

Medicines adherence—evidence for any intervention is disappointing

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ABSTRACT

Interventions to improve adherence with medicines have been studied for many years. The outcomes, both for improved adherence and clinical indicators, have not been as positive as expected or hoped for. Any improvement in adherence that may occur has not necessarily translated to improved clinical outcomes. The studies are heterogeneous, often of poor quality, with different outcomes and measures of outcome, and with ill-defined interventions, such as a lack of information on specific content of an 'educational' intervention. It appears that interventions are very resource intensive with no cost-effectiveness studies. More research is required into interventions to improve medicines adherence before more health care funding is invested in labour-intensive interventions that appear logical but are not supported by evidence from quality research.

Introduction

Adherence* with medicines therapy is important for achieving the outcomes expected from clinical trials. It is estimated that about 50% of medicines are not taken as prescribed and 20–50% of people do not take their medicines as prescribed.¹ Approximately 50% of non-compliance may be intentional, or a deliberate choice by the patient.² This can be selective non-compliance with a particular medicine. People may also vary their compliance with a particular medicine over time.³

Research into compliance with medicines is complex, with difficulty identifying suitable definitions and measurement of compliance such as prescription refills, electronic monitoring of container opening, self-reporting and changes in clinical indicators such as HbA1c. There are also different reasons for non-compliance and hence different barriers to be overcome, including unintentional non-compliance (e.g. forgetting,

excessive complex medication regimens) and intentional non-compliance due to lack of information, different priorities.⁴

Improving patient compliance with medicines is expected to have improved health outcomes and consequently interventions to improve medication compliance are promoted and funded.^{5,6} Many of these interventions, usually involving pharmacists or nurses, are labour intensive requiring in-depth consultations or education sessions.^{7–9} Unfortunately, while the interventions appear reasonable and logical, there is a tendency to ignore the evidence which indicates that only about 50% of intervention studies have shown any improvement in compliance at all.^{10,11} In the 'positive' studies, any improvement in compliance is small (average 11% improvement), raising concerns about resource intensity and cost-effectiveness.¹² There has been a very disappointing correlation between any improvement in compliance and any improvement in clinical outcome.^{1,8}

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* There is much discussion about the use of 'compliance' versus 'adherence'. In this paper the terms are used interchangeably depending on the terms used in the studies. Both refer to the degree that patients take medicines according to the directions of the prescriber.

When there is evidence of benefit for an intervention, there is a risk of adapting the evidence to suit the environment, work patterns and skills of the provider, rather than adopting the methodology in its entirety. This is particularly relevant to 'counselling' or education and information-giving interventions, when the theoretical framework for interventions is rarely discussed in the studies. There is a risk of generalisation of how and what education or counselling is provided to suit providers when the intervention is implemented in practice, rather than the adoption of the evidence-based techniques.

General compliance interventions

The 2008 meta-analysis by Haynes et al.¹⁰ found that for short-term treatment courses, four of 10 interventions (40%) in nine randomised controlled trials (RCTs) showed an effect on both adherence and at least one clinical outcome. One intervention significantly improved patient adherence, but not the clinical outcome. For long-term medicines therapy 36 of 83 interventions (43%) in 70 RCTs were associated with improvements in adherence, but only 25 interventions (30%) led to improvement in at least one treatment outcome. Of the interventions that were considered effective for long-term therapy, almost all were complex. This involved combinations of more convenient care, information, reminders, self-monitoring, reinforcement, counselling, family therapy, psychological therapy, crisis intervention, manual telephone follow-up, and supportive care. Even the most effective interventions did not lead to large improvements in adherence and treatment outcomes.

The authors concluded that several relatively simple interventions could increase adherence and improve patient outcomes for short treatment courses (e.g. telephone follow-up), but still the effects are inconsistent and less than half of studies showed improvement. Another systematic review found 20 of 37 studies (54%) had an improvement in at least one measure of compliance.¹ The most consistent improvement was that all three studies

that reduced dosing demands showed benefits (large effect size (ES)[†] of 0.9 to 1.2). For improving adherence to chronic therapy the interventions were mostly complex and not very effective.

Monitoring and feedback was successful in three of four studies (medium ES of 0.3–0.8). Three other 'behavioural' studies showed no impact for specialised packaging or cognitive behavioural therapy. Six of 12 multi-session informational studies were positive (ESs from 0.3 to 1.1). The other 50% of the studies showed no benefit.

A meta-analysis reviewed physician–patient collaboration and found that better collaboration resulted in better patient adherence. While the studies failed to examine the specific charac-

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teristics of collaboration, this was generally the inclusion of the patient's perspective and preference during consultations.¹³ Another meta-analysis correlated good physician communication with good patient adherence to treatment.¹⁴ The studies in this meta-analysis used measures and ratings of physician communication including patient questionnaire or observation and so, although the communication style was not defined, it was rated by set measures.

Compliance interventions for specific medical conditions

A systematic review of 11 studies of interventions to improve adherence to lipid-lowering medicines showed a decrease of 3% to an increase

[†] Effect size: A value of < 0.2 is a very small effect; 0.2–0.5 is a small effect; 0.5–0.8 is a medium effect and ≥ 0.8 is a large effect.

of 25% in compliance.¹⁵ Patient re-enforcement and reminding was the most promising category of interventions with four of six studies showing improved adherent behaviour (increase = 24%, 9%, 8% and 6%). Other interventions associated with increased adherence were simplification of the drug regimen (increase = 11%) and patient information and education (increase = 13%). Unfortunately, the methodological and analytical quality of some studies was low.

For improving compliance to blood pressure-lowering medicines, 58 different interventions were used in 38 studies.¹⁶ Simplifying dosing regimens increased adherence in seven of nine studies (average 11.6% improvement). Motivational strategies were partly successful in 10 of 24 studies with generally small increases in adherence. Patient education alone was largely unsuccessful.

The authors concluded that reducing the number of daily doses appears to be effective in increasing adherence to blood pressure-lowering medication, although noted the lack of evidence of this having an effect on blood pressure reduction per se. Some motivational strategies and complex interventions appeared promising but still lacked evidence from well-designed studies. This is important because for resource-intensive studies there needs to be a cost-effectiveness analysis before widespread acceptance of such interventions.

Compliance interventions for older people

Conn et al.¹⁷ reviewed 33 studies investigating interventions to improve compliance in older people. Some interventions statistically significantly improved medication knowledge (medium ES = 0.5), adherence (small ES = 0.3), and diastolic blood pressure (very small ES = 0.2). Non-significant effects were found for systolic blood pressure (small ES = 0.21), other health outcomes (very small ES = 0.04), and health services utilisation (very small ES = 0.16). The greater adherence effect sizes were for interventions employing reduced number of doses, special medication packaging, participant monitoring of medication effects, succinct written instructions, and standardised rather than individualised

interventions. Behavioural-based strategies and prompts (telephone, alarms) appeared more effective than cognitive/educational strategies.

Another systematic review located eight studies longer than four weeks and with more than 60 people that investigated compliance interventions in the elderly.¹² Only 50% of the studies had a positive impact on compliance, with the mean improvement being 11%. Three of the eight studies used dose administration aids along with written and/or verbal information and 'follow-up'. These three studies were variable in the extent of interventions used in conjunction with compliance aids such as medication reviews, special labelling, written and/or verbal information and follow-ups. These were all generally undefined. Only one of the three studies showed a significant improvement in compliance, but in this study 49% of control patients also used a dosage administration aid, suggesting that the impact of the compliance packaging was not a major factor in the results. Also the intervention group had more frequent tablet counts than the control group—a possible driver for improved compliance.

The other three studies that had a positive impact on compliance involved regimen simplification (x2) and group education plus medication card (x1).

Summary

Non-adherence is multifactorial, and interventions are likely to differ depending on the reason for non-adherence that they are aiming to address. Even the most effective interventions to improve adherence do not lead to large improvements in adherence. There appears to be even less impact on treatment outcomes. Behavioural interventions such as dosage simplification and self-monitoring for effects and adverse effects appear to be more effective than cognitive interventions such as informational strategies.^{1,17} The variability in information strategies such as single sessions versus multiple sessions, provider of the information or education and one-on-one versus group sessions has resulted in conflicting effect sizes for these interventions. It does appear that multiple sessions for information is more effective¹ than single sessions and any written information needs to be succinct.¹⁷

Evidence-based interventions to improve compliance are:

Reducing the pill burden—reduce the number of tablets and doses per day, e.g. use fixed drug combinations (ACE inhibitor plus thiazide) and once-daily dosing, and stop minimally effective medicines.

Monitoring, reinforcement and reminders (brief interventions, telephone follow-up).

Physician–patient communication and collaboration improves compliance.^{13,14}

Conflicting results for interventions to improve compliance are:

Patient education/information-giving—this requires a structured, consistent (and proven) model and is not very effective when used as a sole strategy.

Compliance packaging—this is not a panacea and needs to be used in conjunction with other strategies for a targeted population. The effect size is small.

Conclusion

Current interventions to get people to comply with their medicines are not very effective, even those that are labour- and resource-intensive. Just because it sounds like a good idea, doesn't mean that it will work, and this appears to be the situation with interventions to improve compliance with medicines therapy, compounded by the fact that even if an intervention may improve compliance, outcomes are not necessarily improved. With limited health care resources there is a need for interventions to be cost-effective. Based on current evidence it would seem that the simple interventions may be more cost-effective than the complex, resource-intensive interventions.

The area of adherence to medicines requires new concepts, especially around the differing needs of individuals (e.g. is the non-adherence intentional or unintentional?) and the nature of their information needs. The complexities of non-adherence

may need a range of 'tools' to select from depending on the person. This requires more research, but perhaps we are missing a basic starting point—that of communication skills and health literacy. This vast and poorly addressed area may have to be addressed first.

References

1. Kripalani S, Yao X, Haynes R. Interventions to enhance medication adherence in chronic medical conditions. *Arch Intern Med*. 2007;167:540–50.
2. Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med*. 1990;150(4):841–5.
3. Segal E, Ish-Shalom S. Two years adherence to anti-osteoporotic medications in postmenopausal Israeli women. *Arch Gerontol Geriatr*. 2009;49(3):360–3.
4. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487–97.
5. Lee E, Braund R, Tordoff J. Examining the first year of Medicines Use Review Services provided by pharmacies in New Zealand: 2008. *N Z Med J*. 2009;122:3566.
6. Brandt T, Harrison J, Sheridan J, Shaw J, Jensen M. The evaluation of Auckland District Health Board's medicines use review pilot: the ADMiRE report. 2009 [Cited 2011 Apr 21]. Available from: <http://www.adhb.govt.nz/PHO/documents/ADMiRE%20report%20final.pdf>
7. Eussen S, van der Elst M, Klungel OH, Rompelberg C, Garssen J, Oosterveld M, et al. A pharmaceutical care program to improve adherence to statin therapy: a randomized controlled trial. *Ann Pharmacother*. 2010;44:1905–13.
8. Pladevall M, Brotons C, Gabriel R, Arnay A, Suarez C, de la Figuera M, et al. Multicenter cluster-randomized trial of a multifactorial intervention to improve antihypertensive medication adherence and blood pressure control among patients at high cardiovascular risk (the COM99 study). *Circulation*. 2010;122:1183–91.
9. Powell L, Calvin J, Richardson D, Janssen I, Mendes D, Leon, C, Flynn K, et al. Self-management counselling in patients with heart failure: the heart failure adherence and retention randomized behavioural trial. *JAMA*. 2010;304:1331–8.
10. Haynes R, Ackloo E, Sahota N, McDonald H, Yao X. Interventions for enhancing medication adherence. *Cochrane Database of Syst Rev* 2008;Issue 2. Art. No.: CD000011
11. Schlenk E, Bernardo L, Organist L, Klem M, Engberg S. Optimizing medication adherence in older patients: a systematic review. *J Clin Outcomes Manag*. 2008;15:595–606.
12. George J, Elliot R, Stewart DC. A systematic review of interventions to improve medication taking in elderly patients prescribed multiple medicines. *Drugs Aging*. 2008;25:307–24.
13. Arbutnot A, Sharpe D. The effect of physician-patient collaboration on patient adherence in non-psychiatric medicine. *Pat Educ Couns*. 2009;77:60–7.
14. Zolnierok K, DiMatteo M. Physician communication and patient adherence to treatment: a meta-analysis. *Med Care*. 2009;47:826–34.
15. Schedlbauer A, Davies P, Fahey T. Interventions to improve adherence to lipid lowering medication. *Cochrane Database of Syst Rev* 2010;Issue 3. Art. No.: CD004371.
16. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure lowering medication in ambulatory care. *Arch Intern Med*. 2004;164:722–32.
17. Conn V, Hafidahl A, Cooper P, et al. Interventions to improve medication adherence among older adults: meta-analysis of adherence outcomes among randomised controlled trials. *Gerontologist*. 2009;49(4):447–62.