

Medication non-adherence: an overlooked target for quality improvement interventions

Bryony Dean Franklin, Gary Abel and Kaveh G Shojania

Quality improvement initiatives often focus on closing the gap between routine practice and the care recommended in guidelines—ensuring, for instance, that patients with chronic conditions receive prescriptions for medications demonstrated to improve health outcomes. However, this focus often ignores the even more basic problem - that many patients prescribed medicines for chronic conditions take them inconsistently or not at all. In one US study,[1] patients who had recently experienced a myocardial infarction took key medicines intended to prevent further cardiac events only 35% to 50% of the time, depending on the class of medication. Perhaps surprisingly, providing the medicines for free improved adherence by only a few percentage points. Other studies also report adherence rates of around 50% or less.[2-5]

Medication adherence thus constitutes one of the ‘big hairy problems’ or ‘big hairy audacious goals’ [6] of healthcare. As well as affecting patients’ long-term outcomes, non-adherence can increase healthcare costs through consumption of medicines below the threshold of adherence required for required for clinical benefit, as well as contributing to healthcare resource use such as hospital admissions.[7] Disposal of what can amount to significant quantities of unused medication also presents an under-recognized problem.

Evidence for how best to address non-adherence remains unclear, with relatively few well-designed studies.[2] We therefore welcomed the opportunity to publish an initial, positive report of an intervention to improve adherence in patients prescribed a new medicine for asthma or chronic obstructive pulmonary disease, hypertension, type 2 diabetes or an anticoagulant/antiplatelet agent.[8] The intervention comprised an initial interview with a pharmacist (in person or by telephone) within 7–14 days of prescription, and then a follow-up interview (by telephone) 14–21 days later. The interviews identified problems related to adherence but also any areas for which patients felt they needed further information or support. This initial study, published in 2016, presented the findings at ten-week follow-up. This revealed an absolute increase of 10% in the proportion of patients adhering to their new medicine, from 61% in the control arm to 71% in the intervention arm ($p=0.04$ for unadjusted analysis) with only 37 (15%) of patients having dropped out in the control arm and 16 (6%) in the intervention arm. In an adjusted analysis taking into account clustering and potential confounders, the odds ratio was 1.67 (95% confidence interval 1.06 to 2.62; $p=0.027$) in favour of the intervention. These results therefore suggested the intervention to have a relatively small but statistically significant benefit, with a general trend towards reduced costs for the health system [8] and 97% probability of cost-effectiveness based on more detailed economic modelling.[9] As a result, the English National Health Service commissioned this New Medicines Service for routine use.[10]

Results of a longer-term follow-up of the same patients at 26 weeks are now reported by Elliott and colleagues in this issue of *BMJ Quality & Safety*. Unfortunately, by 26 weeks, the proportion of adherent patients had dropped in both the control and intervention arms (to 57% and 66% respectively), with loss of statistical significance for this difference ($p=0.113$).[11] So what do these findings tell us about the effectiveness of the intervention, how adherence may change over time, and the implications for practice, policy and research?

First, in terms of the effectiveness of the intervention, the follow-up data leave us in a difficult position. By 26 weeks, 41 patients (16%) had dropped out in the control arm and 25 (10%) in the intervention arm,[11] leaving a study that was powered based on 10-week follow-up with less power to detect a difference by 26 weeks. It is therefore not possible to know whether the lack of statistical significance by 26 weeks is simply due to the smaller sample size and thus lower power due to further study drop-outs, the effect of the intervention itself being attenuated, or a combination of the two.

Second, while the follow-up study shows that adherence generally reduces over time, as might be expected, it also suggests that it is dynamic. Between ten and 26 weeks, not only did some adherent patients become non-adherent (15% of all those who were adherent at ten weeks), but non-adherent patients also became adherent (25% of those who were non-adherent at ten weeks). These changes occurred in similar proportions in the control and intervention arms. While a reduction in adherence to long term medication over time is well-documented, this more dynamic nature of adherence behaviour highlighted by Elliott and colleagues [11] suggests a far more complex picture, together with questions about what causes a non-adherent patient to become adherent as well as vice versa. The implications of this dynamic nature of adherence for research in this area are also unclear but are likely to affect the choice of adherence measure. For example some studies, including this work by Elliott and colleagues, consider a single time point such as adherence over the last seven days, whereas others ask whether patients “ever” forgot doses of their medicines.[12]

Third, we clearly need longer term studies to evaluate the impact of interventions aimed at improving medication adherence. Even a 26-week follow-up, as in the present paper,[11] seems on the short side when assessing adherence to medications that patients will take for many years. A Cochrane review suggests 26 weeks as the minimum follow-up for studies of adherence to medications used for long term conditions such as asthma, chronic obstructive pulmonary disease, hypertension and type 2 diabetes, for which patients are likely to need to take medications for many years and not just six months.[2] Longer studies are therefore needed, which will also require considerable effort to minimise participant attrition over these greater time frames.

While studies lasting several years present practical challenges, perhaps the bigger challenge lies with developing effective interventions. Many commonly used solutions, from

multi-compartment compliance aids with sections for each day's medications to more sophisticated electronic containers and smartphone reminder apps, assume that that non-adherence simply reflects forgetfulness. For some patients, forgetting may indeed be a problem. But, for others, non-adherence is instead associated with beliefs about their need for medication, such as patients who believe that they only need to take medication for high blood pressure on days when they feel anxious or unwell.

Non-adherence can also be associated with ambivalence about the importance or desirability of taking long term medicines, concerns over side effects,[13] or arise due to medication-related harm, all of which require exploration and shared-decision making. Motivational interviewing, health coaching and other counselling techniques, often delivered by pharmacists, can help to address some of these more complex and often legitimate reasons patients choose not to their medicines.[14] For instance, a recent trial [15] evaluated medication management tools delivered through a commercial electronic health record (EHR) with and without an accompanying nurse-led intervention educating patients about their medications aiming to support improved adherence. The intervention arm of the study involving EHR tools improved medication reconciliation but led to worse blood pressure control compared with the control group, whereas the combination of EHR tools and nurse-led education improved control. In discussing this unexpected result, the authors speculated that patients in the group receiving EHR tools only might have seen the adverse drug effects outlined on medication information sheets and stopped or reduced the medications involved. Patients in the group receiving education and counselling from nurses would have had the opportunity to ask about the seriousness or likelihood of these adverse effects and presumably felt more comfortable adhering to the prescribed antihypertensives.

The original study [8] of the New Medicines Service was funded only for a ten-week follow-up.[11] It is thus commendable that the authors decided to also collect data at the 26-week point. While the intervention's benefits may not have persisted over this longer follow-up period, the results highlight the importance of further attention to this problem. So much effort by those engaged in quality improvement research and practice has focused on addressing shortfalls in the provision of evidence-based care, such as prescribing proven medicines for long term conditions. These efforts will achieve limited impact if we continue to ignore the degree to which patients take these medications as intended, and if we fail to address the often legitimate reasons for their not doing so. And, just as called for in other areas of quality improvement, efforts to increase adherence will likely benefit from greater involvement by patients in developing the interventions – co-producing them with the patient groups intended to benefit.[16-18]

References

1. Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M, et al. Full coverage for preventive medications after myocardial infarction. *New England Journal of Medicine*. 2011;365(22):2088-97.

2. Nieuwlaat R, Wilczynski N, Navarro T et al. Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews* 2014, Issue 11. Art. No.: CD000011. DOI: 10.1002/14651858.CD000011.pub4.
3. Cheen MHH, Tan YZ, Oh LF, Wee HL, Thumboo J. Prevalence of and factors associated with primary medication non-adherence in chronic disease: A systematic review and meta-analysis. *Int J Clin Pract.* 2019;73(6):e13350.
4. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *American Journal of Medicine.* 2012;125(9):882-7.e1.
5. Petry NM, Rash CJ, Byrne S, Ashraf S, White WB. Financial reinforcers for improving medication adherence: findings from a meta-analysis. *American Journal of Medicine.* 2012;125(9):888-96.
6. Nanji KC, Ferris TG, Torchiana DF, et al. Overarching goals: a strategy for improving healthcare quality and safety? *BMJ Qual Saf* 2013;22:187–93. doi:10.1136/bmjqs-2012-001082
7. Mongkhon P, Ashcroft DM, Scholfield CN, Kongkaew C. Hospital admissions associated with medication non-adherence: a systematic review of prospective observational studies. *BMJ Qual Saf.* 2018 Nov;27(11):902-914.
8. Elliott RA, Boyd MJ, Salema NE et al. Supporting adherence for people starting a new medication for a long-term condition through community pharmacies: a pragmatic randomised controlled trial of the New Medicine Service. *BMJ Qual Saf* 2016;25:747-58. doi: 10.1136/bmjqs-2015-004400
9. Elliott RA, Tanajewski L, Gkountouras G et al. Cost Effectiveness of Support for People Starting a New Medication for a Long-Term Condition Through Community Pharmacies: An Economic Evaluation of the New Medicine Service (NMS) Compared with Normal Practice. *Pharmacoeconomics.* 2017;35:1237-1255. doi: 10.1007/s40273-017-0554-9.
10. Pharmaceutical Services Negotiating Committee. <https://psnc.org.uk/services-commissioning/advanced-services/nms/> [accessed 22 August 2019]
11. Elliott RA et al The 'New Medicine Service': Supporting adherence in people starting a new medication for a long-term condition: 26-week follow up of a pragmatic randomised controlled trial *bmjqs-2018-009177*
12. Nelson R, Reid CM, Ryan P, et al. Self-reported adherence with medication and cardiovascular disease outcomes in the Second Australian National Blood Pressure Study (ANBP2). *Medical Journal of Australia* 2006;185:487-89
13. Horne R , Chapman SC , Parham R , et al . Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. *PLoS One* 2013;8:e80633.doi:10.1371/journal.pone.0080633

14. Palacio A, Garay D, Langer B, Taylor J, Wood BA, Tamariz L. Motivational Interviewing Improves Medication Adherence: a Systematic Review and Meta-analysis. *J Gen Intern Med.* 2016;31(8):929–940. doi:10.1007/s11606-016-3685-3
15. Persell SD, Karmali KN, Lazar D, Friesema EM, Lee JY, Rademaker A, Kaiser D, Eder M, French DD, Brown T, Wolf MS. Effect of Electronic Health Record-Based Medication Support and Nurse-Led Medication Therapy Management on Hypertension and Medication Self-management: A Randomized Clinical Trial. *JAMA Intern Med.* 2018 Aug 1;178(8):1069-1077.1:
16. Elwyn G, Nelson E, Hager A, Price A. Coproduction: when users define quality. *BMJ Qual Saf.* 2019 Sep 5. pii: bmjqs-2019-009830. doi: 10.1136/bmjqs-2019-009830. [Epub ahead of print] Review. PubMed PMID: 31488570.
17. Batalden M, Batalden P, Margolis P, Seid M, Armstrong G, Opiari-Arrigan L, Hartung H. Coproduction of healthcare service. *BMJ Qual Saf.* 2016 Jul;25(7):509-17. doi: 10.1136/bmjqs-2015-004315. Epub 2015 Sep 16. PubMed PMID: 26376674; PubMed Central PMCID: PMC4941163.
18. Sabadosa KA, Batalden PB. The interdependent roles of patients, families and professionals in cystic fibrosis: a system for the coproduction of healthcare and its improvement. *BMJ Qual Saf.* 2014 Apr;23 Suppl 1:i90-4. doi: 10.1136/bmjqs-2013-002782. Review. PubMed PMID: 24608555.