

review title

Interventions for enhancing medication adherence (Haynes et al 2008)

focus of the review

The aim of this Cochrane review was to examine the effectiveness of interventions to help people adhere to prescription medicines for medical (including psychiatric) problems, taking into account both adherence and treatment effects.

Review authors identified themes and groupings of interventions of included trials:

- More instruction for patients; counselling; automated telephone or computer-assisted patient monitoring and counselling; family intervention; increasing involvement of patients through self-monitoring; reminders; dose-dispensing medication units and medication charts; differing medication formulations; augmented pharmacy services; psychological therapy.

Outcomes of interest to review authors:

- Adherence;
- Treatment outcomes.

key results of the review

What this review shows about interventions to improve adherence to medications:

- Compared with control, various interventions may improve medication adherence. For short-term treatment, some quite simple interventions may improve adherence; for long-term treatment, effective interventions are typically complex;
- Compared with control, different interventions to improve adherence may also improve treatment outcomes; however, interventions effectively improving adherence do not necessarily improve treatment outcomes in either short or long term treatments.

What this review does not show about interventions to improve adherence: gaps in the evidence:

- The effects of interventions to improve adherence to prescription medications upon adherence and treatment outcomes including harms.
- The effects of the range of different simple and complex interventions to improve medication adherence across diseases and medications with rigorous examination of the effectiveness of the components of multifaceted interventions, including effects upon both adherence and treatment outcomes, including harms.

This bulletin summarises a recently updated Cochrane systematic review

This page highlights key aspects of the review

Pages 2-4 summarise the review

The evidence table on pages 5-8 contains more detail of the review

This evidence bulletin is provided by The Cochrane Consumers & Communication Review Group with funding from Department of Human Services, Victoria, Consumer Participation and Information, Quality and Safety Branch.

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25 JUNE 2008

Summary of the review

Background to the review

Many people when prescribed medications do not take them as instructed. Research has estimated that on average 50% of people do not adhere to their prescribed medication regimen. Given that both the dose and duration of therapy are critical to effective treatment with medication, lack of adherence can dilute any possible therapeutic benefit.

There are many reasons for people not to adhere to the medication they are prescribed. These can include problems with the drug itself, such as adverse effects. They can also include poor instructions about how and when to take the medication; inability to remember to take the drug as directed; and inability to afford to pay for the medications they require. Patients may also disagree with the need to take medication or receive treatment, and so may deliberately or actively choose not to take the medication, or to take it as prescribed.

The need to increase adherence to medication regimens is recognised as an important priority, in order that people achieve the potential benefits of treatment across many different diseases, both acute and chronic. Ethical standards also state that interventions for increasing medication adherence must not be judged only on their effects on adherence, but also on the clinical benefits that they achieve. It must also be noted that increasing adherence cannot necessarily be assumed to do more good than harm: increasing adherence to medication can also increase the number or severity of adverse treatment effects. It is therefore essential that interventions to improve medication adherence accurately and comprehensively assess possible adverse effects, as well as improvements in clinical outcomes.

This review evaluated the effects of all interventions to enhance medication adherence. It specifically examined both adherence outcomes and treatment outcomes, and looked for both possible benefits and harms arising from treatment.

The breadth and scope of this review are important as medication adherence has broad

implications for effective therapy across many different types of disease groups and for many different types of patients.

Trials included in the review

This review updates the 2005 review, by the same authors, with 21 new trials. Seventy eight trials (randomised controlled trials) were included in the review, involving more than 9,300 participants and assessing 91 interventions. Interventions were directed to consumers, in various settings including the workplace, home, community centres, hospitals and clinics. Outcomes of adherence and treatment outcome were collected and reported by this review.

Description of interventions

Review authors included trials of any intervention intended to affect adherence to prescribed, self-administered medications. Authors referred to interventions in some trials as *simple* eg. counselling about the importance of adherence, simplification of dosage regimen, and use of adherence enhancing packaging, while other interventions, often including several components, were referred to as *complex*.

Authors stated that a taxonomy of simple labels for interventions would not do justice to the complexity of many of the interventions tested. Their list illustrates common themes and groupings:

- more instruction for patients;
- counselling;
- automated telephone or computer-assisted patient monitoring and counselling;
- manual telephone follow-up;
- family intervention;
- increased convenience of care;
- simplified dosing;
- increasing involvement of patients through self-monitoring;
- reminders;
- reminder packaging;
- dose-dispensing medication units and medication charts;
- appointment and prescription refill reminders;

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Summary of
the review
continued...

- reinforcement or rewards for improved adherence and treatment response;
- differing medication formulations;
- crisis intervention when required;
- direct observation of treatment;
- lay health mentoring;
- augmented pharmacy services;
- psychological therapy;
- mailed communications;
- group meetings.

Description of outcomes

Included trials examined medication adherence, with at least one measure of each of adherence and treatment outcome. Trials of long-term regimens with initially positive findings were required to have at least 6 months of follow-up (from patient trial entry); while trials with initially negative results and shorter follow-up periods were included (based on the rationale that initial failure was unlikely to be followed by success at later time points).

Results are outlined in the review in relation to short-term and longer-term treatments. Longer-term treatments (involving 81 interventions) are presented by disease group or another category (eg. dosing schedule; complex regimens in the elderly), while short-term treatments (10 interventions) are not, as authors did not find enough trials on any one disease group to enable such grouping. Results are presented here under adherence and treatment outcomes headings.

What the review shows: summary of key findings

Medication adherence

There is some evidence from trials that interventions might improve medication adherence, with less than half of the interventions examined (41 of 91 interventions) significantly improved medication adherence, compared with control. The effective interventions represented five of ten **short-term** interventions; and 36 of 81 **long-term** interventions.

While some *quite simple* interventions

(counselling, written information, telephone calls) improved adherence for short-term treatments, almost all effective interventions for long-term treatment were *complex*. (The latter interventions included combinations of the following: more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up and supportive care.)

Treatment outcomes

There is some evidence from trials that approximately one third of interventions (30 of 91) significantly improved treatment outcomes, compared with control. Effective interventions represented four of ten **short-term** interventions and 26 of 81 **long-term** interventions.

Harms and adverse effects

There is some evidence from trials that six trials examining the effects of telling patients about adverse effects of treatment found no effects on adherence. Authors also note that interventions, even if they do improve adherence, cannot be assumed to do more good than harm in terms of clinical outcomes.

What the review does not show

Other outcomes

There is insufficient evidence to support or refute interventions to improve adherence on major clinical outcomes including major **morbidity** or **mortality**, as these outcomes were not measured by the review.

There is insufficient evidence to decide between interventions to improve adherence and control for disease-specific measures or for other process measures such as **knowledge** and **understanding**, **satisfaction**, **decision-making** or other outcomes, as these outcomes were not measured by the review.

Conclusions

Based on the interventions and findings of the included trials, the conclusions of this review have not substantially altered those of the 2005 version. For short-term treatments some quite simple interventions improved medication adherence and treatment outcomes though

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results between trials were inconsistent and less than half of trials reported benefits in both outcomes.

For long-term treatments almost all beneficial interventions were complex though even the most effective intervention did not lead to large improvements in adherence and treatment outcomes—while less than half improved adherence even fewer improved clinical outcomes.

Recommendations from authors

Authors stress that adherence problems are common across disease categories and treatment regimens: interventions to improve adherence are therefore essential and are likely to have important effects upon the effectiveness of therapy for many diseases.

Authors strongly recommend rigorous research into factors affecting adherence and

interventions to improve adherence. Authors recommend future trials include assessment of major clinical outcomes, including major morbidity and mortality. Future trials must also be powered to detect clinically important effects of interventions if they exist, including adverse effects.

The effectiveness of individual intervention components should be examined in future trials in order to understand the underlying mechanism and to optimise the interventions themselves.

Authors recommend that objective measures of adherence be used in future trials. Trials must also examine long-term effects of interventions on adherence and clinical outcomes, including effects upon discontinuation of the intervention. Finally, innovative interventions to improve adherence should be tested in rigorous, long-term trials.

Funding

This Evidence bulletin is provided by The Cochrane Consumers & Communication Review Group (CC&CRG) with funding from the Department of Human Services, Victoria, Consumer Participation and Information, Quality and Safety Branch. Bulletins in this series are created for the Health Knowledge Network (HKN) and in support of *Evaluating effectiveness of participation* (EEP) projects.

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Evaluation of bulletin service

You are invited to participate in an [online questionnaire](#) that is currently underway that aims to evaluate the Health Knowledge Network bulletin service. It consists of 20 questions about accessibility and comprehensibility of bulletins and about the reach of the network. This **evaluation** will inform future development of such health information and services. Go to the [HKN bulletin page](#) (hyperlinked here) for participant information and a link to the online questionnaire.

Bulletins housed on Health Knowledge Network website

Evidence bulletins (as well as Resource bulletins) are available on the Health Knowledge Network website at: www.latrobe.edu.au/cochrane/HKN/

Summary of the review continued...

See the evidence table and key to results on pages 5-8

Funding

Bulletin evaluation

Online questionnaire

Cochrane Consumers and
Communication Review Group



A Victorian
Government
initiative



Full citation for the review:

Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD000011. DOI: 10.1002/14651858.CD000011.pub3 Full text is available in The Cochrane Library at: www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000011/frame.html

This table is part of an overview of the review created by Dr Rebecca Ryan, at The Consumers & Communication Review Group. It contains detailed data extracted from the review. The summary on the previous pages of this EVIDENCE bulletin draws on content from both this table and the review. This table uses standardised wording developed by the Review Group. A key to this wording follows the table and should be used to interpret the data.

Review title: Interventions for enhancing medication adherence

Authors: Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X

Description of main features

Aim: To examine the effectiveness of interventions to help people to adhere to prescription medicines for medical (including psychiatric) problems, taking into account both adherence and treatment effects.

Trial design:

RCT; authors additionally note that, in order to be included, the trial had to allow an unconfounded examination of interventions designed to affect adherence.

Participants:

Included: Patients prescribed medication for a medical, including psychiatric, condition. Of included trials the following conditions were represented: HIV (12 trials); hypertension (11); asthma/COPD (11); schizophrenia/ acute psychosis (10); diabetes (6); depression (4); hyperlipidaemia (3); rheumatoid arthritis (2); complex regimens in the elderly (2); and one trial each in epilepsy, ischaemic heart disease, heart failure, hypertension and hyperlipidaemia, TB, oral anticoagulant therapy and contraception.

Excluded: Trials in which patients were prescribed medication for an addiction; trials lacking participant follow-up of at least 80%.

Interventions:

Included: Any intervention intended to affect adherence to prescribed, self-administered medications. Intervention themes identified in included trials included the following: more instruction for patients; counselling; automated telephone or computer-assisted patient monitoring and counselling; manual telephone follow-up; family intervention; increased convenience of care; simplified dosing; increasing involvement of patients through self-monitoring; reminders; reminder packaging; dose-dispensing medication units and medication charts; appointment and prescription refill reminders; reinforcement or rewards for improved adherence and treatment response; differing medication formulations; crisis intervention when required; direct observation of treatment; lay health mentoring; augmented pharmacy services; psychological therapy; mailed communications; group meetings.

Comparison arms:

Intervention versus usual care or comparable control.

Outcomes:

Included: Trials examining medication adherence, with at least one measure of each of adherence and treatment outcome. Trials of long-term regimens with initially positive findings were required to have at least 6 months of follow-up (from patient trial entry); while trials with initially negative results and shorter follow-up periods were included (based on the rationale that initial failure was unlikely to be followed by success at later time points).

Note that outcomes of adherence and treatment outcome were collected and reported by this review only: conclusions about effects of interventions to improve adherence therefore cannot be made with regard to outcomes outside these parameters.

Number of trials included: 78 (6 trials await assessment; 3 are ongoing trials); assessing 91 interventions.

Types of trials included: RCT

Number of participants included: >9,300

Meta-analysis performed: No; narrative synthesis. Meta-analysis was not appropriate due to the variability in participants, settings, interventions, medication regimens and outcome measures.

Review methods: Standard Cochrane Collaboration review methods were used, including the following: *a priori* research design provided; extensive searching for trials; selection criteria were specified in advance and applied; list of included and excluded trials provided; quality criteria for assessment of included trials were reported and applied; methods of analysis were reported; conflict of interest stated.

Quality:

Included trials: Quality of allocation concealment assessed. Review inclusion criteria also restricted eligibility of trials based on the following: unconfounded randomised controlled trial; at least 80% participant follow-up; including one or more measures of each of adherence and treatment outcomes; and follow-up of at least 6 months for long-term trials with initially positive findings. Restriction of included trials based on methodological requirements meant included trials had to meet established quality criteria. However, only 24/78 included trials adequately concealed allocation, with concealment rated as unclear, inadequate or not done in the remaining trials. Authors also note that none of the trials adjusted for multiple comparisons but generally conducted only two to three statistical tests of the data; and that generally many of the included trials were underpowered to detect clinically important effects on patient outcomes.

Review AMSTAR rating (out of possible 11): 9 - high quality review.

Comments: The review methods adequately met all items of the AMSTAR checklist with the exception of two items: one item evaluated assessment of publication bias: the likelihood of publication bias was not explicitly addressed by the review. The other item assessed whether publication status was used as an exclusion for the review: the review included only published trials and authors note that this may represent a source of bias (published trials may overestimate interventions effects).

Setting: *Country:* Not stated. *Intervention:* Variable; authors note that interventions took place in a range of venues and settings, these included the workplace, home, community centres, hospital (both inpatient and outpatient settings) and clinics (focussing on the treatment and/or management of various specific diseases or purposes).

Recipient: Interventions directed to the consumer.

Provider: Variable; providers included nurses, nurse research assistants, specialists, psychologists, educational instructors, physiotherapists, psychiatrists, physicians and pharmacists.

Format: Variable: Ranged from face-to-face instruction; information provision and discharge plans; individual, group and family counselling, including psychoeducational approaches, cognitive behaviour interventions and psychotherapy; general or disease-specific education sessions at different intensities and conducted in groups, for individuals and for families; and direct observation; to written instruction and information; specialised 'reminder' medication packaging; and other (eg telephone, mailed) reminder systems.

*Full text of paper about AMSTAR: http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17302989&ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum



EVIDENCE TABLE
CONTINUED...

Intervention	Results of review
Interventions to improve adherence versus control (usual care or other control)	<p><u>Primary outcomes:</u></p> <p>Some evidence from trials: Less than half of the interventions examined (41 of 91 interventions) significantly improved medication adherence, compared with control. The effective interventions represented five of ten short-term interventions; and 36 of 81 long-term interventions. While some quite simple interventions (counselling, written information, telephone calls) improved adherence for short-term treatments, almost all effective interventions for long-term treatment were complex*.</p> <p>(*Complex interventions that effectively improved adherence in the long term included combinations of the following: more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up and supportive care.)</p> <p>Some evidence from trials: Approximately one third of interventions (30 of 91) significantly improved treatment outcomes, compared with control. Effective interventions represented four of ten short-term interventions and 26 of 81 long-term interventions.</p> <p><u>Other outcomes:</u></p> <p>Insufficient evidence in relation to measurement to support or refute interventions to improve adherence on major clinical outcomes including major morbidity or mortality.</p> <p>Insufficient evidence in relation to measurement to decide between interventions to improve adherence and control for disease-specific measures or for other process measures such as knowledge and understanding, satisfaction, decision-making or other outcomes.</p> <p><u>Harms and adverse effects:</u></p> <p>Some evidence from trials: Six trials examining the effects of telling patients about adverse effects of treatment found no effects on adherence. Authors also note that interventions, even if they do improve adherence, cannot be assumed to do more good than harm in terms of clinical outcomes.</p>



KEY TO RESULTS

The table on this page presents the standardised wording that should be used to interpret the data in the results section of the EVIDENCE table on the previous two pages.

SUMMARY STATEMENT	TRANSLATION
<i>Sufficient evidence from trials</i>	<p>Evidence to support conclusions about the effect of the intervention(s) in relation to a specific outcome(s). This includes evidence of an effect in terms of:</p> <ul style="list-style-type: none"> • benefit or • harm. <p>Statistically significant results are considered to represent sufficient evidence to support conclusions, but a judgement of ‘sufficient evidence’ is also based on the number of trials/ participants included in the analysis for a particular outcome.</p> <p>A grading of ‘sufficient evidence’ is often based on meta-analysis producing a statistically significant pooled result that is based on a large number of included trials/ participants.</p> <p>This judgement may also be made based on the number of trials and/or trial participants showing a statistically significant result - for example (in a narrative synthesis) a result where 12 trials of a total of 14 for a specific outcome showed a statistically significant effect of an intervention would be considered to represent ‘sufficient evidence.’</p>
<i>Some evidence from trials</i>	<p>Less conclusive evidence to make a decision about the effects of a particular intervention(s) in relation to a specific outcome(s).</p> <p>This may be based on narrative syntheses of review results. In this case, the result is qualified according to the findings of the review - for example, ‘some evidence (5 trials of 9) reported a positive effect of’</p> <p>{This would be based on a more equivocal set of results than those obtained for ‘sufficient evidence’ above. For example, while 12/14 statistically significant trials would be classed as ‘sufficient evidence’, 5/9 statistically significant trials is more equivocal and would be classed as ‘some evidence.’}</p> <p>This may also be based on a statistically significant result obtained in a small number of trials; or a statistically significant result obtained from trials with a small number of participants.</p>
<i>Insufficient evidence from trials</i>	<p>Not enough evidence to support conclusions about the effects of the intervention(s) on the basis of the included trials. This should be interpreted as ‘no evidence of effect’, rather than ‘evidence of no effect’.</p> <p>Statistically non-significant results are considered to represent insufficient evidence.</p> <p>Where the number of trials is small, and/or the number of participants included in the trials is small, ‘insufficient evidence’ might reflect underpowering of the included trials to be able to detect an effect of the intervention.</p> <p>Where the number of trials is large, and/or the number of participants included in these trials is large, ‘insufficient evidence’ may reflect underlying ineffectiveness of the intervention to affect the outcomes being examined.</p>
<i>Insufficient evidence in relation to measurement</i>	<p>Not enough evidence to support conclusions about the effects of the intervention due to a lack of reporting on the specified outcomes.</p> <p>This can be the result of :</p> <p>(i) the review electing not to report on a particular outcome, or set of outcomes, despite being reported by the included trials; or</p> <p>(ii) the review was not able to report on the outcome, as data for the outcome was not reported by the included trials. Note: used for reporting against outcomes only.</p>
<i>N/A</i>	<p>Not applicable to the outcome category of interest. Note: used for reporting against outcomes only.</p>