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COMMENTARY

How do we better translate adherence research into improvements in patient care?

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Introduction

Adherence to medicines in patients with chronic disease remains poor despite better recognition of the challenges of non-adherence and a concerted effort to address these challenges. Adherence research has progressed in recent years, both conceptually with the recent development of a taxonomy of adherence [1] and improved, if still flawed, evidence for the efficacy of some interventions [2]. However, a key challenge remains unmet: the translation of adherence research into clear advice for health professionals of effective strategies to better support the medication adherence of their patients. We outline some of the difficulties of improving the translation of adherence research into improvements in the care of individuals with chronic disease, and consider possible solutions. We have two suggestions for improving translation of adherence research: (1) better incorporation of what we know about adherence into interventions to improve adherence and (2) more sophisticated measurements of adherence. Implementing these suggestions has implications for research and practice.

Interventions to improve adherence

There should be a greater focus on assessing and implementing *targeted* and *tailored* adherence interventions. By "targeted" we mean that an adherence intervention is offered to people that have been identified as non-adherent. By "tailored" we mean that a specific adherence intervention is selected based on the primary cause that has been identified for the individual's non-adherence. To deliver targeted and tailored adherence interventions we need instruments to measure adherence that are easy to use, widely available, and accurately identify non-adherence and its causes. Many of the points we make have been made elsewhere in the literature: Vervloet et al. [3], in their systematic review of the effectiveness of electronic reminders, lament the lack of studies that targeted non-adherent patients; Nunes et al. [4] articulate the importance of health professionals identifying and then tailoring adherence support to individual patients and; Garfield et al. [5] highlight the importance of practice-ready tools for measuring adherence. We aim to highlight the importance of these views and explore the arguments that support them.

Evidence for targeted and tailored adherence interventions

A commonly cited Cochrane Review of interventions to improve medication adherence makes for bleak reading, especially with regard to adherence to long-term treatments. The most promising interventions assessed in patients with chronic disease were complex, resource intensive, and not particularly effective in terms of adherence or clinical outcomes. Haynes et al. [6 p. 17] conclude:

> [Trials of adherence interventions] provide little evidence that medication adherence can be improved consistently, within the resources usually available in clinical settings, and that this will predictably lead to improvements in clinical outcomes.

This assessment needs to be put in the context of the studies included in the review. Specifically, studies of

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adherence interventions focussing on long-term treatments were only included if clinical outcomes were measured, the study had at least 80 % follow-up, and early improvements in adherence and clinical outcomes were maintained for 6 months from the time of participant enrolment. The majority of studies included in the review employed a multimodal intervention on a participant population with a shared disease with no attempt to target patients with poor adherence to medicines. Few studies in the review were adequately powered to detect important clinical outcomes (benefits or harms). Haynes et al. answers an important question regarding the availability of well-conducted randomized-trial evidence for the improvement of clinical outcomes following adherence interventions (the answer: limited). This provides insight into the current status of adherence research, but it does not provide the best indication of whether (and which) adherence interventions improve adherence.

A more recent meta-analysis focussed on randomized trials of adherence interventions that assessed electronically compiled drug dosing histories, such as those provided by Medication Event Monitoring Systems (MEMS) [2]. This meta-analysis included smaller trials and those that did not assess clinical outcomes. Included randomized trials assessed a wide range of interventions with over half of the trials testing a combination of strategies to improve adherence. Overall, participants randomized to an intervention group were more likely to adhere than those randomized to control. Interestingly, the two categories of intervention that contributed most to the effectiveness of adherence interventions were interventions based on participant feedback of their electronically compiled drug dosing history and cognitive-educational interventions focussed on educating and motivating participants regarding their condition and its treatment. The selection criteria for the meta-analysis may have biased findings in favour of interventions that relied on electronically compiled drug dosing histories. Nonetheless, it is of note that the principle rationale for the effectiveness of providing feedback on electronically compiled drug dosing histories is that it provides detailed information that can be used by health professionals to identify and address the types and causes of non-adherence specific to the patient [2]. Well-conducted cognitive-educational interventions also work to identify and address patient-specific barriers to adherence [7–12]. On the basis of this meta-analysis, the two interventions that appear to contribute most to the effectiveness of adherence interventions permit some degree of tailoring the intervention to the patient.

A systematic review of adherence interventions in patients with cardiovascular disease provides a similar message [13]. This review focussed on randomized trials of adherence interventions in patients with cardiovascular disease or diabetes. They stratified studies into three categories, those that were targeted to non-adherent patients (they used the term "focussed"), those that were untargeted ("broad") and those that utilised tailored interventions based on feedback from an adherence measure ("dynamic"). Few studies were targeted to non-adherers (4 of 59). A meta-analysis of effect sizes was not possible due to study heterogeneity. For the same reason the authors acknowledge that caution is needed in drawing inferences based on the number of "successful" studies in each group. Nevertheless, the findings of this systematic review are broadly consistent with the meta-analysis of Demonceau et al. [2]: those studies that featured tailored interventions based on measurement and feedback of adherence were more likely to be successful than studies targeted to non-adherers, which in turn were more likely to be successful than studies that enrolled an untargeted population. Together these three systematic reviews provide *prima facie* evidence in favour of tailored interventions. Whether or not adherence interventions need to be targeted to non-adherent patients most likely depends on the nature of the intervention. Viswanathan et al. [14] identifies a number of policy interventions in the US setting that reduce medicine-related expenses and improved adherence. Such policy interventions are by their nature untargeted, other adherence interventions are less likely to be effective unless they are targeted. Vervoloet 2012 (like Haynes et al. and Cutrona et al.) identifies many studies that employ an intervention focussed on rectifying non-adherence due to forgetfulness that were ineffective when implemented on a non-targeted population [3].

A shared understanding of adherence

The benefits of targeting and tailoring adherence interventions are to be expected given what we know about adherence. Non-adherence is not one thing. There are multiple ways to be non-adherent to a medicine. With most individuals with chronic disease taking multiple medicines, there is a distinct possibility that many individuals exhibit different types of non-adherence to different medicines. More consistency in identifying types of adherence is possible with the recent development of a adherence taxonomy; we discuss this taxonomy below [1]. In addition to the different types of non-adherence, there are many *reasons* for non-adherence. There is considerable research linking various factors to adherence at a population-level. Factors consistently linked to non-adherence include: healthcare team/healthcare system, condition-related, patient-related, therapy-related and social/economic factors [15]. A focus on the individual decisions that people make is likely to better support adherence in individual patients. Individuals with chronic disease make decisions about their care on a daily basis.

These decisions are informed by beliefs relating to the condition and treatment as well as additional factors including cost, burden of care, and the many other commitments and factors that influence an individual's decision to take their medicine or their ability to enact their preference to do so. Some beliefs or barriers may be stable for an individual over time, but many others will fluctuate as the individual's condition and environment changes.

This characterisation of adherence has implications for the role of health professionals in supporting adherence and for designing interventions to improve adherence. First, health professionals have an important role to play in helping individuals navigate their changing environment and inform their decisions about treatments over time. To play this role health professionals need to develop strong relationships with their patients based on a shared understanding of the condition, its treatment and the circumstances and beliefs of the individual. Second, interventions that provide health professionals with better tools for identifying and responding to individual-specific types of non-adherence and its causes will likely improve adherence. To some degree this is borne out in the evidence collected in the systematic reviews.

A pre-condition for accurately measuring non-adherence is the existence of clear definitions of the types of non-adherence. Adherence research has been limited by the absence of a consensus on key terms. There has been an inclination in the past to label *patients* as adherent or non-adherent based on a simple dichotomisation of an adherence measure. Beyond the category mistake (adherence refers to medication-taking *behaviour* not patients), this approach makes little sense in patients with chronic disease whose condition will fluctuate along with other factors that influence adherence and whose medication-taking behaviour can be expected to vary over time and across their medications. While there remains significant variation in the use of terms in the adherence literature there is reason for optimism with the recent development of a taxonomy for adherence. Vrijens et al. [1] systematically searched the literature and held a number of European meetings to develop a consensus on adherence terms. The resulting taxonomy defines adherence in terms of medication-taking behaviour (alone) and identifies three elements of adherence: *initiation, implementation* and *discontinuation*. Thus, an individual may manifest non-adherent medication-taking behaviour by failing to initiate treatment following a prescription, initiating late, poorly implementing the medication regimen or by discontinuing treatment early.

Vrijens and colleagues' taxonomy represents a significant opportunity for improving the consistency of identifying and describing important variations in medication-taking behaviour. There are alternative conceptualisations of adherence and associated terminology, including Gearing et al. [16] and a considerable literature on "primary non-adherence" (patients who fail to initiate treatment) [17–20]. Benefits of the Vrijens et al. taxonomy include the consultative process that was employed and the relative simplicity of the framework. A disadvantage, we believe, is the decision to identify adherence solely with medication-taking behaviour. The World Health Organization provides a widely-recognised, if not unanimously adopted, definition of "adherence" as: "The extent to which a person's behaviour—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [15]. The two components of this definition are the shared decision between the individual and their health care provider and the individual's behaviour in relation to this shared decision. Despite widespread support for use of the term "adherence" in preference to "compliance" to recognise the importance of shared decision-making in relation to treatment, there has been very little systematic research into this component of adherence. The difficulty of observing, documenting and measuring shared decision-making is a major barrier for such research and seems to have played a role in the decision of Vrijens et al. [1] to exclude this aspect from their definition. However, defining adherence without reference to the shared decision between the individual and their health professional risks obscuring the importance of this aspect of adherence. In our view, explicitly retaining the shared decision as part of the definition of adherence more clearly captures the work that needs to be done in understanding what leads individuals to take (or not take) their treatment as discussed with their health professional. Explicit recognition of adherence to a shared decision between the individual and their health professional, in addition to more clearly identifying initiation, implementation and discontinuation as elements of *medication-taking behaviour* would strengthen the conceptualisation of adherence provided in Vrijens et al.

Practice-ready measures of adherence

Translating adherence research into benefits for patients with chronic disease requires accurate measurement of initiation, implementation and discontinuation and methods to identify individual-specific reasons for non-adherence. Ideally such tools need to capture medication-taking behaviour with respect to multiple treatments, and be available to, and practical for, health professionals providing routine care. As Garfield et al. [5] note, no single measure performs well in each of these areas.

Electronically compiled drug dosing histories, such as those provided by MEMS, provide the best way to identify and measure initiation, implementation and discontinuation. Indeed, electronically compiled drug dosing histories

are purpose-built for this task. This makes electronically compiled dosing histories the "gold standard" for measuring adherence for research purposes. The main limitation on the use of MEMS and MEMS-like systems in routine care is accessibility and coverage. The cost of these systems limits the use of MEMS-like systems outside of the research environment. Even within the research environment, MEMS-like systems are typically only used for one of an individual's medications; covering multiple medicines for individuals with chronic disease is rarely feasible. Demonceau et al. [2] suggest that feedback from MEMS-like systems facilitates conversations about reasons for non-adherence. It is an open question whether the addition of self-report scales that attempt to identify reasons for non-adherence would add to the effectiveness of interventions based on feedback from electronically compiled drug dosing histories.

There are additional sources of data that provide information on an individual's medication-taking behaviour, but these sources have their own limitations. Dispensing data can provide coverage of individuals taking multiple medications, but the utility of this source of data depends significantly on the details collected and accessibility. Data on dispensing is collected for a range of purposes. In Australia, dispensing data is recorded within the dispensing pharmacy, but this data is neither complete (individuals often go to a number of pharmacies) nor readily accessible outside of the pharmacy. Dispensing data is also collected by the government for the purpose of subsidising medicine costs, but this data is primarily collected for the purposes of payment and does not capture medicines that are not subsidised. Even when patient-level dispensing data is available it is limited in the ability it provides to identify initiation, implementation and discontinuation unless additional data on prescribing is also available. Patient-controlled electronic health records are currently being developed for use in Australia and provide a tantalising opportunity for collecting patient-level information on an individual's contact with the health system and medication supply, however there are considerable barriers to overcome before this system could provide a reliable source of information on medication-taking behaviour [21].

Self-report adherence scales provide another source of information that can have advantages for use in the clinic. Specifically, there are a number of self-report scales that are quick to administer and have been well correlated with objective measures of adherence such as MEMS [22]. Limitations include the lack of detail self-report scales provide regarding medication-taking behaviour. Even when they are well correlated with overall medication-taking rates as measured by MEMS, they provide limited information on implementation and very little on initiation and discontinuation [22]. Further problems include recall bias and the possibility of respondents providing answers that are considered socially acceptable. Not all self-report adherence scales focus on medication-taking behaviour. Some scales elicit information on individual-specific *reasons* for non-adherence, such as beliefs about medicines and/or the barriers the individual experiences in adhering to medicines. Studies using the Beliefs about Medicines Questionnaire (BMQ), for example, consistently identify a link between an individual's beliefs regarding their medicine and their adherence [23–26]. Scales such as the BMQ may be used in addition to other measures to provide a more comprehensive picture of the factors that influence an individual's medication-taking behaviour.

To improve adherence in patients with chronic disease health professionals require practice-ready tools for measuring types of non-adherence and identifying reasons for non-adherence. Two avenues of research may improve management of adherence in patients with chronic disease. Both rely on the sophisticated use of adherence measures. First, the use of self-report adherence scales focussed on identifying reasons for non-adherence as a basis for delivering a *tailored* intervention in patients with chronic disease. There is little research to date assessing the effectiveness of health professionals using information elicited from self-report adherence scales to inform individualised interventions to improve adherence. Given the apparent success of tailored interventions based on electronically compiled drug dosing histories, it is worth assessing similar interventions based on scales used to elicit reasons for non-adherence. Second, combining multiple sources of data to provide a snapshot of an individual's adherence and using this information to inform tailored interventions. There are multiple aspects to adherence and no single measure available to practitioners provides a reliable and comprehensive assessment of an individual's adherence. Such a snapshot would incorporate medication-taking behaviour across a number of key medicines, perhaps using dispensing data in addition to a self-report scale, with insight into individual-specific reasons for non-adherence focussed on eliciting beliefs about medicines and barriers to adherence. Clearly, the development and assessment of such a tool would be a significant project.

Conclusion

Non-adherence is complex. Not in the sense that it is hard to understand, rather that it comes in several varieties and has many causes. Attempts to address non-adherence that fail to identify individual-specific behaviours and causes are less likely to succeed. The progress that has been made in adherence research over the last couple of decades

provides an opportunity to consider how best to translate these advances into improvements in patient care. We think there are good a priori and evidence-based reasons for focussing on interventions that are tailored to the individual's behaviour, barriers and beliefs. Such interventions rely on the further development and assessment of practice-ready tools that measure and identify medication taking behaviour and the factors that influence an individual's decision or ability to take their medicines.

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