M, Schulz M, von Bormann S, White J, Anderson KH, Chien WT

Is adherence therapy an effective adjunct treatment for patients with schizophrenia spectrum disorders? A systematic review and meta-

analysis **BMC Psychiatry 2016; 16: 90** View review abstract online	
Comparison	**Adherence therapy (a brief psychological intervention based on the principles of motivational interviewing and cognitive behavioural therapy) vs. standard care.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, mostly precise, direct) finds no benefit of motivational interviewing based adherence therapy for treatment adherence over standard care, although there is some benefit for improving symptoms.**
Treatment adherence	
No significant differences in attitudes towards adherence; 6 RCTs, N = 708, SMD = 0.25, 95%CI -0.05 to 0.55, $p = 0.11$, $I^2 = 66\%$, $p = 0.01$ *No significant differences in adherence behaviour;* 3 RCTs, N = 591, SMD = 0.43, 95%CI -0.43 to 1.29, $p = 0.33$, $I^2 = 95\%$, $p < 0.00001$	
Mental state	
A medium-sized, significant effect of greater improvement in symptoms with adherence therapy; 6 RCTs, N = 707, SMD = -0.56, 95%CI -1.03 to -0.09, $p = 0.02$, $I^2 = 86\%$, $p < 0.00001$	
Consistency in results	Inconsistent
Precision in results	Precise for attitudes and symptoms.
Directness of results	Direct

McIntosh A, Conlon L, Lawrie S, Stanfield AC

Compliance therapy for schizophrenia

Cochrane Database of Systematic Reviews 2006; Issue 3. Art. No.: CD003442

View review abstract online

Comparison	**Compliance therapy (manual directed, five sessions 30-60 mins)**

	vs. nonspecific counselling.
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess consistency or precision, direct) finds no benefit of compliance therapy over non-specific counselling for treatment attitudes, symptom severity, insight, global state or quality of life. Imprecise evidence also suggests no significant benefit for compliance rates or study attrition.**
Medication compliance and attitudes to treatment	
At one year, there were no significant differences for medication compliance or attitude to medication; Medication compliance: 1 RCT, N = 56, RR 1.23, 95%CI 0.74 to 2.05 Attitude to medication scores (DAI): 1 RCT, N = 50, WMD -2.10, 95%CI -6.11 to 1.91	
Leaving the study early	
At one year, there was no significant difference for attrition rates; 1 RCT, N = 56, RR 0.50, 95%CI 0.10 to 2.51	
Mental state, insight and quality of life	
At one year, there were no significant differences for mental state PANSS scores; 1 RCT, N = 50, WMD 6.10, 95%CI -4.54 to 16.74 *No significant difference reported for global state (GAF scores);* 1 RCT, N = 50, WMD -4.20, 95%CI -16.42 to 8.02 *No significant difference reported for insight (SAI scores);* 1 RCT, N = 50, WMD -0.50, 95%CI -2.43 to 1.43 *No significant difference reported for quality of life (QLS score);* 1 RCT, N = 50, WMD -3.40, 95% CI -16.25 to 9.45	
Risks	1 death was reported in compliance therapy group and no deaths were reported in control group.
Consistency in results	Not applicable, one RCT.
Precision in results	Imprecise for compliance and attrition rates. Unable to assess other outcomes.
Directness of results	Direct

Nose M, Barubui C, Gray R, Tansella M

Clinical interventions for treatment non-adherence in psychosis: meta-analysis

British Journal of Psychiatry 2003; 183: 197-206

View review abstract online

Comparison	**Targeted psychosocial interventions for treatment non-adherence, including educational programs, telephone prompts, psychotherapeutic interventions (with cognitive or psychodynamic approaches) vs. treatment as usual or a non-specific placebo intervention.** **Note – this review includes a sample of non-specific psychosis and is not limited to schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (large samples, some consistency and precision, indirect) suggests psychosocial interventions (including family therapy, education, prompts, psychotherapy or services) may have some benefit for improving medication adherence.**

Treatment adherence

Significant, medium-sized effect of more medication adherence with targeted psychosocial interventions;

19 studies, OR = 2.59, 95%CI 2.21 to 3.03, $p < 0.05$, $\chi^2 = 57.49$, $p < 0.001$

5 studies, SMD = 0.36, 95%CI 0.06 to 0.66, $p < 0.05$, $\chi^2 = 5.14$, $p = 0.274$

Subgroup analysis: Study design – no differences between results;

9 studies, N = 1,119, investigated non-adherence using RCT; OR = 2.60, 95%CI 1.99 to 3.39

10 studies, N = 2,030, investigated non-adherence using CCT; OR = 2.58, 95%CI 2.12 to 3.14

Subgroup analysis: Length of follow up – effect was greater in studies with shorter follow up periods;

11 studies, N = 1,502, investigated non-adherence with <6 month follow up; OR = 2.27, 95%CI 1.78 to 2.90

3 studies, N = 324, investigated non-adherence with >6 month follow up; OR = 1.70, 95%CI 1.04 to 2.78

5 studies, N = 1,323, investigated non-adherence, follow up immediately post treatment; OR = 3.17,

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

95%CI 2.52 to 3.99 *Subgroup analysis: Diagnosis – effect was greater in studies assessing only schizophrenia patients;* 7 studies, N = 537, investigated non-adherence in schizophrenia; OR = 3.21, 95%CI 2.19 to 4.68 12 studies, N = 2,612, investigated non-adherence in severe mental illness; OR = 2.47, 95%CI 2.08 to 2.94 *Subgroup analysis: Intervention type – effect was greatest in studies assessing family therapy;* 7 studies, N = 895, investigated non-adherence with education; OR = 2.41, 95%CI 1.72 to 3.37 2 studies, N = 170, investigated non-adherence with psychotherapy; OR = 2.83, 95%CI 1.36 to 5.87 2 studies, N = 1,029, investigated non-adherence with prompts; OR = 1.87, 95%CI 1.45 to 2.42 4 studies, N = 863, investigated non-adherence with service policies; OR = 3.63, 95%CI 2.68 to 4.92 4 studies, N = 192, investigated non-adherence with family therapy; OR = 4.45, 95%CI 2.52 to7.83 *Subgroup analysis: Adherence measurement – no differences in results;* 9 studies, N = 2,211, investigated non-adherence to appointments; OR = 2.52, 95%CI 2.10 to 3.02 10 studies, N = 938, investigated non-adherence to medication; OR = 2.81, 95%CI 2.03 to 3.88 *Subgroup analysis: Setting – effect was greater in studies assessing follow up from hospital discharge;* 2 studies, N = 123, investigated non-adherence in inpatients; OR = 1.65, 95%CI 0.38 to 7.18 10 studies, N = 1,664, investigated non-adherence in outpatients; OR = 2.16, 95%CI 1.72 to 2.70 7 studies, N = 1,362, investigated non-adherence following hospital discharge; OR = 3.13, 95%CI 2.50 to 3.91 *Subgroup analysis: Meta-regression;* A diagnosis of schizophrenia showed the greatest predictive value over other diagnoses for improved non-adherence following non-adherence interventions. Follow up period of less than 6 months showed significant benefit for improving adherence compared to longer term follow up periods.

Consistency in results	Inconsistent for ORs, consistent for SMD, unable to assess subgroup analyses.
Precision in results	Imprecise for ORs, precise for SMD, unable to assess subgroup analyses.
Directness of results	Indirect comparison (various treatment and control conditions are combined).

Psychosocial treatments for treatment non-adherence

Explanation of acronyms

CBT = cognitive behavioural therapy, CCT = controlled clinical trial, CI = Confidence Interval, DAI = Drug Attitude Inventory, GAF = Global Assessment of Functioning, 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), PANSS = Positive and Negative Syndrome Scale, QLS = Heinrich's Quality of Life Scale, RCT = randomised controlled trial, RR = risk ratio, SAI = Schedule for the Assessment of Insight, SMD = standardised mean difference, vs. = versus, WMD = weighted mean difference

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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[8].

† 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 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) 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[8].

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[9]. 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[8];

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

§ 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[10].

‖ 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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References

1. Dolder CR, Lacro JP, Leckband S, Jeste DV (2003): Interventions to improve antipsychotic medication adherence: review of recent literature. *Journal of Clinical Psychopharmacology* 23: 389-99.
2. Zygmunt A, Olfson M, Boyer CA, Mechanic D (2002): Interventions to improve medication adherence in schizophrenia. *American Journal of Psychiatry* 159: 1653-64.
3. McIntosh A, Conlon L, Lawrie S, Stanfield AC (2006): Compliance therapy for schizophrenia. *Cochrane Database of Systematic Reviews*.
4. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
5. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
6. Nose M, Barbui C, Gray R, Tansella M (2003): Clinical interventions for treatment non-adherence in psychosis: meta-analysis. *British Journal of Psychiatry* 183: 197-206.
7. Gray R, Bressington D, Ivanecka A, Hardy S, Jones M, Schulz M*, et al.* (2016): Is adherence therapy an effective adjunct treatment for patients with schizophrenia spectrum disorders? A systematic review and meta-analysis. *BMC Psychiatry* 16: 90.
8. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
9. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
10. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*