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Review article

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Improving medication adherence in cardiovascular disease

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Abstract

Non-adherence to medication is a global health problem with far-reaching individual-level and population-level consequences but remains unappreciated and under-addressed in the clinical setting. With increasing comorbidity and polypharmacy as well as an ageing population, cardiovascular disease and medication non-adherence are likely to become increasingly prevalent. Multiple methods for detecting non-adherence exist but are imperfect, and, despite emerging technology, a gold standard remains elusive. Non-adherence to medication is dynamic and often has multiple causes, particularly in the context of cardiovascular disease, which tends to require lifelong medication to control symptoms and risk factors in order to prevent disease progression. In this Review, we identify the causes of medication non-adherence and summarize interventions that have been proven in randomized clinical trials to be effective in improving adherence. Practical solutions and areas for future research are also proposed.

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Key points

- Medication non-adherence remains a global health problem that is not fully appreciated and is under-addressed in the clinic.
- The label of being 'non-adherent to medications' is often considered in a binary (and pejorative) manner; however, medication-taking behaviour is a complicated process with multiple phases and potential barriers.
- Several methods for detecting non-adherence exist, with many providing complementary rather than gold-standard information.
- Clinicians need to understand the importance of simplifying medication regimens and encouraging the use of blister packs, whereas health systems need to explore multifaceted, multidisciplinary interventions for complex non-adherence.
- Multiple interventions for improving medication adherence have proven efficacy, but a one-size-fits-all solution is unlikely to be successful; both precision and population approaches are required and need further evaluation.

Introduction

A substantial proportion of cardiovascular disease (CVD) is preventable by controlling risk factors with lifestyle changes and the use of medications[1]. However, despite an increasing armamentarium of well-tolerated and efficacious drugs for CVD, up to 30% of prescriptions are never filled and up to 50% of medications are discontinued within 12 months[2]. Non-adherence to medications is a global health problem and represents a failure to translate decades of immense financial and human capital invested in the development of proven therapies into improving clinical outcomes. Medication adherence is particularly relevant to patients with CVD given that treatment for CVD is generally lifelong and adherence tends to decrease over time. Multiple lines of evidence link non-adherence with adverse cardiovascular outcomes, worsening health status and increased mortality[3–8]. Accordingly, non-adherence is also responsible for a large burden of preventable health-care costs due to avoidable CVD-related emergency department visits and inpatient hospital days[9]. Links between non-adherence and cardiovascular outcomes persist despite extensive adjustment for demographic, socioeconomic and clinical characteristics, suggesting that the main deleterious effects of non-adherence relate to the loss of benefit from cardiovascular protective medications rather than just the absence of a 'healthy adherer' effect[3,6,10,11].

In this Review, we consider how non-adherence to medication can be detected and measured and the causes of such non-adherence among patients. We evaluate the variety of interventions that have been shown to improve adherence in randomized clinical trials (RCTs) of patients with CVD and consider how these strategies might be applied across populations. Finally, we discuss knowledge gaps and priorities for future research in this field.

Defining medication adherence

Adherence is defined by the WHO 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'[12]. In clinical trials, adherence is often defined as when at least 80% of a medication at the prescribed dose and regimen is taken. However, defining adherence in this manner is an oversimplification and an artificial dichotomy.

Medication adherence can be considered in three key phases[13]. Phase 1 starts with initiation, when the patient takes the first dose of a prescribed medication. Phase 2 represents the implementation of a dosing regimen and is defined as the extent to which the actual dosing corresponds to the prescription (specifically, the correct doses at the correct times). Phase 3 is discontinuation, which marks the end of medication therapy, either consistent with clinician recommendations or when a patient independently discontinues taking a medication. With the increasing availability of pharmacy data combined with electronic medical records, there is increasing focus on what has been referred to as 'primary non-adherence', which occurs when a clinician prescribes a new medication but the order (or an appropriate alternative) is not dispensed within an acceptable period of time[14].

Detecting non-adherence in patients

Adherence is a complex behaviour that is continuous and dynamic[15]. Evidence exists that even oversupply of medications (that is, >120% prescribed days) is associated with non-adherence[16]. Accordingly, multiple ways to measure and detect non-adherence have been developed, which can be categorized as subjective or objective and direct or indirect (Table 1).

With the exception of direct observation of the patient, no gold standard for the measurement of adherence exists and each metric has strengths and weaknesses[17]. Of note, clinician belief as to whether a patient is adherent has been shown to be no more accurate than a coin flip[18]. At least 40 instruments for subjective measurement of medication-taking behaviour are available, with several validated for use in CVD, and some that can also identify underlying barriers to optimal adherence behaviour[19,20]. In addition, several objective measures have been developed, which vary in their acceptability, cost, and ease of implementation and might overestimate adherence[21,22].

Pharmacy dispensing records can be used to assess non-adherence in a quantitative manner; however, these tend to overestimate adherence (that is, they cannot confirm if medication is taken) and require integration of dispensing data with electronic medical records. Pill counting is objective and often used in clinical trials but requires the patient to save and bring their empty packets to each clinic visit, does not inform about the timing of medication-taking behaviour and is susceptible to 'pill dumping' (whereby patients intentionally dispose of their tablets before an appointment in order to falsify or exaggerate adherence). Monitoring devices, such as electronic pill bottles and medication event monitoring systems (MEMS), record every time a pill container is opened (or more importantly, not opened), thereby providing granular information about medication-taking behaviour. However, electronic monitoring comes with several limitations. Assessment of adherence is indirect, as only package opening is detected rather than medication ingestion, and this technology requires an upfront investment for the hardware, although the individual cost of the reusable container caps is modest (<US$ 100).

Chemical adherence testing for drug metabolites can be performed on urine and blood samples and is recommended for the evaluation of patients with resistant hypertension to definitively exclude non-adherence[23,24]. Although sensitive, chemical testing is prone to white-coat or Hawthorne effects, whereby measured adherence improves in the days prior to planned sampling. Therefore, this

Table 1 | Methods for assessing adherence or non-adherence to medication

Measure	Description or example	Direct or indirect	Subjective or objective	Advantages	Disadvantages	Ready for the clinic?
Unstructured inquiry	'How often have you missed your tablets in the past 7 days?'	Indirect	Subjective	Quick	Non-standardized; unvalidated; likely to overestimate adherence; subject to white-coat effect	Yes
Multi-domain questionnaire	Patient reporting their own adherence, usually through the use of a validated questionnaire	Indirect	Subjective	Validated; semi-quantitative; can assess trends; might be able to identify causes of non-adherence	Might overestimate adherence; need to purchase (or obtain permission) for use	Could be integrated into clinical workflow, likely to be easier with mHealth strategies
Pharmacy dispensing records	Assess how often patients collect their medication: adherence inferred	Indirect	Objective	Easy to obtain; can be linked with prescribing data to determine primary non-adherence; easy to assess trends over time	Needs seamless integration with clinical workflow or EMR; does not work for over-the-counter medications (such as aspirin); inaccurate if not collecting from all sources; fill data might not correspond to pill consumption and thus might overestimate adherence	Yes
Digital pill sensing	Pills that can record use, through a localized sensor, after ingestion	Direct	Objective	Granular, high-fidelity (real-time) understanding of timing and frequency of ingestion	Requires adherence to patch placement; needs to interact with smartphone; expensive; might not be sustainable long term; only measures 'one' pill, even if patients are taking multiple classes	Possible
Electronic monitoring devices	Multiple iterations from electronic dosettes to bottles, which detect opening and, thus, inferred adherence; can be linked with reminder systems	Indirect	Objective	Granular, high-fidelity (real-time) understanding of timing and frequency of opening of pill bottle or packaging	Multiple monitors required for multiple pills; not useful for patches, injectables or medications with special packaging requirements; bottle opening might not correspond to pill consumption; can be difficult to operate and prone to failure	Possible
Pill counting	Counting the number of pills remaining after a specific period	Indirect	Objective	Can detect medication-level adherence	Requires cooperation from patient (keeping old pill packets); time consuming; not practical if intervals between appointments; does not capture timing of dose administration, hence potential for 'pill dumping'	Yes
Chemical adherence testing	Detection of metabolites from urine or serum sample	Direct	Objective	Sensitive; included in guidelines for exclusion of non-adherence as cause of resistant hypertension	Hawthorne (or white-coat) effect if not performed randomly; more useful for screening rather than long-term evaluation; might not be able to test for all drugs taken; able to detect non-adherence but not partial adherence; only assesses adherence at a single timepoint; not actionable immediately	Increasingly available in pathology laboratories but still likely to be prohibitively expensive for long-term adherence monitoring

EMR, electronic medical records; mHealth, mobile health.

approach might be more useful for screening than for long-term monitoring of adherence[25,26]. However, the value of chemical testing (and to some degree, MEMS) is less about detecting a continuous value of adherence but rather about detecting the binary presence of 'non-adherence' (that is, the absence of MEMS opening or the absence of metabolites provides certainty that the drug was not taken).

An emerging technology to detect non-adherence is the use of digital pills with ingestible sensors, which are minerals that are activated by gastric fluid and detected by a patch placed on the skin, allowing direct, real-time, high-fidelity monitoring of medication-taking behaviour[27]. Passive attainment of granular data on adherence is potentially appealing for both patients (continuous feedback loop) and physicians (detailed and actionable data). However, such a technology could compromise patient autonomy and privacy and contribute to an erosion of trust between physician and patient by implying the fallibility of self-reporting[28]. Given their potential downside, robust data are needed to demonstrate the incremental benefit of digital pills, particularly given that there are likely to be financial and regulatory implications of this technology[29].

Causes of non-adherence

Non-adherence can occur in any of the three phases of medication taking. Recognizing the multidimensional nature of non-adherence, the WHO have grouped the causes of non-adherence under the following five categories: condition-related factors, therapy-related factors, patient-related factors, socioeconomic factors, and health-care team and system factors (Box 1).

Common barriers to optimal medication-taking include costs, lack of belief in the role and effect of medications, perceived or demonstrable adverse effects, forgetfulness, complex and changing regimens, lack of family or social support, depression, lack of knowledge about disease process, and inconvenient access to medications or care.

Box 1

Causes of medication non-adherence

Health-care team and system factors
- Patient–provider relationship
- Lack of continuity, leading to fragmentation
- Inadequate follow-up
- Overburdened systems
- Short consultation time
- Misaligned incentives
- Knowledge gap about adherence

Treatment-related factors
- Patient expectations and goals
- Complex regimens
- Frequent titration
- Adverse effects (actual or perceived)
- Lack of feedback
- Stigma (such as insulin injection)
- Interference with lifestyle (such as frusemide causing urination)

Condition-related factors
- Lack of symptoms
- Lifelong condition
- Uncertain 'modifiability'
- Long asymptomatic phases (delayed gratification)

Patient-related factors
- Age
- Cognitive impairment
- Hearing impairment
- Visual impairment
- Impaired dexterity or arthritis
- Patient expectations, goals and belief in the therapy
- Psychosocial (stress, anxiety, anger, fear)
- Language barriers
- Forgetfulness
- Stigma or social embarrassment

Socioeconomic factors
- Race or ethnicity
- Health literacy
- Insurance
- Employment
- Language barrier
- Spouse and social network
- Access to pharmacy
- Medication cost
- Education level

Specific CVD-related barriers to optimal medication adherence include the absence of symptoms to motivate adherence (such as in hypertension and dyslipidaemia), lifelong treatment duration, lack of positive reinforcement or delay in gratification from therapeutic control (for example, patients do not feel better with lower LDL-cholesterol levels), and the additive burden of concomitant lifestyle change (such as smoking cessation and weight loss).

Improving adherence to CVD medications

Our intention in this narrative Review is to summarize the interventions used in clinical trials of patients with CVD that have proven to be effective in improving medication adherence. A systematic review of all adherence intervention studies is outside the scope of this work. The PubMed database was searched for RCTs involving ≥50 participants, published between 2002 and 2023, using the medical subject heading terms 'medication adherence' and 'cardiovascular disease'. An attempt was made to group studies by dominant intervention mode and to include exemplary studies that were either seminal or most recent (rather than all), with preference given to those that included a novel intervention or were of high methodological quality. Studies that clearly had three or more intervention components were considered 'multifaceted'.

Simplifying regimens and polypills

Simplification of a medication regimen is a low-intensity intervention and improves adherence. Simplification can include discontinuing unnecessary (or less necessary) medications, reducing overall pill burden, decreasing the frequency of medication administration and the use of single-pill combination therapies. In a meta-analysis of prospective CVD studies, patients prescribed once-daily dosing regimens had at least 30% higher adherence compared with twice-daily or thrice-daily regimens[30]. Similarly, in the modest-sized (n = 305), open-label, controlled ALL-IN-ONE trial[31], patients with hypertension who were randomly assigned to single-pill combination therapy had higher adherence (and blood pressure control) at the 3-month follow-up compared with a multiple-pill regimen. This finding is supported by several other studies of varying designs[32].

Leveraging this reductionist approach, there has been substantial interest in the use of a polypill[33] — a single pill containing two or more classes of medications used to treat multiple diseases such as hypertension and dyslipidaemia. Polypills have several advantages — not only do they reduce pill burden but they also result in the administration of key classes of medications that might otherwise have been under-prescribed in resource-limited settings where follow-up and titration are problematic[34]. In a meta-analysis of five trials involving >10,000 patients investigating the association between polypill use and cardiovascular outcomes[35], adherence was significantly increased among polypill recipients compared with usual care (relative risk (RR) 1.34, 95% CI 1.11–1.55)[36–40]. These findings were consistent with the large SECURE trial[41], in which 2,499 European patients were randomly assigned to a polypill or usual care strategy within 6 months of a myocardial infarction. High levels of adherence were more commonly reported in the polypill group compared with usual care (74.1% versus 63.2%; RR 1.17, 95% CI 1.10–1.25), which could have contributed to a reduction in major adverse cardiovascular events (9.5% versus 12.7%; HR 0.76, 95% CI 0.60–0.96)[41].

Patients with CVD have complicated medication regimens[42,43] that can result in them visiting the pharmacy an average of 20 times per year, with 10% of patients visiting the pharmacy ≥40 times annually[42]. A simple medication adherence solution is the use of synchronization, in which patients can collect all their medications in a single visit[43–45]. In a meta-analysis of varying study designs, medication synchronization programmes were associated with increased adherence (pooled OR 2.29, 95% CI 1.99–2.64)[46], although high-quality data from RCTs in patients with CVD is lacking.

Another strategy to overcome physical barriers to access (such as mobility, transportation and time) is the provision of home medication delivery and longer refill periods (90 days compared with 30 days). Both of these interventions have been associated with higher rates of adherence compared with usual care cohorts[47,48]. However, no RCTs of these strategies have yet been performed.

Packaging

The packaging of medications in a 'blister' pack labelled for daily use could support adherence by providing a visual reminder of whether any given dose has been taken or missed and also allows a third party to quickly determine the degree of recent medication adherence[49,50]. Consistent with evidence from systematic reviews[51,52], a small RCT (n = 73) showed that a calendar blister pack modestly improved medication adherence and blood pressure control compared with usual care[53]. An iteration of the packaging approach has been the development of 'smart' blister packs that link to a reusable electronic monitoring module and record when each blister is opened[54]. A small proof-of-concept study (n = 141) has shown that smart blister packs are acceptable to patients and usable[55], although further evaluation is needed to demonstrate the cost-effectiveness of such an approach at scale and among patients with low health literacy, for whom the additional complexity of 'smart' monitoring might be limiting.

Behavioural and motivational interventions

Behavioural interventions, such as counselling, cognitive behavioural therapy and motivational interviewing, attempt to promote patient self-management and overcome dysfunctional emotions related to medication use.

Motivational interviewing. Distinct from directive, expert-driven counselling, motivational interviewing is a collaborative, patient-centred form of communication that attempts to engage and activate the intrinsic motivation for change of a patient through four guiding principles: expressing empathy, promoting self-efficacy, recognizing resistance, and identifying discrepancies between the current state and future goals[56]. Individuals trained in motivational interviewing use open-ended questions, affirmation, reflective listening, summarizing, informing and advising. A systematic review of RCTs evaluated the effect of motivational interviewing on medication adherence among adults with chronic conditions[57]. For the subgroup analysis of 14 trials enrolling patients with CVD, medication adherence was the primary outcome in 10 studies, of which 7 demonstrated a significant improvement among patients in the intervention group[57]. Moreover, a later study demonstrated the benefit of motivational interviewing specifically among non-adherent older adults (aged ≥65 years) with diabetes mellitus and hypertension[58]. Given the heterogeneous nature of the motivational interviewing interventions studied, several uncertainties persist, including the durability of effect (the longest studies were 6–12 months in duration), whether face-to-face and telephone delivery are equivalent to each other, and how often motivational interviews should be performed and by whom (for example, a nurse, research assistant or pharmacist). Nonetheless, evidence exists to support the use of either motivational interviewing or cognitive behavioural intervention in patients with hypertension[59], heart failure[60], stroke[61–63] or dyslipidaemia[64].

Nudges. Nudges are another form of behavioural intervention that present patients (or clinicians) with positive structuring of a preferred option that will generate a desired, long-term outcome. Nudges are grounded in behavioural science theory and have been studied in trials of smoking cessation[65] and weight loss[66]. However, fewer such studies have been undertaken on medication adherence. In the ENCOURAGE RCT[67], 182 patients with an indication for statins (93.4% had coronary artery disease) were randomly assigned to personalized, weekly nudge content based on their psychographic profile of motivations and self-perceived abilities or to standard care. Patients in the nudge intervention group had significantly higher rates of adherence compared with the control group (66.3% versus 50.5%; P = 0.036)[67].

Therapeutic relationships and SDM. Shared decision-making (SDM) seeks to overcome some of the barriers that might lead to non-adherence such as inadequate anticipatory guidance, false expectations about symptom relief[68], ambiguous instruction on duration of therapy[69], and misalignment between prescriber assessment of the need for information by a given patient and the perception by the patient of this need[70,71]. Specifically, the SDM framework involves a dialogue about available treatment options, preferences, and goals and, ultimately, agreement on a collaborative plan for management. An established body of evidence links SDM with favourable patient-related outcomes, enhanced education and experience of care; however, links to improved medication adherence are less well established[72]. Notably, in one of the largest RCTs of SDM in patients with CVD, a SDM tool designed to help patients with atrial fibrillation to decide on stroke prevention strategies did not improve either primary or secondary adherence to anticoagulant medication compared with usual care despite adequate fidelity to the intervention[73]. This finding could be related to the increasing adoption of SDM principles in contemporary 'usual care', which might attenuate the effect of a dedicated SDM intervention. A targeted approach towards patients with intentional non-adherence might produce more beneficial outcomes for SDM interventions.

Accountability interventions. Accountability is defined as the expectation to later account for our personal actions. Therefore, psycho-behavioural interventions of this type tend to focus on creating the expectation of account-giving in a perceived future, direct or indirect, social interaction. Accountability interventions attempt to invoke a sense of duress (avoidance of guilt) and extend to the 'white-coat adherence' effect, in which patients become more adherent around an anticipated clinical interaction[74]. The principles of accountability are leveraged in some multifaceted interventions, in which patients are informed that their adherence data are being tracked and will either be discussed at their upcoming clinical follow-up or be fed back directly using two-way reminder systems. Establishing a sense of accountability between a patient and a family member or caregiver can be an effective means to increase adherence; however, data on this approach are limited and conflicting. In a small, randomized controlled study of 126 patients prescribed statins, a weekly feedback report provided

to a partner or family member increased adherence compared with a control strategy involving just a pill-monitoring device with no alarms or feedback (86% versus 67%; $P = 0.001$)[75]. However, the gains were not sustained after the intervention ceased.

Educational interventions

Educational interventions aim to increase patient understanding of their condition, and several have proved to be effective. In a meta-analysis of 18 RCTs that evaluated an educational intervention in patients with hypertension, hyperlipidaemia or diabetes, the interventions were delivered by a variety of clinicians, ranged from one-off to monthly sessions, and were frequently supplemented by pictograms or written material[76]. Medication adherence was significantly higher among those receiving educational interventions, with particular benefit observed among those receiving three or more sessions and when delivered at home or face-to-face[76]. Elements of successful interventions include personalized and contextual education[77] (confirmed with teach-back methods or written information[78] and delivered in proximity to an event such as a hospitalization[79], stent insertion[80] or myocardial infarction) and those using frequent and repeated interactions[81–84].

Educational interventions could be of particular benefit if tailored to patients with lower health literacy — potentially up to 40% of the population of the USA[85]. In a post hoc analysis of an RCT ($n = 435$), the use of non-written material, such as printed images and pictograms of medication regimens, was shown to benefit those with cognitive impairment and baseline polypharmacy, although this finding requires confirmation in a larger trial[86]. Other approaches involve the use of voice-activated self-management applications, which avoid the need for text or smartphone inputting; however, these technologies are still in the proof-of-concept phase[87].

Reminders. Reminder-based interventions aim to overcome forgetfulness (unintentional non-adherence) and generate habits associated with optimal medication-taking behaviour. In an attempt to address the primary non-adherence component of phase 1, 5,000 patients receiving a first statin prescription who did not collect their medication within 1 week were identified through integrated pharmacy records and randomly assigned to a reminder intervention or usual care (no reminder)[88]. Of the patients assigned to receive telephone reminders and a personalized letter emphasizing the importance of statin use, 42% collected their medication in the follow-up period compared with 26% in the usual care group[88]. By contrast, in another study, among patients who had not picked up their initial prescription for asthma, hypertension, diabetes or hyperlipidaemia medication despite two automated messages and one telephone call from a pharmacy, additional nurse-led outreach did not improve uptake of medication compared with control patients[89]. Further study is needed to determine the optimal timing, content, mode and enactor of reminder interventions. However, closed feedback loops between prescription and dispensing data could be an effective way to identify early primary non-adherence.

Reminder interventions aimed at improving implementation of adherence (phase 2) range from simple, passive and infrequent prompts to more explicit MEMS, bidirectional text messaging services, and comprehensive monitored and unmonitored mobile health applications (mHealth apps), which are discussed below.

Text messages. With its automated and dynamically tailored content, text messaging has the potential to be a low-cost and scalable intervention. In several systematic reviews, text messages have been reported to have a generally favourable effect on medication adherence in various chronic diseases, albeit with the inclusion of only small studies of modest quality and evidence of substantial heterogeneity[90,91]. Some of this heterogeneity relates to the multiple variables inherent in text message interventions, including but not limited to composition, sophistication and frequency. Short-duration studies (mostly up to 6 months) involving 30–500 participants have demonstrated that daily or weekly text message reminders are associated with modestly increased rates of self-reported adherence (between 5% and 10% absolute difference in the proportion of days covered) compared with usual care[90–94]. However, larger, more recent and rigorous studies have demonstrated limited effectiveness of text message-based interventions[95–97].

Whether interactive and personalized text message content offers incremental benefit is unknown and could vary by timing and type of content (such as educational, instructional or motivational), adherence barriers, and personal preferences[98]. A saturation point might also exist in which additional messaging, even interactive, produces diminishing returns. In a small cohort of 90 patients with established CVD, adherence to statins and antiplatelet drugs at 30 days was higher among the two groups randomly assigned to a predominantly educational text message intervention compared with usual care[93]. However, two-way interaction produced no incremental benefit compared with push-information alone[93]. Similarly, in a study of >1,000 participants with hypertension, weekly text messages in a variety of languages significantly improved adherence compared with usual care[99]. However, two-way educational message content aimed at addressing common barriers to adherence had no additional effect compared with information only[99].

Alert fatigue could also contribute to the waning of effectiveness of an intervention over time. One approach to overcome alert fatigue is to use a MEMS device that identifies occasions when a patient has forgotten to take their medication, thereby directing an intervention 'just-in-time' rather than routinely. In a study of patients with a history of non-adherence, those randomly assigned to a text message reminder if they had not opened their pillbox by midday had higher rates of adherence at 6 months compared with those who did not receive reminders[100].

In general, reminder interventions have been shown to, at least in the short term, increase adherence among those with forgetfulness and low levels of baseline adherence; however, many unanswered questions remain. Few studies have evaluated the effect of text message interventions on adherence beyond 12 months, and very little is known about the optimal content and frequency of messages and whether two-way interaction (and personalization) is desirable or even necessary. Furthermore, little evidence exists of attempts to segment populations by preferences or adherence behaviours or whether end-users are involved in iterative content creation.

mHealth apps. Although similarly scalable to text messages, mHealth apps have several additional benefits. They allow patients to engage on their own terms, content can be titrated by the user with the capacity for personalization, they have the capability for moderated two-way information sharing, and they can provide data for the patient to discuss with the clinician. Unsurprisingly, with the potential for commercialization of this technology, >350,000 mHealth apps are available on digital stores, with approximately 250 added per day in 2020 during the COVID-19 pandemic, and up to 20% aimed at chronic disease management[101].

Several systematic reviews and meta-analyses have concluded that mHealth apps have a favourable effect on medication adherence among patients with CVD[102–104]. However, fewer than 1,000 patients in total have been evaluated in high-quality studies, in which the duration of follow-up was generally <12 months, adherence was predominantly self-reported and the heterogeneity of app content meant that the benefits of individual elements could not be determined. The AHA has called for larger and more rigorously designed studies with adaptive trial methodology to adequately understand the effectiveness of apps and their individual components in the management of medication adherence[105]. Attention must be paid to the needs of patients with low health (and technological) literacy[106], and apps should align their functionality with behavioural theory[107].

Providing adherence information to clinicians

Routine provision of patient adherence data could prompt clinicians to proactively identify and address barriers to optimal medication-taking behaviour. A Cochrane review evaluated the effect of providing clinicians with historical data on patient adherence and whether this strategy affected future adherence[108]. Four of the included studies enrolled patients with (or treated for) CVD. Most interventions involved prescribers receiving a printed adherence report (or a reminder), with some studies also including suggested clinical actions according to adherence status. Improvements in process metrics of care quality and patient satisfaction were reported in one study[109]. However, there was no improvement in adherence compared with the control group in any of the trials[110–112]. Therefore, reporting of non-adherence metrics alone, without the additional tools to identify and overcome barriers, might be insufficient to effect improvements.

Incentives

Incentive-based interventions offer a reward for a behaviour change that leads to medication adherence, thereby reinforcing this activity over time. Studies that have evaluated financial incentives for patients (and physicians) have yielded mixed results. In a cluster randomized study, 340 primary-care physicians and their assigned 1,503 patients who were prescribed a statin were allocated to one of four groups — control (usual care), patient incentives, physician incentives, or shared patient and physician incentives[113]. In the patient-incentive group, patients were eligible to enter a lottery (for US$ 10–100) only if they had taken their statin the day before. In the physician-incentive group, physicians were eligible for US$ 256 per quarter for every patient who achieved their LDL-cholesterol goal over the course of the study. In the shared-incentives group, both patients and physicians were eligible for the aforementioned incentives, although the value of the rewards was halved. At the 12-month follow-up, only patients in the shared-incentives group significantly improved their LDL-cholesterol levels compared with the control group. Adherence was highest in the shared-incentives group, with no significant change compared with control in the patient-only or physician-only groups, suggesting that financial rewards might require both patient and physician participation to be successful[113]. In a smaller study involving a loss aversion incentive, 130 patients admitted to hospital for acute coronary syndrome were randomly assigned to receive up to US$ 50 per month if they took their medicine daily, with US$ 2 per day deducted if a dose was missed[114]. Adherence at 90 days, assessed using an electronic pill bottle, was higher in the intervention group than in the control group but the difference was not statistically significant[114]. Other studies of incentive-based interventions have yielded conflicting results[115–117], and this approach is unlikely to be a durable solution for medication adherence given its ongoing cost and complexity to maintain.

Financial medication assistance

Interventions that provide financial medication assistance (FMA) seek to overcome cost barriers to medication adherence. Up to 25% of patients in the USA describe difficulty in paying for their prescription medication[118], leading to a decrease in medication adherence and poor clinical outcomes[119,120]. FMA interventions utilizing co-payment reductions, patient assistance programmes, vouchers and discount cards have been associated with moderate improvements in adherence[121]. In the MI FREE trial[122], providing medications free of charge increased prescription refill rates (measured by medication possession ratio) compared with the usual-cost group and was associated with a very modest reduction in major adverse cardiovascular events without increasing overall health-care spending. In the ARTEMIS study[123], patients who received vouchers for either clopidogrel or ticagrelor after acute coronary syndrome had higher rates of continuous self-reported adherence and higher rates of pharmacy fills than those who did not receive vouchers. However, unlike the MI FREE trial[122], which affected multiple classes of cardioprotective medications, changes in adherence to $P2Y_{12}$ inhibitors alone in the ARTEMIS study[123] did not translate into improved clinical outcomes. Furthermore, in the ARTEMIS trial[123], the uptake of the intervention was variable and individuals most likely to benefit from the voucher (such as uninsured patients or those with lower incomes or more comorbidities) seemed less likely to use the intervention, raising concerns that co-payment reduction is not a 'one-size-fits-all' solution.

Pharmacy-led programmes that assist patients with CVD to obtain FMA are likely to be beneficial, particularly among indigent patients, although current evidence is limited to pre–post study design (that is, no control group) and only within single centres[124,125]. Furthermore, the long-term effect of FMA-based solutions is unclear as many vouchers and coupons tend to be time limited, and long-term outcomes among patients are unknown.

Clinician-supported multifaceted interventions

Clinician-supported, multifaceted interventions usually involve harnessing or expanding the role of pharmacists[126–130], nurses[131,132], or community health-care workers[133] and have been shown to be effective in multiple studies. Systematic reviews and meta-analyses of RCTs have shown that pharmacist-led interventions improve adherence among patients treated for hypertension[134] or dyslipidaemia[135], with the most consistent results observed in patients with heart failure[136]. The success of intervention characteristics varied by method of delivery (face-to-face[82,130,132,133,137–144] or phone[126,145]), location of interaction (pharmacy[82,128,142,143], clinic[132,137–141,144] or home[126,133,145]), type of intervention (structured education[128–130,133,137,139,141,142,144], motivational interviewing[140,143] or elements of both[82,126,138]), frequency of follow-up (single[126,141,144] or repeated[82,128,130,132,137–140,142,143,145]) and enactor of the intervention (pharmacist[82,126,128–130,137,140,142–145], nurse[132,138], doctor[141] or community health-worker[133]) as well as by the degree to which the interaction is supported by other elements (packaging aids[128,129,142,144], reminders[126,130,132,137,138,141], blood pressure monitoring[142,143] or progress reports[126,130,139,140,145]). Estimates of pooled effectiveness are limited not only by the heterogeneity of these intervention elements but also by varying participant characteristics and choice of adherence end points. However, elements common to successful interventions include an attempt to identify non-adherent patients at baseline,

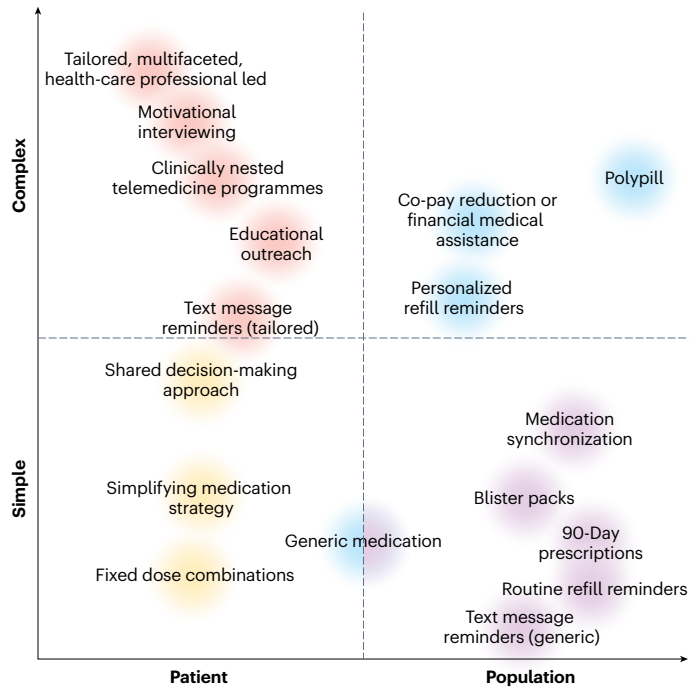

Fig. 1 | Tension between the complexity of an intervention and patient versus population target. The cost and complexity of interventions that are effective at the patient level render them less sustainable when scaled to populations. By contrast, simple, low-interaction and scalable solutions for populations might have only modest effects and leave multiple barriers to adherence unaddressed.

tailoring the intervention to identified barriers and repeated follow-up (often ≥3 interactions). Another element that seems to be of benefit is the ability to coordinate with the primary clinician about patient concerns surrounding medication or the need for medication up-titration, which is somewhat analogous to models of chronic disease co-management[126,129,131,137]. The long-term durability of these interventions is unknown as few studies[128,129] continued beyond 12 months of follow-up, with only limited evidence of widespread adoption by health services[146]. Furthermore, whether an intervention induces sustained behavioural change and can be withdrawn (or attenuated) is also unclear, and there is some evidence of relapse after completion of interventions[139,147]. However, despite the resource intensiveness of clinician-supported, multifaceted interventions, the improved clinical outcomes (particularly among patients with heart failure) are likely to make successful interventions cost-effective[148].

Interventions in under-represented minority groups

A large body of evidence demonstrates that non-adherence is greater among Black and Hispanic patients[149,150], which is likely to contribute to disparities in overall cardiovascular clinical outcomes[151]. Compared with white patients, Black patients are more likely to experience barriers to adherence, including poor understanding of medication regimens and their adverse effects as well as doubts about drug effectiveness[152], which might relate to lower degrees of shared decision-making[153]. Stereotype threat, which is the threat of being identified with a negative stereotype about race or ethnicity, can also contribute to medication non-adherence[154]. If a patient is fearful of being labelled as unintelligent, they might not ask questions or raise concerns about their treatment[49]. The HYVALUE study[154,155], which focused on combating stereotype threat using a values affirmation writing exercise that was designed to reinforce self-worth and offset the potential threat of negative health information, was not successful in improving medication adherence among Black (or white) patients despite improved patient activation.

A systematic review and meta-analysis found that much of the successful adherence intervention literature pertains to white, middle-income individuals, with less convincing evidence of effectiveness among Black patients[156]. The researchers concluded that some of this disconnect might relate to the lack of involvement from the Black community in the design of adherence interventions or arise from the paucity of empirical research in the Black community. One study that was designed with and for the Black community was the TEAM cluster randomized trial[130] of 28 pharmacies and 576 Black patients with hypertension. The TEAM study utilized a multifaceted toolkit that was implemented by 14 pharmacies. Compared with the 14 control pharmacies, patients who engaged in the TEAM intervention had significantly higher refill adherence rates at 6 months (60% versus 34%; P <0.001) and significantly improved blood pressure[130].

Precision and population approaches

Despite the prediction by the WHO that 'increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments'[12], substantial, sustainable improvements in adherence have been elusive. A consistent finding across many studies is that multilevel, multifaceted interventions are generally superior to those with single elements and that some degree of tailoring is preferable to a one-size-fits-all solution. However, these conclusions generate tension when extrapolating from patients to populations. The cost and complexity of interventions effective at the patient level render them less sustainable when scaled to populations (Fig. 1). By contrast, simple and low-intensity solutions that could be scaled for populations might have only modest or less durable effects and leave multiple barriers to adherence unaddressed. Thus, the loosening of this 'Gordian knot' is likely to require complementary approaches. For complex non-adherence, a precision approach might be required whereby adherence barriers experienced by an individual would be phenotyped and aligned with specific elements of more intensive interventions, thereby increasing the effect size and reducing the number needed to treat. For unintentional non-adherence, mHealth interventions with demonstrable effectiveness that are low-cost, low-intensity and deployable at scale might be fit-for-purpose for a population approach.

Practical approaches in the clinic

Clinicians should familiarize themselves with the risk factors for and causes of non-adherence. Establishing a routine component of medication history taking that includes a question, such as 'how many times did you miss your tablets in the past 7 days?' might be sufficient to identify non-adherence and encourage a conversation about attitudes[157,158], beliefs and barriers to optimal medication use. If woven into routine clinical workflow, this approach will not only provide temporal evaluation of self-reported adherence by an individual but also build anticipated and direct accountability. These discussions with patients need to be non-judgemental and solution focused and attempt to normalize the difficulty of long-term medication adherence. Methods through

which non-adherence programmes can be increasingly funded also need to be sought (Table 2).

Future interventions and research

Studies in this field have been limited by the inadequate enrolment of non-adherent patients. Even when these patients were enrolled, few studies have included delineation or phenotyping of the baseline barriers to adherence or the phases of medication-taking behaviour in which they were occurring. Increased efforts are needed to align intervention components with established taxonomies of non-adherence causes, which would allow for fairer comparisons between studies.

Achieving the mutually exclusive goals of explanatory trials with those of pragmatic implementation studies is challenging, the former being crucial to precisely estimate effectiveness, the latter needed to determine scalability[159,160]. Studies of adherence interventions that focus on outcomes and implementation fidelity over follow-up periods >1 year and outside the study environment are also needed. Given that adherence tends to improve as soon as it is mentioned, longer study periods are required to allow any white-coat adherence effect to dissipate. Understanding the durability of interventions is crucial as many causes of adherence change over time and most studies demonstrate regression towards suboptimal medication-taking behaviour after the intervention has ceased or becomes less intense[161].

The treatment of chronic CVD used to rely on oral medications. However, over the past 5 years, several novel therapies have emerged, particularly in the lipid-lowering space, that are parenteral and less frequently administered (monthly or even twice annually)[162]. Limited real-world data suggest that adherence to injectable

Table 2 | Actionable approaches to non-adherence from professional society, clinician and health system perspectives

Approach	Professional societies	Clinicians	Health system
Develop and foster an awareness of the importance of non-adherence in clinical care	CME or courses on how to identify, track and address non-adherence	Routinely screen for known risk factors for suboptimal medication-taking behaviour: elderly patients, polypharmacy, low socioeconomic status, low health literacy, history of missed clinic appointments, poor social supports; consider routine assessment of health literacy	Provide dashboards of patient adherence by discipline, clinic and physician
	CME or courses on how to perform motivational interviewing	Develop skills in adherence-related medical history taking or build into clinic workflow via pharmacist, nurse or mHealth app: how often did you remember to take your medications in the past 7 days? What helps to remind you to take them? What makes it difficult? Identify constructive relationships to assist as adherence partners (such as spouse, children or friends)	Incentivize (and display) adherence performance within the health system using HEDIS and Medicare star ratings systems
	Advocate for teaching in medical school relating to adherence: core component of medication history taking and documentation; how to assess adherence; behavioural constructs underpinning adherence; behaviour or counselling techniques to address barriers; and importance of shared decision-making	Becoming familiar with available toolkits, such as the Million Hearts initiative[166]	Identify opportunities for collaborative practice agreements between physicians, psychologists, pharmacists and payers
Intervene and follow up on non-adherence	Consider advocating for reimbursement or funding of pharmacy or collaborative practice agreements to definitively address non-adherence in clinical care	Incorporate adherence in routine clinical documentation (structured elements of EMR or .dot phrases) to address trends over time; patients do not feel 'targeted' if this assessment is routine	Develop systems that feed back adherence data to the EHR at the point of care
		Reinforce shared decision-making principles: normalize the difficulty in taking lifelong medications and attempt to bring meaning to medication-taking	Support pharmacy services to provide integrated adherence offerings such as synchronization, 90-day prescriptions and home delivery
	Consider specific reimbursement or funding options for interventions such as motivational interviewing	Normalize the most easily achieved goals as part of medication management: prioritize fixed-dose combinations, use generic medications when possible and provide 90-day refills	Consider supporting electronic monitoring devices for patients who are most likely to derive benefit
		Develop knowledge of (and promote): local pharmacy offerings and payer programmes designed to improve adherence (such as medication synchronization, home delivery, multifaceted interventions and co-payment reduction)	Develop value propositions for adherence interventions by tracking adherence or non-adherence and outcomes
		Offer free-of-charge mHealth opportunities such as MediSafe[167], MyTherapy[168], Express Scripts[169], EveryDose[170], Sprout[171], CareClinic[172], DoseCast[173] and medications on the App store for iWatch	

CME, continuing medical education; EHR, electronic health records; HEDIS, Healthcare Effectiveness Data and Information Set; mHealth, mobile health.

lipid-lowering agents might be better than for oral tablets but remains suboptimal[163,164]. Thus, novel models of care, such as pharmacy administration clinics, could ensure adherence and optimize the value proposition of these more expensive therapies[165]. Nonetheless, given that medication-taking behaviour is dynamic, and that adherence barriers vary over time, multilevel approaches (such as those directed towards the patient, clinician, health-care system and policymakers) are likely to be needed. Clearly, a need exists to create a toolbox of solutions rather than relying on just one or two interventions.

Finally, this Review demonstrates that most interventional studies focus on improving metrics of medication adherence and few studies evaluate effects on clinical outcomes. Improved medication adherence is a reasonable surrogate; however, larger studies powered for end points that matter to patients (such as clinical events and quality of life) remain an important area for future research on medication adherence.

Conclusions

Medication non-adherence is a global health problem that remains underappreciated. Medication-taking behaviour needs to be routinely evaluated in the clinic and an assessment of potential barriers undertaken in a non-judgemental manner. Professional societies need to elevate the importance of non-adherence among their constituents, clinicians should avail themselves of the various resources available, and health systems have a duty to explore integrated and collaborative practice agreements to facilitate funding of multifaceted and tailored solutions. Effective strategies to improve adherence do exist but they need to be tailored to the patient and be subjected to long-term evaluation.

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Author contributions

A.J.N. and N.J.P. researched data for the article. All the authors discussed its content, wrote the manuscript, and reviewed and edited it before submission.

Competing interests

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