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The continuing challenge of medication adherence

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The continuing challenge of medication adherence

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Table of contents

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Editorial: The continuing challenge of medication adherence

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Editorial on the Research Topic
The continuing challenge of medication adherence

Over 20 years ago the World Health Organisation (WHO) published their influential report, entitled "Adherence to long-term therapies: evidence for action" (Sabaté, 2003), in which they provided an authoritative account of the extent, causes and effects of non-adherence to medication. Although this has been heavily cited and followed by substantial research, treatment adherence continues to be a massive problem with huge impacts on clinical, economic and social outcomes, which the Organisation of Economic Co-Operation and Development (OECD) have described as a major public health scandal (Khan and Socha-Dietrich, 2018).

Since the time of the WHO report, there have been considerable advances in our understanding of the barriers and facilitators of medication adherence. Many interventions have been developed, and these are being increasingly facilitated by the rapid developments in digital technologies and artificial intelligence. While there have been many systematic reviews of the causes of non-adherence and of the interventions for improving adherence, these are widely spread across many journals, which creates a major challenge for the interested clinician or researcher wanting to keep up with the extensive research findings which have accumulated. Moreover, since publication of the WHO report, there is little evidence that adherence has improved and there is continuing evidence that healthcare systems have failed to address the adherence challenge both at a policy and educational level. The purpose of this Research Topic is to allow the reader to gain an overview not only of the state of the art in adherence research and practice but also of some of the continuing issues in this area. Recent science in this area is presented addressing five key interrelated questions:

i. What is the nature and prevalence of non-adherence?
ii. What are the causes of non-adherence?
iii. What is the best way to assess adherence?
iv. What are the clinical, social and economic impacts of poor adherence?
v. What are the most effective adherence support interventions?

The first paper by Chapman and Chan addresses the first three of these questions. It begins by examining the evolution in the definitions of non-adherence, showing that adherence is now best understood as involving different stages, from treatment initiation through to long-term persistence. They indicate how the estimated prevalence of non-adherence varies according to the stage and type of behaviour since approximately 20% of patients may never start a newly prescribed treatment whereas around double that number fail to take their medicines regularly and even more do not persist over longer periods. They emphasize that part of the variation in these rates depends on how adherence is measured, and they summarise some of the main methods for this. In examining the many causes of non-adherence, they highlight the use of various explanatory models, such as the Capability Opportunity Motivation (COM-B) framework (Jackson et al., 2014) or the Perceptions and Practicalities Approach (Horne et al., 2019).

Even though adherence prevalence estimates vary across studies, there is very consistent evidence that non-adherence has profound effects on a range of important patient and societal outcomes. These impacts are documented in the paper by Achterbosch et al. Their overview of the cumulative findings from 43 systematic reviews provides an extensive picture of the reduced treatment effects, the increased healthcare utilization, morbidity and mortality together with all the financial implications for individuals and healthcare systems. These findings provide a compelling argument for the need to develop effective adherence support interventions in order to reduce the massive clinical, personal and economic costs of non-adherence.

The search for more valid and reliable measures of adherence remains a challenge. Although measures based on electronic monitoring (EM) are often cited as the gold standard (El Alili et al., 2016), these devices are not without their problems, and the next two papers address some of these. Rohay and Dunbar-Jacob examine various operational definitions derived from EM adherence measures and provide important guidelines on calculation methods. However, even the most sophisticated EM methods can only indicate when medicine containers are opened and still do not provide definitive evidence that medicines have been ingested. The search for adherence biomarkers has a chequered history but good evidence is now emerging for the use of chemical adherence testing (CAT). Thus, in the following paper, Rabbitt et al. review the growing number of recent studies showing how CAT is being used in the investigation and management of adherence to antihypertensive medications. Their review indicates that there is a need for greater consistency in the ways in which CAT is used for monitoring and defining adherence. Although CAT could be used to provide patient feedback for improving adherence, this still needs to be developed in an ethical and patient-centric way.

The next two papers provide an overview of the nature and scope of interventions provided by healthcare professionals (HCPs), and those delivered via digital technology. HCP interventions have traditionally targeted patients' knowledge, understanding and memory since many early studies were based on the assumption that non-adherence was due to a failure of one or more of these processes. However, recent work has shown that reminder-based interventions, although widely used, may have limited impact (Choudhry et al., 2017). The substantial evidence that the causes of non-adherence are many and varied means that interventions need to be carefully chosen to target each individual's barriers in a personalised way (Allemann et al., 2016). This critical issue is discussed by Crawshaw and McCleary in their overview of HCP led interventions. They show how the variation in the efficacy of these interventions reflects their content and approach. The more effective interventions go beyond the simple provision of information and reminders and are more likely to be tailored to the individual. They also recognise the potentially important role of healthcare systems in embracing the adherence challenge and allowing time and resources for clinicians to engage in adherence support in a meaningful way.

Since clinicians may lack the tools they need for managing the adherence problems they face, the emergence of digital approaches is now seen as a viable way of achieving more widespread interventions, which have been made possible by the global adoption of mobile phone technology. In their paper, Moon and Walsh review the rapid progress in the use of digital adherence interventions. While they outline and recognise the huge potential of digital interventions, they also acknowledge the many challenges inherent in optimising their effective use in practice. There are now a huge number of adherence apps, a large proportion of which are based on providing reminders with varying levels of sophistication and personalisation. Even with the inclusion of artificial intelligence (AI) methodologies, there is still some way to go before their full potential can be realised. There is an enthusiastic but still rather naïve belief that developments in AI, interactive digital technology and precision medicine will solve the adherence problem and, in doing so, obviate the need for HCPs to directly address the adherence challenge. Ultimately these developments may well provide important ways of ensuring that medicines are taken more systematically and effectively but current evidence indicates that they are not instant solutions. For example, a recent review of the use of AI tools in adherence interventions concluded that the evidence is still both limited and weak (Reis et al., 2025). Digital systems will need to be based on a more complete understanding of the individual drivers of non-adherence combined with the targeted use of evidence-based behaviour change techniques (BCTs) and should address patients' perceptions of the treatment as well as the practicalities of adhering to it (Chapman et al., 2020). A recent example of the types of challenges which app developers need to more effectively tackle has been provided by Wright et al. (2025). Their detailed analysis of the adherence barriers and linked BCTs provides recommendations for the design of apps for supporting better adherence to reliever medication in people with asthma.

The final two papers make use of detailed investigation of experts' views to identify their perspectives on the adherence challenge and how to improve healthcare practice. The paper by Tan et al. explores the experiences of a group of international clinicians from a range of specialities. Despite the diversity in the countries and specialties represented, all the clinicians acknowledge the central importance of good medication adherence in effective clinical care as well as the difficulties in monitoring and supporting better medicines use. The paper offers a unique perspective by focusing on healthcare professionals' first-hand experiences with medication non-adherence, a dimension often underrepresented in the literature. Their insights and experiences mirror many of the themes and issues in other papers in this Research Topic. While it is crucial to understand an individual's reasons for their reluctance or

unwillingness to take their medicines in order to provide targeted support, the key role of the HCP has not been sufficiently emphasized. One unfortunate finding from a recent study of HCP's views of non-adherence was that they perceived that the largest barrier to medication adherence management was lack of patient awareness rather than any shortcoming in their own practice such as the ability to ask about adherence as part of their routine consultations (Hafez et al., 2024). However, almost all the respondents in that survey did recognise their own limitations and the need for better training on medication adherence management. Part of this is due to rushed and poor communication combined with a lack of understanding and skill in the use of behavioural diagnosis and behaviour change techniques. The science of behaviour change has grown massively in the past decade but the learnings from this have not sufficiently filtered through to healthcare training and clinical practice. The reasons for this include the narrow biomedical focus in HCP education, a lack of any reinforcement value for HCPs in aiming for 'adequate adherence', and inadequate skills in behavioural scientists in collaborating with HCPs.

The final paper by Kardas et al. also involves the involvement of international experts to identify the key achievements of adherence research since the WHO report as well as looking ahead to the future. In addition to the more effective harnessing of new technologies, they emphasize the crucial need for a much greater recognition and prioritization of the adherence challenge at a healthcare system and policy level. Increasing clinician awareness and skill through undergraduate and postgraduate HCP training will also need to be a key element of future progress. In an era of evidence-based medicine, it is truly perplexing that the adherence issue has not been taken more seriously by health policymakers or healthcare providers (HCPs). Even though such influential organisations as the WHO and OECD have emphasized the global extent and impact of poor adherence, there is very little evidence that the situation has improved significantly in daily healthcare practice. Many years of behavioural science research has provided us with detailed evidence and insights into the nature, reasons for and impact of low adherence, not only to medication but also to other key health advice such as dietary and exercise recommendations. Quantitative and qualitative research involving people with the full spectrum of major health problems has shown that there are a wide range of cognitive, motivational and contextual reasons why people do not follow medical treatment or advice at each phase of adherence from initiation to longer term persistence.

Where does this leave us in making progress with the adherence challenge? It is obvious that there is an urgent need for all those involved in healthcare policy, training and practice to take this challenge much more seriously. The human and financial costs of non-adherence cannot be ignored any longer, and so we hope that this selection of papers will provide an impetus towards a better future.

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Chemical adherence testing in the clinical management of hypertension: a scoping review

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Background: Despite growing use, questions remain surrounding the utility, acceptability and feasibility of chemical adherence testing (CAT) as part of hypertension management in clinical practice.

Objectives: This scoping review aimed to (i) identify and summarise studies using CAT in hypertension management, and (ii) describe and critically evaluate how CAT is currently being used in the clinical management of hypertension.

Eligibility criteria: Peer-reviewed and published studies in English, reporting original research in any setting, with any study design, were included. Search concepts included hypertension, medication adherence, CAT, and their synonyms.

Sources of evidence: Searches were carried out using Ovid Medline, EMBASE, and PsycInfo (EBSCO), alongside manual searching of reference lists. Using Covidence software, we screened titles and abstracts, followed by full-text articles. Data from the included articles were tabulated and summarised.

Results: Of the 618 studies identified, 48 were included. The studies cover diverse clinical settings, and were mostly observational in design. 7 studies reporting adherence analyses within clinical trials for hypertension therapies. The use of theoretical frameworks to guide reporting was rare, and there was considerable variation in key terminology and definitions, most notably in the definition of adherence.

Conclusion: The current body of evidence demonstrates considerable variability in the approach to implementing CAT for hypertension management in clinical practice, and a paucity of randomised controlled trials to evaluate its impact. Future research could (i) adopt a cohesive theoretical framework including clear operational definitions to standardise the approach to this important topic; (ii) further explore the impact of CAT on clinical outcomes using RCTs.

KEYWORDS

hypertension, adherence-compliance-persistance, chemical adherence testing, mass spectrometry, blood pressure, antihypertensive

Introduction

Using medicines as prescribed can be a particular challenge in those common chronic conditions that are asymptomatic (Burnier and Egan, 2019). The pain-relief provided by long-term analgesia use, e.g., paracetamol, or the reduction in respiratory symptoms provided by some anti-inflammatory agents, e.g., corticosteroids, can provide a potent means of supporting patient initiation and persistence with long-term therapies (Rottman et al., 2017). In these instances, patients directly experience the benefits of using medicines and the aversive consequences of prematurely terminating medicine use. However, the most frequently used medicines, particularly in older adulthood, are those used for diseases where there is no discernible experience of an illness, such as hypertension (Choudhry et al., 2022).

Hypertension represents the greatest burden of non-communicable disease associated morbidity and mortality globally with a worldwide adult prevalence of disease estimated at 31% and affecting 1.39 billion individuals (Forouzanfar et al., 2015; Mills et al., 2016). Internationally, blood pressure remains above target in 63% of all diagnosed hypertensive patients in high-income western countries (Zhou et al., 2019). Several factors contribute to poor blood pressure control including undiagnosed or unrecognised secondary hypertension, so-called treatment resistant hypertension, physician inertia, and non-adherence to anti-hypertensives (Bunker et al., 2011; Durand et al., 2017; Hayes et al., 2019; Kjeldsen et al., 2015).

Adherence to antihypertensive drug (AHD) therapy is central to sustained control of blood pressure, reducing clinic visits and reducing complications of undertreated hypertension (Berra et al., 2016; Hill et al., 2011; Mazzaglia et al., 2009). Moreover, identifying non-adherence in patients who are not meeting BP targets could help providers avoid over-prescription and unnecessary investigation, and to prioritise patients who require more detailed investigation for secondary causes of hypertension, thereby having substantial clinical and economic impact (Schoonhoven et al., 2018).

Hypertension care providers report having little time and few tools to support detecting and improving adherence in their patients (Burnier et al., 2021). Objective assessment of adherence using chemical adherence testing, where available, is recommended by the 2023 European Society of Hypertension (ESH) guidelines for the management of arterial hypertension and the 2024 European Society of Cardiology (ESC) Guidelines for the management of elevated blood pressure and hypertension, and has been described as one of the most reliable methods for assessing adherence (Hayes et al., 2019; Tomaszewski et al., 2014; Curneen et al., 2022; Mancia et al., 2023; McEvoy et al., 2024; Wunder et al., 2019).

High performance liquid chromatography tandem mass spectrometry (LC-MS/MS), can measure anti-hypertensives and their metabolites within patient urine or blood samples, providing point-in-time estimation of anti-hypertensive adherence. LC-MS/MS of urine is usually employed as a qualitative method, describing presence or absence of drugs only, and results are influenced by inter-drug and inter-individual differences in pharmacokinetics (Berra et al., 2016; Wunder et al., 2019). Urine LC-MS/MS analysis can also detect drug metabolites which may be detectable for longer periods of time than the parent drug itself. In this way, urine analysis tends to refer to a longer period of time than serum analysis. LC-MS/MS analysis of serum may provide a more accurate point-in-time estimation of adherence as it allows for quantitative assessment to determine the drug level, which can be used to optimise drug dosage or estimate the time since last intake (Ritscher et al., 2020). Analysis of oral fluids and hair have also been suggested though neither is currently commonly used (Sharma et al., 2023; Lauder et al., 2020).

LC-MS/MS, has several advantages over other methods of adherence assessment. Self-report has been shown to correlate poorly with direct or objective methods of adherence measurement (Osterberg and Blaschke, 2005). Pharmacy dispensing records may not adequately reflect adherence if prescription data are not captured from all potential sources or patients do not take the dispensed medications (Ruzicka et al., 2019). Electronic pill boxes may not always be available and are less acceptable and feasible for those on multiple medicines, such as people with resistant hypertension (RH) (El Alili et al., 2016; Van Onzenoort et al., 2012). Directly Observed Therapy (DOT) combined with ambulatory BP monitoring (ABPM) has also been successfully employed (Hjørnholm et al., 2019). It may present feasibility challenges as it requires resources for monitoring, given the potential to cause symptomatic hypotension (Ruzicka et al., 2019).

However, despite growing consensus that chemical adherence testing (CAT) represents a potentially valuable tool in hypertension management (Mancia et al., 2023; Wunder et al., 2019), particularly in hypertension which has proven difficult to treat, the optimum manner of its use remains unclear. A disparate literature on CAT use in hypertension is developing where agreement on key terminology, definitions and methods is only beginning to emerge over the last 5 years (Wunder et al., 2019). There is a pressing need, therefore, to carry out evidence syntheses, as relevant studies have straddled multiple basic science and clinical literatures.

As distinct from systematic reviews, scoping reviews allow for a broader focus and present results in descriptive formats that highlight what kinds of evidence exist, where there are evidence gaps, and the quality of the existing evidence (Nyanchoka et al., 2019; Arksey and O'Malley, 2005). Scoping reviews are also recommended when there is a need to clarify the key constructs and operational definitions employed in an area of research, to examine the ways in which research in an emerging area is being conducted and to identify the factors associated with a specific concept (Munn et al., 2018; Noone et al., 2021).

For these reasons, we elected to conduct a scoping review to assess the characteristics of research in which chemical adherence testing is implemented in the clinical management of hypertension. The aims of this review were to (i) identify and summarise studies using CAT in hypertension management, and (ii) describe and critically evaluate how CAT is currently being used in the clinical management of hypertension. We report here our findings with reference to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist (Tricco et al., 2018).

Methods

Protocol and registration

The protocol for this scoping review was registered prior to data extraction on Open Science Framework Registries (Rabbitt et al., 2024).

Research question

To address our aims, we formulated the following research questions:

1. What are the characteristics of research methods on the implementation of CAT for anti-hypertensive pharmacotherapy in clinical practice?
2. What characteristics of CAT implementation can be discerned (e.g., clinical setting, what type of CAT, where in the patient journey)?

Information sources and search strategy

The search was conducted with the assistance of a health sciences librarian. Synonyms for three core concepts were iteratively tested: *medication adherence, chemical adherence testing,* and *hypertension.* Three electronic databases were searched from inception to April 2024: MEDLINE (Ovid); EMBASE; and PsycINFO (EBSCO). These databases were chosen given their relevance to the core concepts. In addition, we manually screened the reference lists of review articles identified during screening for relevant references. We used standardised medical subject headings and subject headings provided by the chosen databases. Synonyms were joined by the Boolean operator *OR*; thereafter, the search strings for each concept were combined with the Boolean operator *AND*.

Search concepts

1. Medication adherence
2. Chemical adherence testing
3. Hypertension

Search terms (examples–for full search strategy see Supplemental Data Sheet 1)

1. Treatment adherence and compliance; patient compliance; medication adherence
2. Chemical adherence testing; drug monitoring; therapeutic drug monitoring; mass spectrometry
3. Hypertension; blood pressure; antihypertensive drugs

Eligibility criteria

The inclusion and exclusion criteria are shown in Table 1.

Data sought

The types of data collected included clinical data on people with a diagnosis of hypertension, taking antihypertensive medication(s), in any healthcare setting. Methods and outcomes of interest were CAT, with or without comparisons with other methods of measuring medication adherence.

Study selection and synthesis

All identified records were imported into Covidence, a web-based collaboration software platform that streamlines the production of systematic and other literature reviews (Veritas Health Innovation Melbourne Australia, 2024). Duplicates were removed and the titles and abstracts of the remaining records were screened for eligibility by at least one of the authors. Uncertainty or conflict was resolved by discussion until consensus was reached. Full-text articles were then screened independently by two of the authors. Again, conflict or uncertainty were resolved through discussion until consensus was reached. The Covidence data extraction and critical appraisal templates were adapted to address the aims of this review.

The following data were extracted and tabulated:

1. General information: Authors, publication year, country of origin, clinical setting, study aim and study design
2. Participant information: Diagnoses, basic demographic details, number of participants enrolled,
3. CAT details: substrate and method for CAT, whether participants were informed in advance of CAT, whether CAT results were fed back to participants, definition of adherence, phase of adherence targeted, CAT carried out once or on multiple occasions.
4. Results: Key findings with respect to adherence, key findings with respect to blood pressure control or other pertinent clinical outcomes.

Critical appraisal

Depending on the study design, the following quality appraisal tools were applied to the included studies: the Joanna Briggs Institute Critical Appraisal Checklist for analytical cross-sectional research (Moola et al., 2020), and the Cochrane Risk of Bias Tool (Sterne et al., 2019) for Randomised Controlled Trials. Quality assessment was carried out by one reviewer and checked by another. The major confounders considered included the potential for white-coat adherence if participants were informed in advance of the intention to carry out CAT. In addition, we assessed whether studies published in 2018 or later included the four minimum reporting criteria set out by the European Society for Patient Adherence (ESPACOMP) in the ESPACOMP Medication Adherence Reporting Guideline (EMERGE) (De Geest et al., 2018). These guidelines represent an attempt to improve the reporting in adherence research by providing a theoretical framework.

Results

We identified 699 records, of which 683 (97.7%) were identified through database searches, and 16 (2.3%) through manual searches of reference lists in the review articles. After removal of duplicates, we screened titles and abstracts of 618, and the remaining 120 were assessed for eligibility through full-text review. Of these 120, 72 were excluded for the reasons shown in Figure 1, and 48 were included in the scoping review.

TABLE 1 Eligibility criteria.

Inclusion criteria	Exclusion criteria
-Prospective studies reporting original research published in biomedical journals -Systematic reviews, meta-analyses -Letters to the editor, guidelines, policy documents -Any study design -English language	-Non-peer-reviewed data -Review articles, opinion articles -Studies demonstrating the technical procedure of CAT without use in a clinical population

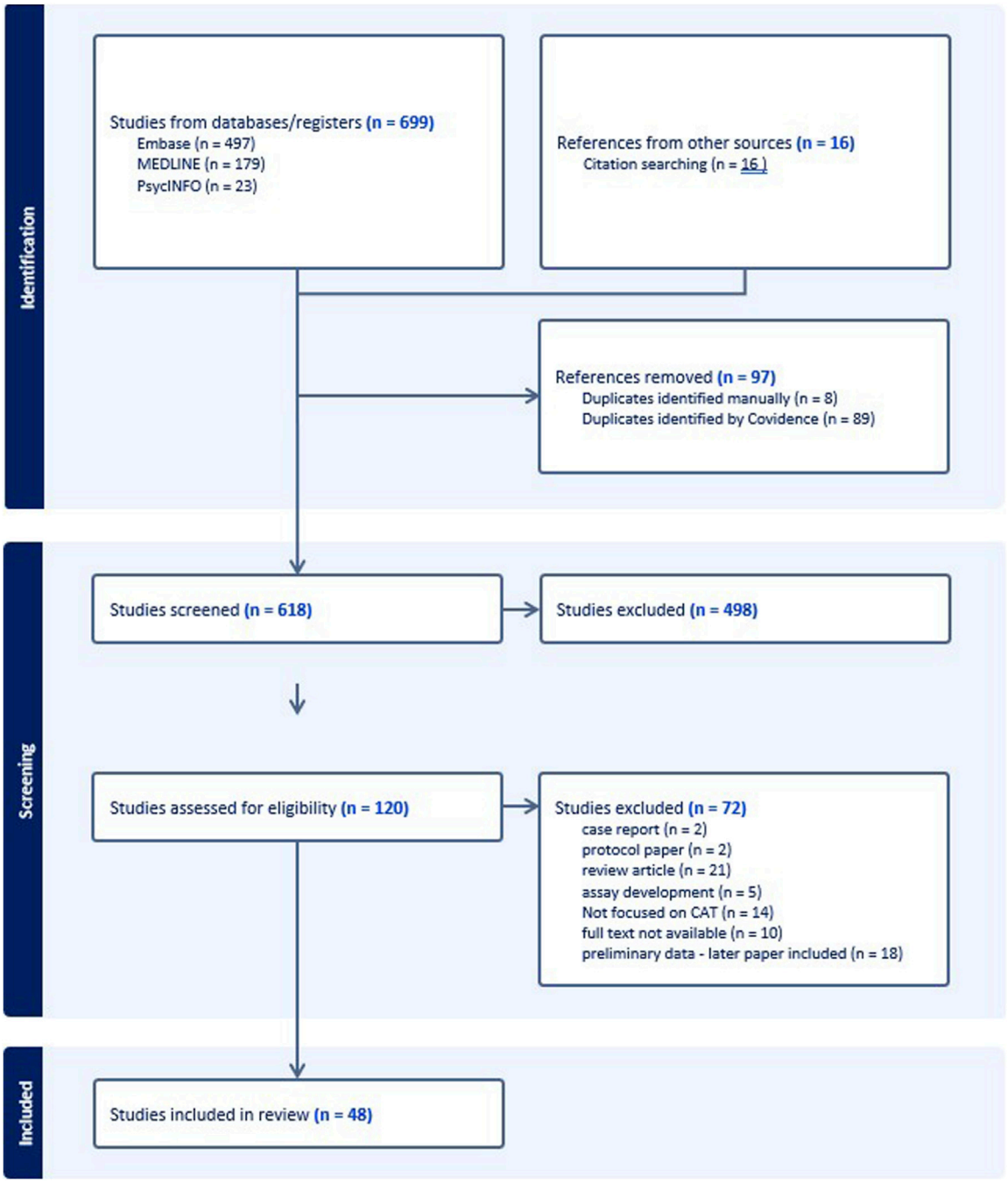

FIGURE 1
PRISMA flow diagram.

TABLE 2 Characteristics of included studies.

Author, year	Country	Setting	Primary aim of study	Study design	Total number of participants
Peeters 2024	Netherlands	Vascular, cardiology and nephrology hospital departments	To determine whether a CAT intervention combined with feedback using a communication tool leads to a decrease in resistant hypertension	RCT	100
Kario 2023	Japan	Clinical trial	Post-hoc analysis of stored urine samples in order to evaluate medication adherence	Post-hoc analysis within RCT	58
Kustovs 2023	Latvia	University hospital	To establish a target population of patients with possible changes in drug compliance despite the wide range of fixed-dose combinations and in whom it would be useful to determine the concentration of amlodipine in the blood	Prospective cross sectional study	81
Seleznev 2023	Russia	Regional Clinical Cardiological Dispensary	To test the concentration of antihypertensive drugs in patients with uncontrolled and controlled arterial hypertension	Cohort study	46
Curneen 2023	Ireland	Specialist hypertension clinic	To compare patient reported antihypertensive adherence with objective evidence using mass spectrometry spot urinalysis	Prospective cohort study	73
Peeters 2023	Netherlands	Hospital nephrology and vascular clinics	To determine the adherence to antihypertensive drugs in patients visiting the nephrology and vascularoutpatient clinics using CAT	Prospective cross sectional study	142
Osman 2023	United Kingdom	University hospital renal clinic	To demonstrate and highlight the usefulness of CAT to determine the prevalence of nonadherence to cardio-metabolic medications in patients attending routine renal clinics	Prospective cross sectional study	106
Bourque 2023	Canada	Multiple	To report on the overall prevalence of nonadherence in the apparent treatment resistant hypertension population and the quantitative contributions to nonadherence based on different methods of assessment, with an emphasis on attempting to explain the heterogeneity of the data	Systematic review and meta-analysis	71,353
Georges 2022	Belgium; Italy	Cardiology Dept; Hypertension Expert Centre	To document associations between psychological profile, drug adherence, and severity of hypertension in a representative sample of patients with apparent treatment resistant hypertension, using controlled hypertensive patients as the comparator	Prospective cross sectional Study	144
Sheppard 2022	United Kingdom	Primary care	To investigate whether it is feasible to collect urine samples in a primary care setting and analyse them using the LC-MS/MS method to measure adherence to antihypertensive medications	Prospective cohort study	191
Groenland 2022	Netherlands; United Kingdom	Hospital outpatient clinics	To develop and externally validate a screening tool, based on easy to collect clinical variables, to estimate the probability of non-adherence in patients with uncontrolled hypertension	Cross sectional study	735

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TABLE 2 (*Continued*) Characteristics of included studies.

Author, year	Country	Setting	Primary aim of study	Study design	Total number of participants
Peeters 2022	Netherlands	Clinical trial	To illustrate the importance and difficulties that can arise using a three-step approach to medication adherence	Case series within RCT	3
Osula 2022	United States	Internal Medicine and Cardiology Clinics in a large urban safety net health system	To compare the sensitivity, specificity, and predictive values of pharmacy fill data measures of adherence obtained from a nationwide prescribing database against CAT in detecting nonadherence with cardiovascular medications in patients with uncontrolled hypertension in the safety net health system	Prospective cross sectional study	77
Wang 2021	China	Hospital	To ensure drug compliance during a catheter-based therapy for treatment of hypertension	Cross sectional study	92
Buffolo 2021	Italy	Hypertension unit of university hospital	To evaluate the aldosterone:renin ratio changes, before and after ARB/ACEi initiation, as a means to assess adherence to ARB/ACEi prescription	Prospective cohort study	40
Beernink 2021	Netherlands	Hospital/Trial	To assess the prevalence of nonadherence to oral antidiabetics, antihypertensives, and statins within a cohort study of type 2 diabetes patients managed in a specialist setting using CAT	Prospective cohort study	457
Schäfer 2021	Germany	Hypertension clinic in university medical centre	To analyse patients' suitability for baroreceptor activation therapy and reasons for non-eligibility in patients with apparently resistant hypertension	Retrospective cross sectional study	75
Lauder 2021	Germany	Emergency Department of University Medical Centre	To identify treatment-related and psychosocial characteristics, including anxiety, depression, and health literacy, associated with nonadherence to BP-lowering medication among patients with previously diagnosed hypertension presenting with hypertensive urgencies at an emergency department	Prospective cross sectional study	104
Schesing 2020	United States	Outpatient clinics in an integrated health system which provides care for a low- income, uninsured population	To explore patients' and providers' knowledge, attitudes, beliefs and concerns about using a blood test to monitor medication adherence and how best to introduce and use CAT in a respectful, patient-centred way	Qualitative study	21
Wunder 2019	Belgium, Netherlands	Clinical trial	To give an impression on the reliability of adherence assessment during a trial	Analysis within randomised parallel group trial	18
Pelouch 2019	Czechia	Hospital clinic	To assess the drug non-adherence in stable CHF patients using serum drug levels monitoring	Prospective cross sectional study	81
Hayes 2019	Ireland	Primary care	To examine the feasibility of establishing non-adherence to medication using mass spectrometry urine analysis in primary care	Prospective cross sectional study	235
deJager 2018	Netherlands	Clinical trial	Post-hoc analysis to explore possible determinants of nonadherence in treatment resistant hypertension,	Substudy of open label RCT	98

(Continued on following page)

TABLE 2 (*Continued*) Characteristics of included studies.

Author, year	Country	Setting	Primary aim of study	Study design	Total number of participants
			within a trial to assess the effect of renal denervation on BP 6 months after treatment compared to usual care in patients with resistant hypertension		
vanSchoonhoven 2018	Netherlands, United Kingdom	N/A	To model the cost-effectiveness of performing LC-MS/MS-based analyses in improving adherence in patients with hypertension	Economic Evaluation	N/A
Sandbaumhüter 2018	Switzerland	Hypertension clinic	To use CAT to verify drug adherence during routine laboratory screening for PA and check for potential drug bias of the results	Prospective cohort study	24
Sutherland 2018	United States	Emergency Department	To validate a serum-based LC-MS/MS assay to simultaneously quantify 263 medications used for acute and chronic conditions	Prospective cross sectional study	
Avataneo 2018	Italy	Hypertension Unit	(i) To describe the prevalence of nonadherence in a representative sample of Italian patients with resistant hypertension using therapeutic drug monitoring on plasma samples. (ii) To determine clinical and/or demographic parameters associated with poor therapeutic adherence	Prospective cross-sectional	50
Petit 2018	Belgium	Cardiology department in an academic hospital	(i) To document the level of adherence to drug treatment in a sample of patients with aTRH using a direct evaluation method (ii) to explore the relations between psychological profile assessed by a broad array of validated questionnaires, adherence to antihypertensive medications as measured by LC-MS/MS, and degree of drug treatment-resistance evaluated by on-treatment 24-h ambulatory BP measurement	Prospective cross sectional study	35
Gupta 2017 (Burnier and Egan, 2019)	United Kingdom and Czech Rep	UK: samples processed by University Hospital of Leicester, from 15 UK sites. Czech Rep: Hypertension Unit of University Hospital	To detect nonadherence and explore its association with the main demographic and therapy related factors in patients with hypertension	Retrospective cross sectional study	1,348
Jones 2017	South Africa	Referral hypertension clinic	To determine whether monitoring plasma amlodipine concentrations and inhibition of angiotensin-converting enzyme (ACE) can be adjunct adherence tools	Prospective cross sectional study	100
Hamdidouche 2017	France	Academic medical center specialty hypertension clinic	To assess the prevalence of drug nonadherence under routine clinical conditions, the factors associated with nonadherence, and the impact of directly measured nonadherence on BP control	Prospective cohort study	174
Gupta 2017	United Kingdom and Czech Rep	Hospital blood pressure clinic	To examine the potential therapeutic applications of biochemical screening for the presence of antihypertensive medications in bodily fluids	Retrospective cohort study	331

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TABLE 2 (*Continued*) Characteristics of included studies.

Author, year	Country	Setting	Primary aim of study	Study design	Total number of participants
Kocianova 2017	Czechia	Outpatient hypertension unit in university hospital	To evaluate the ratio of the non-adherent patients according to plasma levels of beta blockers and to study the relation of the plasma levels to patients' office heart rate	Retrospective cross sectional study	106
McNaughton 2017	United States	Emergency department at an academic hospital	To test the hypothesis that higher antihypertensive medication adherence, biochemically assessed by a LC-MS/MS blood assay, would be associated with lower BP in the ED setting after adjusting for multiple patient demographic and clinical factors	Prospective cross-sectional study	261
Bohlender 2017	Switzerland	Hospital hypertension clinic	(i) To verify drug adherence during routine laboratory screening for PA and (ii) check for potential drug bias of the results	Prospective observational pilot study	24
Schmieder 2016	Germany	Clinical research center, dept of nephrology and hypertension	To report adherence rates at baseline and at 6 months after renal denervation and the relationship between adherence and BP measurements in patients with resistant hypertension	Analysis within prospective clinical trial	79
Patel 2016	United Kingdom	Specialist hypertension centre	To examine the extent to which integration of CAT into the diagnostic pathway may affect the ultimate eligibility rates for renal denervation	Retrospective analysis	34
Beaussier 2015	France	Clinical trial	To assess the influence of medication adherence on BP control and target organ damage in a pre-specified analysis of a published trial comparing sequential nephron blockade or sequential renin-angiotensin system blockade in patients with resistant hypertension	Randomised controlled trial	164
Ewen 2015	Germany	Clinical research	To determine the individual intake of antihypertensive drugs in patients with resistant hypertension undergoing renal denervation	Prospective cohort study	100
Florczak 2015	Poland	Clinical research	To evaluate adherence to therapy in patients with resistant hypertension by determining serum antihypertensive drug levels with the use of LC-MS/MS	Cross sectional study	36
Velasco 2015	United States	Specialist hypertension referral clinic	(i) To determine the relationship between primary aldosteronism (PA) prevalence and medication adherence. (ii) To build a decision analysis model to test the cost effectiveness of a CAT-guided approach for PA screening in patient swith apparent TRH, compared with a nonselective approach	Cross sectional study; Economic Evaluation	78
Tomaszewski 2014	United Kingdom	Specialist clinical hypertension centre	To report HPLC-MS/MS analysis of spot urine samples in hypertensive patients attending a specialist clinical hypertension centre	Retrospective cross sectional study	208
Rosa 2014	Czechia	Hypertension centre	To assess the proportion of patients eligible for renal denervation	Cohort study	205

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TABLE 2 (*Continued*) Characteristics of included studies.

Author, year	Country	Setting	Primary aim of study	Study design	Total number of participants
Brinker 2014	United States	Hospital hypertension clinic	(i) To assess the impact of CAT in optimising BP control in patients with resistant hypertension. (ii) To establish cost-effectiveness of CAT	Retrospective study	56
Jung 2013	Germany	Nephrology outpatient department	To use CAT to determine the impact of adherence in patients with apparent resistant hypertension and to assess possible factors related to drug therapy adherence	Retrospective chart review	76
Strauch 2013	Czechia	Hypertension unit within university hospital	To assess the prevalence of pseudo-resistance caused by noncompliance with treatment among patients with severe resistant hypertension and to analyze the contributing factors	Cohort study	339
Ceral 2011	Czechia	Hypertension clinic	To evaluate serum levels of prescribed antihypertensive drugs in individuals with difficult-to-control arterial hypertension	Retrospective cross sectional study	84
Azizi 2006	Multicentre: 16 countries in Europe ad North Africa	General Practice	To assess patients compliance with ACE inhibitor treatment in the DIABHYCAR study	Analysis within randomized, double blind, parallel-group trial	1,871

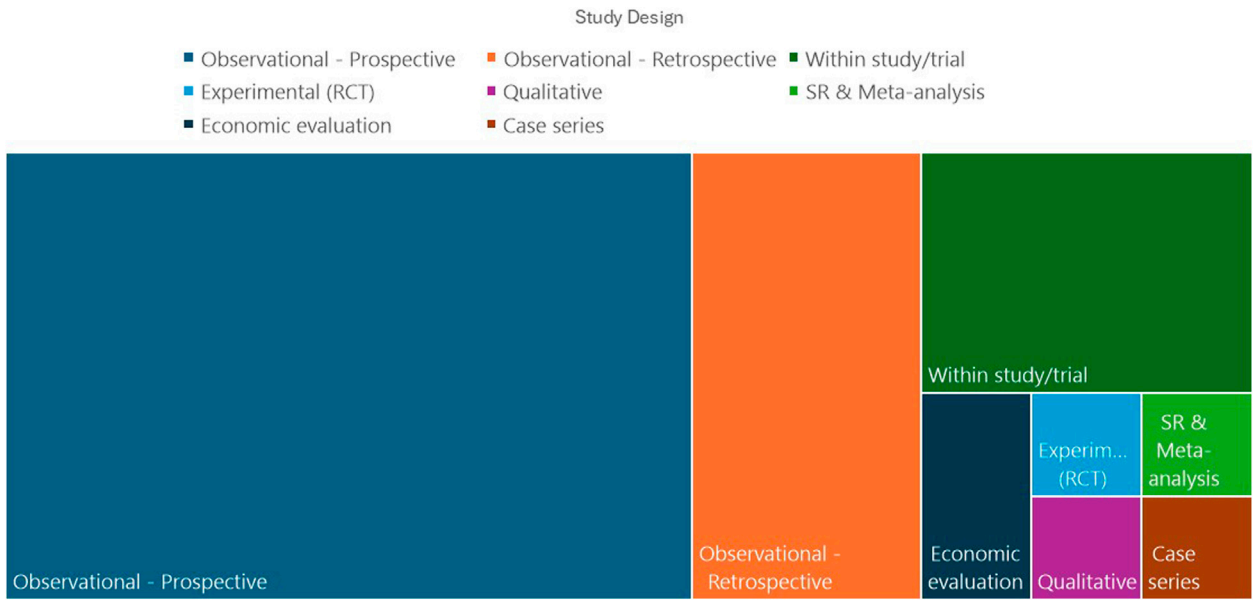

FIGURE 2
Designs of included studies.

Research question 1: characteristics of sources of evidence

Table 2 shows the characteristics of the included studies. Most of the reviewed studies (44/48) were published within the past 10 years. Most (46/48) of the studies originated from North America and Europe. Figure 2 shows the distribution of study designs. The majority of included studies were observational, and despite several authors pointing out the need for randomised controlled trials (RCT) to delineate the contribution of CAT to optimising hypertension management (Osula et al., 2022), only one RCT was identified which directly examined the effect of CAT (Valgimigli et al., 2019).

Seven of the included studies reported adherence analyses carried out within clinical trials (Azizi et al., 2006; Ewen et al., 2015; Beaussier et al., 2015; Kario et al., 2023; de Jager et al., 2018;

Ceral et al., 2011), of which five were clinical trials of renal denervation (RDN). Of these studies relating to RDN, three carried out CAT as pre-specified analyses in the trial design (Azizi et al., 2006; Ewen et al., 2015; Johnson and Hennessy, 2019), and 2 as *post hoc* analyses (Kario et al., 2023; de Jager et al., 2018). In addition, three observational studies reported adherence rates in patients undergoing RDN, or screening for RDN (de Jager et al., 2018; Patel et al., 2016; Ceral et al., 2011). One systematic review and meta-analysis is included (Bourque et al., 2023). This aimed to establish the overall prevalence of nonadherence in resistant hypertension and compare direct (such as CAT) and indirect (such as pill counting) methods of adherence assessment. The authors found that in 42 studies including 71,353 patients, indirect methods reported less than half the rates of non-adherence compared to direct methods. One qualitative study used interviews with patients and providers and discussion with a community advisory panel to explore attitudes towards using CAT in the clinical management of hypertension (Schesing et al., 2020).

The economic impact of CAT is a growing concern in the literature and will be of interest to those managing and designing clinical services for hypertension. Two studies explored the cost-effectiveness of CAT, in view of the potential for CAT to (i) rationalise diagnostic decision-making and investigations, and (ii) improve BP control and thereby clinical outcomes for patients (Schoonhoven et al., 2018; Velasco et al., 2015).

Included populations

The majority of studies took place in hospital-based secondary or tertiary care settings, with just 3 reported from primary care. Some studies deployed CAT in a targeted way, according to specified clinical criteria such as aTRH, or at the discretion of the treating physician (Florczak et al., 2015; Groenland et al., 2022; Gupta et al., 2017a; Schäfer et al., 2021). Others applied CAT in a non-discriminatory manner, to all patients attending a given service. Ten studies explicitly stated that patients with secondary hypertension were excluded but the manner of screening for secondary hypertension was not always detailed. Eight studies only included participants who reported having taken their medicines as prescribed and excluded those who reported non-adherence (Osula et al., 2022; Ewen et al., 2015; Velasco et al., 2015; Avataneo et al., 2018; Strauch et al., 2013; Jung et al., 2013; Kocianova et al., 2017; Gupta et al., 2017b); this has important implications when considering the rates of false positive CAT results. Supplemental Table 2 shows the characteristics of participants in the included studies.

Research question 2: characteristics of CAT implementation

Methods of CAT

The characteristics of CAT used in the studies is summarised in Supplemental Table 1. Of the 45 included primary quantitative studies, 44 studies used mass spectrometry of either urine (22 studies), serum, dried blood spot, or a combination of samples, to directly detect AHDs or their metabolites. LC-MS/MS was most commonly used but gas chromatography-mass spectrometry and spectrofluorometry were also used (Schäfer et al., 2021; Brinker et al., 2014). Five studies used alternative methods, either alone or in conjunction with LC-MS/MS. These were chiefly assays of the renin-angiotensin-aldosterone axis, such as serial aldosterone to renin ratio measurement (Buffolo et al., 2021), serum Z-FHL/HHL (z-phenylalanine-histidine-leucine/hippuryl-histidine-leucine) ratio (Jones et al., 2017), or urine AcSDKP/creatinine ratio (Beaussier et al., 2015; Hamdidouche et al., 2017). These alternative methods may be useful to providers in situations where LC-MS/MS laboratory analysis is not available. In 27% (12/45) of studies, CAT was performed on more than one occasion, while for the remainder it was performed only once.

Interpretation and application of CAT results

There was considerable variation in the definition of adherence. Adherence was variously considered a dichotomous, categorical or continuous variable. Of the studies using LC-MS/MS, three studies considered a participant "fully" adherent if at least 80% of their prescribed AHDs were found to be present (de Jager et al., 2018; Lauder et al., 2021; Schmieder et al., 2016), while the others required 100% concordance to consider someone adherent. Similarly, while most studies differentiated between "partial" and "complete" non-adherence, ten studies considered a participant non-adherent if there was any discrepancy between their prescribed AHDs and the CAT results (Osula et al., 2022; Ewen et al., 2015; Florczak et al., 2015; Brinker et al., 2014; Ceral et al., 2011; Gupta et al., 2017b; Pelouch et al., 2019; Sheppard et al., 2022; Osman et al., 2023; Beernink et al., 2021). Some studies attempted to address the limitations of CAT by combining it with other methods of adherence testing, for example, Beaussier (2015) uses an adherence scoring system which combines two CAT modalities with self-report and pill counting (Curneen et al., 2022; Beaussier et al., 2015). Six (13%) studies described reporting back the results of CAT to patients, while the remainder either didn't provide participants with their results, or did not state whether participants received the results of the CAT. The majority of studies were descriptive cross-sectional studies which did not measure longer-term outcomes for patients. Just 4 studies (9%) reported on the impact that CAT had on clinical outcomes for patients (Velasco et al., 2015; Brinker et al., 2014; Gupta et al., 2017b; Valgimigli et al., 2019).

Critical appraisal results

We applied the 4 minimum reporting criteria from the EMERGE guidelines to the included studies published after the guidelines' publication in 2018 (2019 or later; 22 studies). Of the 22 studies, just 2 (9%) of them included the four minimum reporting criteria set out by the EMERGE guidelines (Groenland et al., 2022; Buffolo et al., 2021). One further study met three of the four criteria (Curneen et al., 2022), while the remaining 19 (86.4%) did not include any of the minimum reporting criteria. It should be noted that most papers did detail the performance of the CAT measure with regard to its validity and reliability but did not consider these factors in reference to the phase(s) of adherence studied. The judgements for each study are included in Supplemental Table 3.

The JBI tool for assessing the quality of cross-sectional studies was applied to 40 studies. For 32 (80%) of these studies, the inclusion criteria were clearly defined, and in 31 (77.5%) the subjects and setting were described in detail. 35 (87.5%) studies used objective, standard criteria when measuring the condition (BP in this case). Confounding variables were identified in 30 (75%) studies, and of these, 13 (43.3%) described a strategy for dealing with these confounding factors. The statistical analysis was considered to be appropriate for 33 (82.5%) of studies. The judgements for each study are presented in Supplemental Table 4.

For the only included RCT which directly assessed the effect of CAT, the Cochrane risk of bias (RoB) tool revealed some concerns, primarily around the unblinded intervention, and the fact that some patients developed an aversion to ambulatory blood pressure monitoring, necessitating the use of alternative BP measures. Moreover, this RCT encountered some difficulties in recruitment and study visits due to the COVID-19 pandemic (Valgimigli et al., 2019).

Discussion

The aim of this review was to identify studies using CAT in hypertension and to describe and critically evaluate how CAT is currently being used in the clinical management of hypertension. We found that the use of CAT in hypertension is gaining significant research interest. We found that research on CAT in hypertension is mostly published in high-income countries, focussed on treatment-resistant hypertension in secondary or specialist healthcare settings, and usually observational in design. Few studies measured the impact that performing CAT has on clinical outcomes for patients, such as BP control. This means that increasing calls for CAT to form part of routine clinical care in hypertension are underpinned by largely observational data. There are relatively few randomised trials to inform CAT use. One recent RCT, published outside the time limit for this review, found no effect of CAT on BP control or adherence, though it was underpowered (Peeters et al., 2024). A number of challenges have been demonstrated with conducting RCTs in the area of adherence (Muntner and Tanner, 2024). The variability in BP control and adherence over time impedes the identification of patients suitable for recruitment. Patients most challenged by adherence may be less likely to be included in trials because of non-attendance, low literacy, low motivation, language barriers, or other psychosocial challenges. Hawthorne effects may influence medication-taking behaviour (Peeters et al., 2023). Recruitment into some recent trials was moreover negatively impacted by restrictions during the COVID-19 pandemic (Halvorsen et al., 2024; Peeters et al., 2024).

The review also identified that CAT methods are primarily based on mass spectrometry, with considerable variability in how the results are interpreted and used. For example,. there is no clear or accepted classification of adherence by CAT, complicating attempts to compare studies. Some studies consider a participant adherent only if there is 100% concordance between their prescribed and detected AHDs, and consider all other results to represent nonadherence, while others differentiate between categories such as "partial" and "complete" nonadherence, though the thresholds for these categories vary. Such discrepancies are a significant barrier to the development of a cumulative evidence base.

Historically, adherence of 80%, adapted from earlier studies based on pill counts and Medication Event Monitoring Systems or MEMS, has been accepted as an acceptable level of adherence, and correlates with cardiovascular outcomes (Valgimigli et al., 2019; Bansilal et al., 2016). Some of the studies in this review have applied this threshold to CAT. However, the validity of this approach with a point-in-time assay such as LC-MS/MS of serum or urine, is questionable. For example, a patient prescribed 4 AHDs who omits their diuretic on a day they have to travel to their hospital appointment, would have an adherence rate of 75% and be considered non-adherent. Labelling such a participant as "nonadherent" (as compared with "partially adherent") may obscure the distinction between "perfect" and suboptimal adherence patterns and their causes and origins, and may impede the ability of clinicians to interpret these results. Indeed, this case example could represent a patient who is fully committed to their hypertension regimen and engaged with appropriate self-management. Omitting the diuretic dose in this instance can be classified as the kind of careful self-regulation that might be required to attend a clinical appointment, particularly for an older person with mobility limitations. Without some qualitative and contextual patient history the CAT result alone may provide a misleading clinical picture of how medicines are being used.

Few studies reported according to a theoretical framework. The minimum reporting criteria set out in the EMERGE guideline are not commonly adopted in clinical research on this topic. This guideline suggests that researchers define phases of adherence clearly including initiation (when the patient takes the first dose of a prescribed medication), implementation (the extent to which a patient's actual dosing corresponds to the prescribed regimen), persistence (the length of time between initiation and the last dose) and discontinuation (the end of therapy, after a last dose is taken and no more doses are taken thereafter without a prescriber's order) (De Geest et al., 2018). It is not clear whether authors are unaware of this guideline or choose not to refer to it for another reason. Recognising the potential for adherence to confound results in blood pressure trials, the Non-adherence Academic Research Consortium within the European Society of Cardiology have produced a consensus report providing a framework for reporting, interpreting and analysing medication non-adherence in cardiovascular clinical trials (Valgimigli et al., 2019). This is particularly relevant for trials of invasive and irreversible interventions such as RDN, and is reflected in the number of studies of RDN included in this review.

There remains considerable variation in terminology used in this topic. Articles published as recently as 2023 use the term "compliance" for medication adherence (Kustovs et al., 2023). A lack of standardised terminology may hinder effective literature searches, making it difficult to compare studies, aggregate data, and draw conclusions. Only one of the included papers used the term "chemical adherence testing" (Osula et al., 2022). Other terms used include biochemical adherence testing, therapeutic drug monitoring, drug screening, drug assays, drug measurement, compliance testing, and many others. The lack of consensus around terminology, definitions and methods may obscure the scope and findings of

research, and is an added challenge to evidence synthesis in this area (Wunder et al., 2019).

There is some evidence that CAT itself improves adherence and BP control, regardless of the CAT result (Gupta et al., 2017b), however the quality of this supportive evidence is currently limited to observational evidence and some preliminary RCTs are beginning to appear (Halvorsen et al., 2024; Peeters et al., 2024; Morrissey et al., 2023). CAT may provide a useful impetus to consultations around medication adherence. When reported, communicating CAT results to patients was found to improve blood pressure control (Gupta et al., 2017b). Despite this, few of the included studies indicated that CAT results were communicated to patients or participants. While it is possible that such feedback occurred as part of clinical practice without being reported in the published research, the impact and optimum manner of such feedback is of crucial importance and requires further elucidation, given the concerns about the potential for CAT to negatively impact the patient-physician relationship (Schesing et al., 2020). Concerns have been raised about the ethicality of CAT, which is problematic if CAT is not introduced in a transparent and sensitive manner, with verbal informed consent (Lane et al., 2022).

Most studies measured adherence at a single point in time. This has valuable diagnostic utility if the clinician's aim is to identify treatment-resistant hypertension, determine whether screening for secondary causes of hypertension is necessary, or to determine a patient' suitability for specialised treatments such as RDN. However, the correlation between point-in-time CAT and longer-term medication adherence patterns remains unclear (Wunder et al., 2019). The potential need for ongoing chemical adherence monitoring, as part of an effort to optimise long-term management and cardiovascular risk reduction, must be considered. With this in mind, the demonstrated utility of CAT in diverse healthcare settings, including primary care and not just in specialised centres, is a welcome development, however appropriate cost-effectiveness evaluations are required to determine whether the resources required to implement CAT are justified.

Limitations and methodological considerations

The strengths of this study include the broad and inclusive search strategy, the number of records reviewed and the rigorous screening and review process. However, we excluded the grey literature such as published abstracts without a full-text manuscript; this could have captured additional studies and may have provided evidence of novel approaches to CAT implementation in hypertension. Our included studies were limited to the English language. Initial screening of title and abstracts did not require decisions by two reviewers but all decisions in the full text screening and quality appraisal were confirmed by a pair of reviewers. Conflicts and uncertainties were resolved through discussion until consensus was reached. This team-based approach to evidence synthesis with reviewers and information retrieval specialists from diverse academic and clinical backgrounds helped to limit the biases that can affect evidence synthesis (Johnson and Hennessy, 2019).

Conclusion

The current body of evidence demonstrates considerable variability in the approach to implementing CAT for hypertension management in clinical practice, and a paucity of randomised controlled trials to evaluate its impact. Future research could (i) adopt a cohesive theoretical framework including clear operational definitions to standardise the approach to this important topic; and (ii) further explore the impact of CAT on clinical outcomes using RCTs.

Author contributions

LR: Conceptualization, Data curation, Formal Analysis, Investigation, Project administration, Writing–original draft, Writing–review and editing. JC: Data curation, Writing–original draft, Writing–review and editing. MD: Conceptualization, Supervision, Writing–original draft, Writing–review and editing. GM: Conceptualization, Formal Analysis, Methodology, Supervision, Writing–original draft, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1452464/full#supplementary-material

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Variation in adherence measures as a function of calculation methods

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Aim: We aim to compare different operational definitions of medication adherence as well as examine the within-patient variability among these measures among patients treated for multiple comorbid conditions.

Methods: Electronically monitored adherence data from a study on comorbid conditions were examined using three different calculation methods. DAILY adherence calculated the number of administrations divided by the number prescribed, without considering inter-dose interval. TIMING used predefined inter-dose intervals. Measures were aggregated to six 30-day periods. A PILLCOUNT approach counted the total administrations divided by the expected number in each 30-day period. Within-patient variability was computed based on DAILY and TIMING results for each 30-day period.

Results: Results varied by adherence calculation method. PILLCOUNT demonstrated the largest adherence rates (89%–92%); DAILY rates were lower (79%–85%); and TIMING was the lowest (62%–68%) over the 6-month period. TIMING within-patient variability (29%–35%) was larger than DAILY (20%–25%).

Discussion: Differences among the three methods confirm the importance of the adherence definition. TIMING may underestimate medicinal effects because patients may take medication as instructed (e.g., with meals) rather than at fixed intervals. PILLCOUNT may overestimate adherence by not accounting for inconsistent use. DAILY may best provide daily estimates of correct administration. Higher variability for TIMING may indicate patients are more likely to vary time between doses. Adherence calculation methods are important in interpreting results. Variability measures provide a more complete picture of adherence and may raise the likelihood of effects on biological outcomes. We propose studies of adherence include calculation method in the definition of adherence.

KEYWORDS

adherence, electronic monitoring, operational definition, calculation method, within patient variability

1 Introduction

Adherence to prescribed medication has been intensively studied since the late 1960s. Reviews consistently find wide ranges of adherence rates across populations. In 1966, Milton Davis, a medical sociologist, reported that a literature review indicated 15%–93% of patients failed to adhere to medical prescriptions (Davis, 1966). Since that time studies continue to show wide ranges of adherence to medications. In 2024, Gaujoux-Viala et al. reported adherence among persons with rheumatoid arthritis ranged from 30% to 80%

(Gaujoux-Viala et al., 2024). Dugunchi et al. (2024) reported non-adherence in coronary artery disease ranged from 33% to 55% (Dugunchi et al., 2024). Using claims and EHR data, Finlayson et al. (2024) reported variations in adherence across medications for persons with diabetes ranging from 52.4% for combination medications to 73.7% for amylin analogs, suggesting one source of variability may be the type of medication (Finlayson et al., 2024). Time may be another factor. In a longitudinal study of adherence following a myocardial infarction, just 29% of patients were adherent for the full year of the study while the average adherence for drug ranged from 62% to 67%, suggesting significant variability within individual patients (Pietrzykowski et al., 2020).

One issue in finding a broad range in adherence is the method of measurement that is used in studies. Davis himself utilized physician questionnaires to determine patient adherence. A study by Roth & Caron (1978) found that physician estimates tended to be inaccurate and that patients were highly variable over time in their medication taking as well as inaccurate in their estimates when compared with medication bottle counts (Roth and Caron, 1978). Since that time numerous studies have reported inconsistencies between adherence reports from differing measures. For example, Alili et al. reported the median adherence overestimate of self-reported adherence was 17% compared with electronically monitored adherence (Alili et al., 2016). In general, these studies have shown higher self-reported adherence rates when compared with objective measures, including medication monitors, pharmacy refills, pill counts, and visual analog scales (Atkinson et al., 2016). Monnette et al. reported a range of −66.3 to 61.5 difference between two self-report and monitoring devices (Monnette et al., 2018). Indeed, a review of self-report measures among cardiovascular populations found none of the existing PROMs (patient reported outcome measures) were recommended for use based upon measurement properties (Oliveira et al., 2023). Further, the ability of measures to detect clinical changes varies, as evidenced by a study by Dunbar-Jacob, et al. which found that electronic monitors and only the Shea, of multiple self-report assessments, predicted cholesterol lowering from use of statins (Dunbar-Jacob et al., 2013). Subsequent investigation by Dunbar-Jacob & Rohay indicated that self-report and electronic assessment (Medication Event Monitoring System [MEMS]) identified different and independent predictors of adherence among individuals assessed at the same time for the same drug (Dunbar-Jacob and Rohay, 2016). Overall adequate psychometric testing of adherence measures is poor, but where conducted are found to be low in sensitivity and specificity (Konstantinou et al., 2022).

Underlying various methods of measuring adherence are the variety of concepts and definitions used in defining adherence as well as the variety of cut points utilized in defining non-adherence or acceptable adherence. Thus, measures may address such issues as the number of pharmacy refills within a specific time period, the patient estimate of how frequently they take their medication as prescribed, the electronic record of accessing a medication, the count of medications missing from a bottle over a specified duration of time, the patient report of their beliefs and/or confidence in taking their medication, the time from onset of medication taking to stopping, each of which may be operationally defined in a different manner. Aremu et al. note that medication adherence can be defined as "the act or extent of conforming to a provider recommendation/prescription based on timing, dosage, and frequency of medication use … (and) as a ratio of the number of drug doses taken to the number of doses prescribed over a given period" (Aremu et al., 2022). Few studies provide such a concise definition, if any definition is provided at all. Shah, Touchette, & Marrs (2023) provide a detailed review of these variations. Each of these methods is likely to yield differing estimates of adherence (Shah et al., 2023).

Many of these methods and definitions do not adhere to the commonly accepted definition of adherence suggested by Haynes in 1979 (Haynes, 1979) and modified by the WHO in 2003 to include "the extent to which a person's behavior, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider" (Sabate, 2003). Further complicating the problems contributing to variability in estimates of levels of adherence is the variability in defining the threshold for satisfactory adherence. A systematic review by Baumgartner et al. revealed the highly varied methods of calculating adherence precluded the possibility of identifying a threshold level for good (clinically effective) adherence (Baumgartner et al., 2018).

These variations in adherence assessments lead to significant challenges in the development of systematic reviews to identify effective interventions as well as predictors or factors associated with adherence. It is the aim of this study to demonstrate the effect of different operational definitions of medication adherence on adherence findings and to examine the within person variability, relatively unexamined, in adherence across measures among patients with co-morbid type 2 diabetes, hypertension, and hyperlipidemia.

2 Methods

Data from the Diabetes Comorbidity study (NIDDK R01 DK59048) designed to improve medication adherence among patients with diabetes were examined to determine the effect that adherence calculation method has on the interpretation of results. Participants in the study were being treated for three chronic conditions–diabetes, hypertension, and hypercholesterolemia. This report focuses on adherence to then diabetes and hypertension medications these participants were prescribed. Medication adherence was monitored for one medication for each of the three conditions using the MEMS (Haberer and Gellman, 2004; Aardex). The MEMS system incorporates a microchip in the pill bottle cap that recorded the date and time that the cap was removed and replaced on the bottle. This recording served as a presumptive medication taking event. Participants were randomized to one of three treatment conditions – (Intervention, Intervention plus maintenance, and Usual Care). Participants completed assessments at baseline, 6 months, and 12 months. The MEMS system was used continuously during the baseline period and for the 12-month follow-up period. To evaluate just the effect of calculation method and not effects due to the intervention, only those participants randomized to usual care were considered in the analyses. Data were divided into six 30-day intervals and MEMS data were used to create six monthly sets of computations.

Additionally, only participants on once-per-day, twice-per-day, or three-per-day regimens were included.

Electronically monitored adherence was calculated using three different methods. The first method examined was similar to a pill count (PILLCOUNT) in which the number of administrations observed in the 30 days interval was divided by the number expected regardless of when they occurred. Next, we examined the average daily adherence (DAILY). DAILY was calculated based on the number of administrations observed on a given day divided by the number prescribed. However, the inter-dose interval was not considered. DAILY was then summed and divided by the total days of observation for an overall adherence rate. The final method (TIMING) used predefined inter-dose intervals in determining the DAILY measure to account for both missed doses and consecutive doses with relatively short inter-dosing intervals (e.g., <2 h).

In all cases, we imposed a behavioral penalty for "over adherence" by "folding" the adherence measure–for example, someone on a twice per day regimen who had 3 events recorded would have an initial adherence rating of 150%. However, they would be penalized for the amount over 100% - i.e., 50% - for a final adherence measure of 50% (100%–50%). For PILLCOUNT this was done on the monthly measure. For DAILY and TIMING adherence this was done on the DAILY measure. The DAILY and TIMING adherence measures were then aggregated into six 30-day intervals by calculating the average adherence rate over the 30 days. Additionally, we assessed within-patient variability by calculating each participant's monthly standard deviation for their DAILY and TIMING adherence measures.

Self-reported adherence, based on the Morisky 4-item Scale (MMAS) (Krapek et al., 2004; Zillich et al., 2005) and the response to the single question *How much of the time do you follow the instructions about when and how much of your medication you should take* at 6 months was also examined.

Analyses were completed using MEMS adherence ratings for both diabetes and hypertension medications. To assess the impact of computational method on health outcome, electronically monitored diabetes adherence rates were examined by level of HBA1c control - good control defined as HBA1c less than or equal to 7; at risk defined as HBA1c between 7 and 9; and poor control defined as HBA1c greater than or equal to 9 (NCQAa). Similarly, electronically monitored hypertension adherence rates were examined by level of blood pressure control - good control defined as systolic blood pressure less than or equal to 120 and diastolic blood pressure less than or equal to 80; at risk systolic blood pressure between 120 and 140 or diastolic blood pressure between 80 and 90; and poor control defined as systolic blood pressure greater than 140 or diastolic blood pressure greater than 90 (NCQAb). Descriptive statistics, including means, standard deviations, and confidence intervals for adherence measures, and frequency counts for categorial variables were used. Computations and analyses were conducted using SAS software v9.4 (SAS Software, 2023).

3 Results

Sixty-eight participants randomized to the usual care group from the Diabetes Comorbidity Study provided MEMS adherence data for both their diabetes and hypertension medications. Participants were diagnosed with diabetes on average 10.7 years prior to the study and were diagnosed with hypertension on average 13.4 years prior to the study. These participants were also assessed for disease control using HBA1c for diabetes and blood pressure for hypertension at baseline and 6 months. They were predominately female (59%) and had mean age of 63.9 (SD = 10.6). Of the 68 participants 59 provided HBA1c data at 6 months. Of these, 11 (19%) were in good diabetic control. Fifty participants provided blood pressure data at 6 months. Of these, 12 (24%) were in good hypertensive control.

Average electronic adherence measures varied by adherence calculation method (see Table 1). Diabetes adherence calculated using the PILLCOUNT method demonstrated the largest adherence rates, averaging 91.2% (SD = 9.9%) and ranging from 94% to 98% over the 6-month periods. DAILY adherence rates were lower, averaging 83.3% (SD = 17.0%) and ranging from 76% to 80%. TIMING was the lowest, averaging 64.7% (SD = 21.6%) and ranging from 59% to 64% over the 6-month period.

The diabetes adherence rates for each computational method were relatively stable over the 6 months (see Figure 1A). PILLCOUNT adherence rates were approximately 90% in each of the 6 months while DAILY adherence rates averaged about 7 percentage point lower at approximately 83%. TIMING was significantly lower than both, at about 65% over the 6 months.

For comparison, self-report adherence based on the MMAS (4-item) was 85% at 6 months. Furthermore, 74% of the participants reported that they usually followed the instructions for their prescribed medication.

Within-participant variability for diabetes medication adherence was larger for TIMING, averaging 32% (range 29%–35%) while DAILY averaged 21% (range 20%–25%). TIMING variability declined slightly by about 0.9% per month over the 6 months from 34.7% to 31.5%. DAILY variability was more stable, declining about 0.6% per month from 23.4% to 20.5%.

Results were comparable when examining adherence to hypertension medications. Average hypertension medication electronic adherence measures varied by adherence calculation method. Adherence calculated using the PILLCOUNT method demonstrated the largest adherence rates, averaging 95.1% (SD = 6.8%) and ranging from 93% to 98% over the 6-month periods. DAILY adherence rates were lower, averaging 84.8% (SD = 15.8%) and ranging from 82% to 88%. TIMING was the lowest, averaging 71.7% (SD = 21.4%) and ranging from 67% to 77% over the 6-month period.

The hypertension medication adherence rates for each computational method were relatively stable over the 6 months (see Figure 1B). PILLCOUNT adherence rates were approximately 95% in each of the 6 months while DAILY adherence rates averaged about 10 percentage points lower at approximately 85%. TIMING was significantly lower than both, at about 72% over the 6 months.

Within-participant variability for hypertension medication adherence was larger for TIMING, averaging 33% (range 29%–39%) while DAILY averaged 24% (range 21%–27%). TIMING variability declined slightly by about 1.1% per month over the 6 months from 38.8% (Month 2) to 28.7%. DAILY variability was more stable, declining about 0.1% per month from 22.9% to 21.0%.

TABLE 1 Adherence rates by computational method and disease outcome.

DIABETES									
Month	PILLCOUNT			DAILY			TIMING		
	Good control	At risk	Poor control	Good control	At risk	Poor control	Good control	At risk	Poor control
1	91.6%	93.9%	92.2%	83.6%	86.1%	88.6%	66.3%	68.7%	60.3%
2	88.1%	92.1%	91.7%	80.5%	88.5%	82.8%	66.4%	63.3%	58.8%
3	89.3%	90.0%	88.4%	82.9%	74.8%	80.8%	67.3%	60.1%	53.2%
4	94.1%	92.9%	91.3%	83.6%	83.8%	86.5%	65.1%	67.2%	57.9%
5	93.0%	90.1%	91.7%	87.0%	79.1%	87.9%	73.4%	64.2%	64.3%
6	92.0%	92.3%	89.8%	85.8%	79.1%	86.1%	68.1%	63.7%	57.5%
HYPERTENSION									
1	96.5%	96.0%	96.4%	91.1%	86.1%	93.2%	80.9%	75.4%	83.0%
2	96.3%	97.5%	91.3%	93.6%	88.5%	81.5%	66.8%	70.1%	62.8%
3	97.4%	97.4%	95.0%	89.8%	74.8%	80.0%	74.9%	67.9%	67.7%
4	97.2%	99.3%	96.2%	90.4%	83.8%	87.0%	74.2%	68.3%	77.9%
5	96.6%	95.9%	96.3%	91.3%	79.1%	79.5%	75.4%	73.0%	73.0%
6	97.9%	98.3%	97.3%	94.4%	79.1%	81.5%	77.1%	72.9%	74.8%

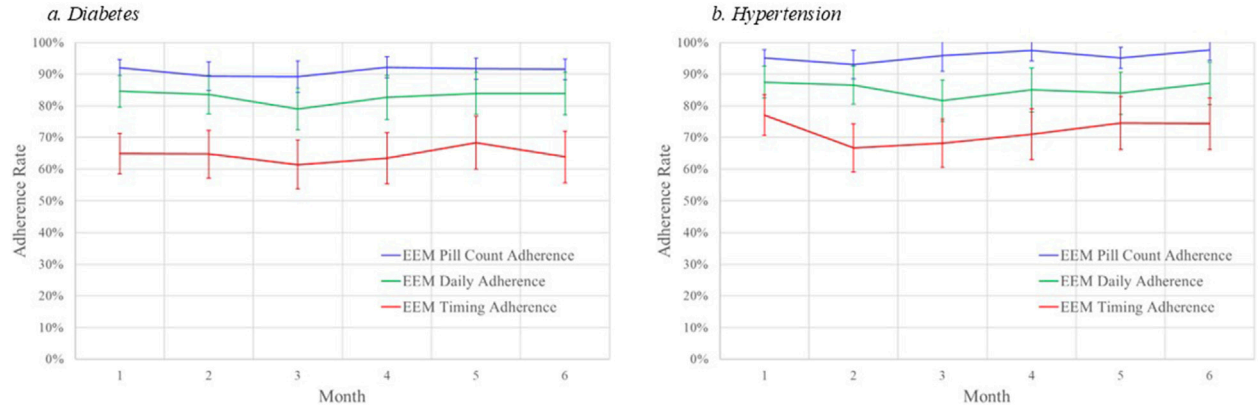

FIGURE 1
Monthly adherence rates by computational method and disease. **(A)** diabetes. **(B)** hypertension.

We also examined level of disease control by adherence computational method. Figure 2A displays the adherence rates by PILLCOUNT, DAILY, and TIMING for participants in good control, at risk, and in poor control of their diabetes based on level of HBA1c at 6 months. Figure 2B displays the adherence rates by PILLCOUNT, DAILY, and TIMING for participants in good control, at risk, and in poor control of their hypertension based on levels of systolic and diastolic blood pressure at 6 months.

For diabetes, PILLCOUNT did not discriminate between disease control among the participants, with adherence rates around 90% across the three HBA1c outcome groups. The DAILY adherence computational method displayed some discrimination among the HBA1c groups. Lower adherence rates were observed for the DAILY computational method for those at risk in Month 5 and Month 6. More pronounced differences were observed for the TIMING computation method over all 6 months, with participants in poor control of HBA1c demonstrating consistently lower adherence rates.

For hypertension, again PILLCOUNT did not discriminate between disease control among the participants, with adherence rates around 95% across the three blood pressure outcome groups. The DAILY adherence computational method displayed some discrimination among the blood pressure groups. Lower adherence rates were observed for the DAILY computational method for those at risk and in poor control over the 6-month

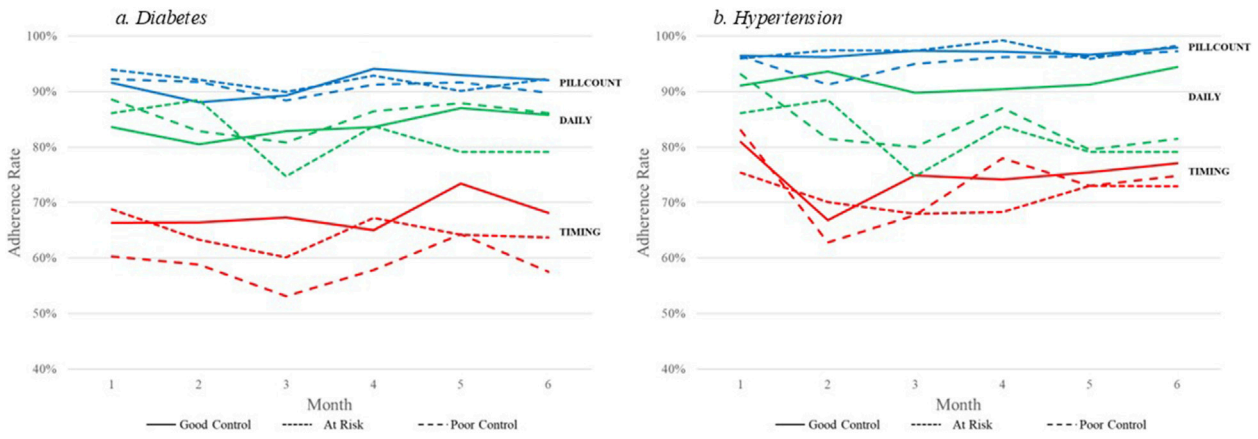

FIGURE 2
Electronic medication adherence by disease outcome computational method. **(A)** diabetes. **(B)** hypertension.

TABLE 2 Area under the curve, sensitivity and specificity by calculation method.

	Diabetes				Hypertension			
Method	N	AUC	Sensitivity	Specificity	N	AUC	Sensitivity	Specificity
Timing	46	0.63	0.80	0.61	41	0.56	0.40	0.71
Daily	46	0.53	0.50	0.72	41	0.65	0.60	0.65
Pill Count	46	0.54	0.60	0.61	41	0.55	0.36	0.88
Variability								
Timing	50	0.61	0.64	0.62	46	0.55	0.60	0.50
Daily	50	0.49	0.45	0.64	46	0.70	0.80	0.56

period. Only minor differences were observed for the TIMING computation method over the 6 months.

For diabetes, adherence levels were comparable within calculation method, with PILLCOUNT demonstrating the largest adherence rates, followed by DAILY, and then TIMING. To identify differences in the predictive ability of the methods, we compared the poor control group (HBA1c ≥ 9) to those not in poor control (HBA1c < 9). We conducted a Receiver Operating Characteristic (ROC) analysis with adherence levels at 3 months used to evaluate the sensitivity and specificity (See Table 2) of calculation method to predict diabetes control. The TIMING method performed best for predicting poor control (Area Under the Curve [AUC] = 0.63) with a sensitivity of 0.80 and specificity of 0.61. DAILY and PILLCOUNT did not perform as well with AUCs around 50% (0.53 and 0.54 respectively).

For hypertension, again adherence levels were comparable within calculation method, with PILLCOUNT demonstrating the largest adherence rates, followed by DAILY, and then TIMING. Again, ROC analyses were conducted to determine if differences in the predictive ability of the methods were present for hypertension. The poor control group (Systolic BP ≥ 140 or Diastolic BP ≥ 90) was compared to those not in poor control (Systolic BP < 140 and Diastolic BP < 90). For comparability we used adherence levels at 3 months to predict hypertension control. Here the TIMING method performed best for predicting poor control (AUC = 0.65) with a sensitivity of 0.60 and specificity of 0.65. TIMING and PILLCOUNT did not perform as well with AUCs around 50% (0.56 and 0.55 respectively).

Variability measures differed between the DAILY adherence method and the TIMING adherence method for both Diabetes adherence and Hypertension adherence, with the TIMING method demonstrating larger variability. ROC analyses using variability were similar to those using adherence measurements. For Diabetes, TIMING variability performed better (AUC = 0.61; Sensitivity = 0.64; Specificity = 0.62) than DAILY variability (AUC = 0.49; Sensitivity = 0.45; Specificity = 0.64). For hypertension, DAILY variability performed better (AUC = 0.70; Sensitivity = 0.80; Specificity = 0.56) than TIMING variability (AUC = 0.55; Sensitivity = 0.60; Specificity = 0.50; see Table 2).

4 Discussion

This study is unique in the process of examining assessment of adherence. The same subjects with the same diagnoses were assessed over the same time period using the same measurement strategy, the MEMs electronic monitor of adherence, to determine the degree of adherence to their medication for co-occurring type 2 diabetes and

hypertension. For each subject, adherence was calculated in three ways, the overall percent of prescribed medication taken (PILLCOUNT), the percent of days in which the medication was taken as prescribed (DAILY), and the percent of doses taken within a window that maximized coverage by the medications (TIMING). This simple act of altering the method of calculation resulted in differences in the reported levels of adherence. The differences were substantial. For example, the average adherence calculated for the diabetes medication was 90% (PILLCOUNT), 83% (DAILY), and 65% (TIMING). The average adherence calculated for the hypertension medication was 95% (PILLCOUNT), 85% (DAILY), and 72% (TIMING). The self-report measures, which asked participants to consider both medications, yielded 6 month estimates of 85% for the MMAS-4 and 74% for the question regarding the amount of time the participant took the medications as prescribed. Thus, it is probable that much of the wide variation seen in reported medication adherence in the literature may be due to the method of calculating adherence, the potential lack of precision in self-reported measures due a small number of possible adherence rates, as well as the measurement strategy, utilized in studies.

The importance of adherence is in its role in leading to good clinical outcomes. Thus, it is important in medication efficacy studies (are the results due to the degree of adherence or to the level of efficacy of the medication), in studies designed to improve clinical outcomes, as well as in clinical practice to obtain the best outcomes for each patient. In each of these cases, the detection of poor adherence is important. Once again, this study showed that within a measurement strategy the method of calculating adherence yielded varying levels of sensitivity and specificity in the detection of good or poor control. For the diabetes medication, sensitivity was 0.80 for TIMING, 0.50 for DAILY, and 0.60 for PILLCOUNT and for hypertensive medication was 0.40 for TIMING, 0.60 for DAILY, and 0.36 for PILLCOUNT. Thus, the ability of adherence values to identify those with poor control also varied by calculation methods. The ability of adherence values to identify those with good clinical control also varied. Specificity in detecting good control in diabetes was 0.61 for TIMING, 0.72 for DAILY, and 0.61 for PILLCOUNT while in hypertension it was 0.71 for TIMING, 0.65 for DAILY, and 0.88 for PILLCOUNT. Thus, the relationship between measured adherence and disease control varied by method of calculation of adherence.

These data suggest that calculation methods within measures are important in the interpretation of studies and individual cases using adherence data to account for level of medication taking. Variability measures also provide a more complete picture of adherence and may raise the likelihood of effects on biological outcomes. Within participant variability was able to be determined within the DAILY and TIMING methods of calculation. For the diabetes medication the average variability was 32% for TIMING and 21% for DAILY. For the hypertension medication the average variability was 33% for TIMING and 24% for DAILY. Thus, there was considerable variability detected in the taking schedule for medication using both TIMING and daily estimates. Once again, sensitivity and specificity of the variability measures varied by calculation method. For diabetes, sensitivity for TIMING was 0.64 and for daily was 0.45 while for hypertension it was 0.60 for TIMING and 0.80 for daily. Specificity for diabetes was 0.62 for TIMING and 0.64 for daily while for hypertension it was 0.50 for TIMING and 0.56 for daily.

Results generated by the different computational methods impact the interpretation of results. While adherence rates were relatively stable, regardless of computational methods, the method used did impact how the level of adherence would be gauged with more complex computational methods resulting in lower adherence rates. The relationship between computational method and disease differed between diabetes and hypertension, even though this was the same person during the same time period taking both drugs. When examining disease outcomes, in this case HBA1c control, little difference was noted among those with good control (HBA1c < 7, at risk (HBA1c between 7 and 9), and those with poor control (HBA1c > 9) based on PILLCOUNT and DAILY calculations. However, when TIMING was incorporated, those in poor control demonstrated lower adherence rates. However, it should be noted that the participants in this study took different diabetes medications, but the sample size precluded medication specific analyses.

Not only do the different operational definitions reflect differences in adherence but also differences in the identified predictors of adherence. Previous work by Dunbar-Jacob & Rohay identified different and independent predictors of higher adherence based on self-report (MMAS) and electronic assessment (MEMS) measures among individuals assessed at the same time for the same drug (Dunbar-Jacob and Rohay, 2016). The chosen method of calculation may vary dependent upon the interest of the investigator or clinician as well as characteristics of the medication and the disease. For example, is the investigator interested in a medication with a long half-life with little effect of variability on efficacy or on a medication with a shorter half-life leading to an effect of variability in taking patterns on efficacy? This study suggests that different information may be gleaned from the different calculation methods. Further there is some additional support for the variation in concordance between measurement methods dependent upon the calculation method. In this study, self-report measures in hypertension appeared to be most closely aligned with 6-month average daily (MMAS-4), 85% and 85% respectively, and TIMING (frequency of adherence question), 72% and 74% respectively, while in diabetes the alignment appeared to be strongest between daily and the MMAS-4 (83% and 85%) and the TIMING and single question (65% and 74%). On the other hand, the MMAS-4 of 85% does not compare well with 6-month TIMING adherence (diabetes – 65%; hypertension – 72%) nor does the single question of 72% compare well with the 6-month PILLCOUNT (90% & 95%) or the 6-month DAILY (83% & 85%).

Thus, the estimation of participant or patient adherence is complex. There is significant variability in estimates between measures and between calculation methods within measures. It is important to understanding the meaning of adherence in any study as well as the conduct of systematic reviews that there is a complete description of the operational definition of adherence, including not only the measurement method but the method of calculation as well. Because the calculation method reveals different elements of the participant/patient's medication taking behavior, an understanding of the calculation and its meaning is important to the assessment of the clinical case and the design of remedial efforts as well. To properly characterize differences (i.e., a difference in the operational

definition of adherence v. Difference in interventions), we strongly recommend that studies of adherence provide a description of the calculation method utilized to estimate adherence along with the method of measurement used for assessment.

Data availability statement

The datasets presented in this article are not readily available because Data are available by request if they meet the requirements of the informed consent signed by each participant. Requests to access the datasets should be directed to dunbar@pitt.edu.

Ethics statement

The studies involving humans were approved by University of Pittsburgh Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JR: Conceptualization, Formal Analysis, Investigation, Methodology, Software, Writing–original draft, Writing–review and editing. JD-J: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing–original draft, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Medication non-adherence: reflecting on two decades since WHO adherence report and setting goals for the next twenty years

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Background: Non-adherence to medication remains a persistent and significant challenge, with profound implications for patient outcomes and the long-term sustainability of healthcare systems. Two decades ago, the World Health Organization (WHO) dedicated its seminal report to adherence to long-term therapies, catalysing notable changes that advanced both research and practice in medication adherence. The aim of this paper was to identify the most important progress made over the last 2 decades in medication adherence management and to initiate a discussion on future objectives, suggesting priority targets for the next 20 years.

Methods: This research used the WHO adherence model as a theoretical framework, categorizing adherence factors into five dimensions: health system, therapy, condition, patient-related, and socioeconomic. Ten international experts, five from Europe and five from the United States, were assigned to these dimensions and participated in structured online discussions. Initially, based on their desk reviews, experts identified significant achievements and future targets. They then ranked these items and provided feedback through several rounds, ensuring anonymity to minimize bias, ultimately reaching a consensus. This iterative process allowed for the creation of top-ten lists of past achievements and future targets for medication adherence management over the next 20 years.

Results: Analysis of the top-ranked achievements affirms that notable progress has been made in medication adherence research and practice over the past 20 years, with increased awareness and a surge in dedicated scientific publications. Despite these advancements, non-adherence remains a prevalent issue, underscoring the need for the ongoing implementation of innovative solutions identified in this work, such as novel digital health solutions. Interdisciplinary collaboration and a holistic understanding of patient behaviours and socio-economic factors are crucial.

Conclusion: While refraining from imposing a rigid "adherence Decalogue," we are confident that this overview of recent achievements and the curated selection of future targets may provide a useful foundation for further discussions aimed at advancing medication adherence management. Our results call for a paradigm shift, advocating the repositioning of medication adherence on national agendas and underscoring the necessity for an adherence-supportive ecosystem that extends beyond mere patient support.

KEYWORDS

medication adherence, drug therapy, innovation, digital health technologies, healthcare costs, patient education, patient outcomes, polypharmacy

Introduction

Non-adherence to medication seems to be the problem as old as medicine itself. In the 5th century B.C., in one of his treatises, Hippocrates, the "Father of Medicine," made a note: Keep a watch also on the faults of the patients, which often make them lie about the taking of things prescribed. For through not taking disagreeable drinks, purgative or other, they sometimes die. What they have done never results in a confession, but the blame is thrown upon the physician (Hippocrates, 2023).

No matter how difficult the non-adherent behaviour may be to understand, it remains highly prevalent even in the 21st century. Unfortunately, the consequences of medication non-adherence at the population level are severe. It is very difficult to estimate the costs associated with this problem, however, the available data are alarming. Non-adherence has been reported to generate €80–125 billions of potentially avoidable direct costs (such as hospitalizations and medication wastage) and indirect costs (including work productivity losses) in the European Union (European Commission/Medi-Voice, 2011). In 2016, the cumulative expense of non-adherence to prescription drugs reached approximately $529 billion in the U.S. (Watanabe et al., 2018), with additional costs per patient ranging from $5,271 to $52,341 (Cutler et al., 2018). Additionally, it is estimated to be associated to nearly 200,000 deaths annually in the European Union (European Commission/Medi-Voice, 2011) and 125,000 deaths per year in the U.S. (Kim et al., 2018).

What is even more important at the individual patient level, medication non-adherence creates a barrier that obscures the benefits of evidence-based medicine. As Robert B. Haynes, a pioneer in this field of research, sadly noted, "The full benefits of medications cannot be realised at currently achievable levels of adherence." (Haynes et al., 2002). If this situation persists, medication non-adherence will continue to pose one of the major obstacles to the advancement of medicine.

Two decades ago, the World Health Organization (WHO) released a seminal report on adherence to chronic treatments (Sabaté, 2003). Although it was not the first publication in the field, it played an unprecedented role. The report marked a significant leap forward in raising awareness about medication non-adherence beyond a limited circle of researchers. With this report, simplified yet memorable statistics entered the public domain: 50% of patients being non-adherent to long-term therapies. Consequently, the issue of non-adherence could no longer be overlooked, prompting a shift in public perception. It transformed non-adherence from being seen merely as a problem of personal loss faced by individual patients to population-based problem requiring a more comprehensive understanding of societal consequences. It also increased the awareness about the impact of medication non-adherence on healthcare systems, payers, and pharmaceutical companies, urging the widespread implementation of effective interventions to both prevent and solve this problem.

However, despite half a century of dedicated research and growing understanding among the stakeholders, medication adherence remains far from perfect. A recent review revealed a high level of non-adherence among multi-morbid patients, ranging from 44.1% to 76.5%, as reported by the studies included (Foley et al., 2021). Although an international research project on adherence funded by the European Commission over a decade ago provided comprehensive policy recommendations for promoting medication adherence in the EU (Ascertaining barriers for compliance), the progress has been slow. Despite the availability of numerous effective interventions capable of enhancing medication adherence, only few are applied in real-world settings and even fewer are reimbursed across Europe (Ágh et al., 2022). Unsurprisingly, a recent report by the Organisation for Economic Co-operation and Development (OECD) demonstrates that medication adherence is not at the top of national health agendas, and a majority of the European countries are neither monitoring adherence nor taking regular actions to improve it (Khan and Socha-Dietrich, 2018).

Does the slow progress in increasing medication adherence undermine the value of the WHO report and suggest that it was a futile initiative? Does this mean that no advancements have occurred in the field since its publication? In this paper, we aim

to assess the progress made over the last 2 decades and initiate a discussion on future objectives, suggesting priority targets for the next 20 years.

Methods

To provide a firm theoretical basis for this research, the framework of determinants of medication adherence proposed by the WHO was used. This framework groups the factors affecting adherence into five interacting dimensions: 1) health system; 2) therapy; 3) condition; 4) patient-related, and 5) socioeconomic factors (Sabaté, 2003).

Ten international adherence experts, representing various backgrounds (e.g., academia, industry, patient organizations), fields of activity (pharmacy, medicine, health services research), and geographical regions (Europe and the United States), were invited by two moderators (TA, PK) to participate in this study, and all of them agreed. Based on their expertise, each of them was assigned to one of the five dimensions of the WHO adherence model. The allocation was structured to include two experts, one from Europe and one from the U.S., who were asked to present the results of their desk reviews within a particular dimension. Remote discussions, facilitated by predesigned online questionnaires, were structured iteratively as described below to enable fair ranking and prioritization of the most appropriate items. To minimize potential bias, the experts worked independently and did not know the identities of the other participants by the fourth round.

In the first round, the experts were requested to describe the three most important achievements in medication adherence which took place within 20 years from publication of the WHO report, within the dimension of their particular expertise. They were also asked to define the three most important targets to be achieved within the same dimension in the next 20 years to come. In the second round, the two experts within each dimension were asked to rank all six achievement items provided for the past, and six targets for the future. In the third round, the experts were asked to comment on and approve the results of this ranking, being informed of a potential overlap between the items. In the fourth and the final round, moderators assisted experts in addressing any potential disputes and facilitated the process of reaching consensus on the entire set of items collected for both past achievements and future targets. As a result of this process, top-ten lists of past achievements and future targets were created, with two items for each of the five WHO model dimensions.

Results

Achievements over the last 20 years

The top-ranked achievement items provided by the experts for the last 2 decades indicate that a notable progress has been made in adherence research and practice during this period. Although the problem of non-adherence remains unsolved, there is an evident increase in general awareness, and research interest, reflected in a boost of dedicated scientific publications (Kardas et al., 2023). Consequently, viable solutions are being formulated, tested, and, albeit infrequently, implemented. Table 1 outlines these accomplishments, which are also briefly discussed below.

TABLE 1 Top-ranked achievements in medication adherence management over the last 20 years.

Social and economic dimension
• Health policies aimed at addressing economic barriers to medication adherence
• Implementation of Value-Based Healthcare and Outcomes-Based Payment Models linking financial remuneration directly to patient outcomes
Therapy dimension
• Simplifying medication regimens and enhancing the ease of therapy administration
• Guidance and frameworks to encourage monitoring, analysis, and reporting of adherence data in the development of new therapies
Patient dimension
• Integration of patient-reported outcome measures for medication adherence
• Growing interest in understanding patient-related reasons for medication non-adherence
Condition dimension
• Recognition of the disease-related issues contributing to decreased medication adherence over time
• Development of the whole-person care concept based on the collaboration between physicians, nurses and pharmacists, positively impacting medication adherence
Healthcare system dimension
• Shift towards placing the patient at the forefront of clinical decision-making for better adherence management
• Digital health technologies and mobile applications to improve medication adherence

Social and economic dimension

Health policies addressing economic barriers to medication adherence

Several countries have implemented health policies to address economic barriers to medication adherence. Wide introduction of generic drugs, enhancements in insurance coverage, and subsidies for essential medications have collectively worked to alleviate economic disparities, fostering a healthcare landscape where a broader population can access necessary treatments (Francois et al., 2023). These policy changes play a pivotal role in addressing structural barriers to adherence by facilitating access to medications. Following the implementation of the model of essential medicines list, introduced by the WHO and updated every 2 years, many governments, such as those in India and China, have focused their policies on rational use of medicines and access to more medications for a wider population (Kar et al., 2010), (Guan et al., 2011).

Value-based healthcare and outcomes-based payment models

The contemporary healthcare landscape has witnessed a paradigm shift from a traditional volume-based model to an

increasingly prevalent value-based approach, wherein the emphasis is placed on enhancing patient outcomes and overall wellbeing (Porter and Lee, 2013). The advent of value-based healthcare models marks a departure from conventional reimbursement structures by linking financial remuneration directly to patient outcomes. This innovative approach creates compelling economic incentives for healthcare providers to invest in interventions that specifically target and enhance medication adherence (Agarwal et al., 2018). Recognizing the pivotal role of adherence in achieving positive health outcomes, this economic policy paradigm encourages the strategic implementation of adherence management strategies such as Value-Based Insurance Designs (VBID) within certain health plans. Consequently, several U.S.-based health plans award prizes to providers when they achieve 80% or more adherence in their patients (Parekh et al., 2019).

Therapy dimension

Simplifying medication regimen and enhancing ease of administration

A significant progress has been made by the pharmaceutical industry in developing novel therapeutic administration in some disease areas. For example, the increased availability and use of insulin pumps and, more recently, digitally-enabled devices such as, e.g., auto-injectors have been observed (Berget et al., 2019). In other therapy areas, ease of administration has been addressed through the development of simplified treatment regimes. These include *inter alia* multi-compound pills, targeting either one disease (combination drugs) or several conditions (so-called polypills), to reduce pill burden (Castellano et al., 2022), once-daily therapies, to reduce the number of dosing occasions, used in disease areas such as anticoagulants, HIV, hypertension and diabetes, once-monthly therapies for osteoporosis, and long-action injectables to replace daily pills (e.g., combination of long-acting cabotegravir and rilpivirine allowing bimonthly injections for the treatment and prevention of HIV) (Bares and Scarsi, 2022).

Development of guidance and frameworks to prompt monitoring, analysing and reporting of adherence data in the development of new therapies

Since the 1980s, an estimated 20%–33% of all approved drugs have been dose-adjusted after market authorisation, and 60%–80% of those adjustments were dose reductions (Heerdink et al., 2002). Non-adherence in clinical trials is widespread and can lead to erroneous estimations of efficacy and safety, as well as emergence of drug resistance (Blaschke et al., 2012). The publication of guidance documents was aimed at addressing the problem (Mantila et al., 2022) (Eliasson et al., 2020). For example, the FDA acknowledged that good adherence increases the power of a study and has provided guidance on strategies to support and control adherence in clinical trials (US Food and Drug Administration, 2019). Similarly, the European Medicines Agency has provided guidance on using estimands framework for accounting for medication adherence in estimating treatment efficacy (European Medicines Agency, 2017). However, these guidance documents have not yet translated into appropriate measurement, analysis and reporting of adherence in clinical trials which risk the potential approval and reimbursement of, and ultimately adherence to, medicines with misguided efficacy and safety expectations.

Patient dimension

Measuring medication adherence with patient-reported outcomes measures (PROMs)

Dedicated PROMs have been developed to enable researchers and clinicians to use tailored medication adherence measures. Recent systematic review evaluated the evidence of as many as 121 different PROMs used to assess this issue in many different indications (Kwan et al., 2020). Although some of them do not meet all evidentiary criteria, PROMs represent a practical and cost-effective solution. These tools are straightforward to implement and could be easily integrated into routine clinical practice by nursing staff, pharmacists, or other healthcare professionals. This practical approach serves as an effective means of screening for non-adherence.

Integration of patient-reported outcome measures for medication adherence

There is also a growing interest in understanding patient-related factors contributing to medication non-adherence (Kvarnström et al., 2021), (Kardas et al., 2013). Consequently, various self-reported scales have been developed to identify the causes of non-adherence. Historically, adherence was often gauged based on pharmacy claims databases. Currently, however, the focus extends beyond simply knowing the rate of non-adherence. There is an increased interest in understanding the reasons behind it as this knowledge is crucial for developing and implementing appropriate interventions (Zekic et al., 2021). In fact, PROMs are the only measures that can capture individual reasons, both drivers and barriers, for adherence or non-adherence. Notably, several pharmaceutical companies and payers are now delving into the reasons behind patient non-adherence to medications, with the intention to proactively respond to them.

Condition dimension

Recognition of the disease-related issues contributing to decreased medication adherence

Over the last 20 years, the two major challenges concerned recognition of the disease-related issues contributing to lower drug adherence over time and increasing the awareness and knowledge on adherence among providers. Indeed, the ability of healthcare professionals to recognise poor adherence in several medical conditions was considered as relatively low and the same was true for their ability to intervene (Clyne et al., 2016). In the last 2 decades improvements have been made to recognise a lot of disease-specific parameters, such as duration of the disease, intensity of symptoms and multi-morbidities, and to integrate them into patient management. This has led to the conclusion that poor adherence is not limited to asymptomatic diseases such as hypertension or dyslipidaemia but is a global problem affecting

all patients with any disease, even those with highly symptomatic pathologies. One important step forward is the increased recognition of the role of comorbidities at all ages, but particularly in older adults, in whom cognitive deficits, which often remain undiagnosed, may play an important interfering role.

The concept of whole person care, embedded in collaboration among physicians, nurses, and pharmacists

Presently, there is a general movement to implement the concept of team-based care in clinical practice to support several aspects of patient management including medication adherence and persistence (Hopkins and Sinsky, 2022). Although this management model is still moderately implemented in many countries because of local regulations, it has been shown to contribute substantially to the improvement of the control of some diseases in other countries (Matsumoto et al., 2024), (Stephen et al., 2022). This approach is particularly effective for the long-term management of patients with complex medical conditions and a high pill burden (Onor et al., 2024). A recent analysis of studies conducted in low- and middle-income countries reveals that team-based care, coupled with education, single pill combinations, and reminders, proves more effective in supporting adherence and persistence than any single intervention (Ogungbe et al., 2021).

Healthcare system dimension

Shift towards placing the patient at the forefront of clinical decision-making

There has been a notable shift towards placing the patient at the forefront of clinical decision-making. Enhanced communication, trust-building and patient education are now recognized as pivotal components, with a growing emphasis on empowering patients to actively participate in their treatment management by shared decision-making (Fiorillo et al., 2020), (Deniz et al., 2021). Additionally, healthcare systems are increasingly recognising the significance of behavioural interventions and considering patients' preferences as integral factors in supporting medication adherence. This evolving approach reflects a comprehensive strategy which focuses not only on treatment but also an active involvement of patients, with consideration given to their values and preferences. Interestingly, one indirect consequence of this shift is the replacement of the previously used term "compliance" with "adherence" due to the paternalistic relationship between doctors and patients that the former term was often perceived to imply (Vrijens et al., 2012).

Digital health technologies and mobile applications to improve medication adherence

Technological advancements including digital health technologies have driven progress in medication adherence management. Mobile applications, wearable devices, and smart pill dispensers have transformed this domain by offering reminders, tracking medication usage, and providing real-time feedback to both patients and healthcare providers (Peng et al., 2020). These innovations empower patients, enhance communication between patients and healthcare providers, and ultimately improve medication adherence rates, as well as health outcomes. Recently, there has been an increasing trend where these technologies also incorporate "gamification" strategies to enhance patient engagement (Ghorbani et al., 2021). These strategies have not only been used in the clinical trial setting to measure medication use, but have also been tested and implemented in real-world practice, owing to their effectiveness.

Targets for the future

Despite all the accomplishments described above, non-adherence remains a highly prevalent problem. Therefore, it becomes obvious that better implementation of available guidance, as well as new ideas and innovative solutions are imperative in the years to come. The evolving landscape of healthcare, advancements in technology, and the dynamic nature of patient needs necessitate a continual re-evaluation and adaptation of strategies. As we move into the future, challenges such as emerging therapeutic modalities, evolving patient demographics, and further integration of digital health solutions underscore the need for a forward-looking approach.

Moreover, the complexities of modern healthcare systems demand interdisciplinary collaboration and a holistic understanding of patient behaviours, preferences, and socio-economic factors. This highlights the importance of fostering a culture of continuous innovation, where patients, researchers, clinicians, and healthcare stakeholders collectively contribute to the development of adaptive solutions. In fact, while the past 2 decades have seen remarkable strides in adherence research and practice, the journey toward enhancing patient outcomes through improved adherence is an ongoing and dynamic process. Embracing new ideas and solutions will be pivotal in navigating the complexities of healthcare delivery, ensuring that patients receive the best possible care tailored to their individual needs, and fostering a healthcare environment that is both responsive and resilient in the face of future challenges. Therefore, presented below are the results of the iterative selection of the ten most important targets for the next 20 years, also summarised in Table 2.

Social and economic dimension

Towards a comprehensive measure of medication adherence

The future landscape of medication adherence measurement necessitates an advanced approach that extends beyond the current standard measures, such as the Proportion of Days Covered (PDC), Medication Possession Ratio (MPR) or patient reports via dedicated PROMs tools (Rickles et al., 2003). While all these measures provide a quantifiable metric, there is a growing recognition that they fall short in capturing the complexity of medication adherence (Lam and Fresco, 2015). It is imperative to move beyond merely measuring the quantity of medication taken and delve into the qualitative impact on health. Future advancements in this field call for development and implementation of more robust measures - ones that not only reflect the "statistical" aspect of medication non-

TABLE 2 Top-ranked targets for medication adherence management over the next 20 years.

Social and economic dimension
• Implementation of comprehensive measures of medication adherence, establishing a stronger connection between adherence metrics and health outcomes
• Thorough examination of the financial implications of medication adherence
Therapy dimension
• Advancing the role of digital technology in improving adherence
• Appropriate management of adherence in the context of polypharmacy and multimorbidity
Patient dimension
• Provision of patient education to enhance their understanding of their illness and medications
• Incorporation of medication adherence as a standard measure in routine clinical practice
Condition dimension
• Implementation of new technologies to support adherence and persistence, directly targeting pathogenic mechanisms contributing to disease development
• Improved identification of patients at high risk of non-adherence in clinical practice
Healthcare system dimension
• Using artificial intelligence in medication adherence management
• Increased access to adherence-enhancing interventions through the expansion of reimbursement and insurance coverage

adherence but also incorporate behavioural, social, and patient-specific factors. Furthermore, the future of medication adherence research requires a stronger link between adherence metrics and health outcomes. By defining more comprehensive measures that integrate patient engagement, health literacy, and digital health technologies, coupled with a strong linkage to health outcomes, we can foster a patient-centred approach that goes beyond the limitations of current adherence metrics. This evolution holds great promise for the future as it may not only enhance adherence but also improve overall health outcomes for individuals managing chronic conditions.

Holistic Exploration of financial impact

The future of medication adherence necessitates a comprehensive examination of its financial implications, recognising the profound influence that cost-related factors can have on medication-taking behaviours among patients. Copayments and overall costs associated with prescribed medications can build substantial barriers to adherence, particularly in some healthcare systems. Current research underscores the negative impact of increased copayments on medication adherence and the benefit of no or low copayments, particularly among individuals with chronic conditions (Choudhry et al., 2014), (Schikowski et al., 2022). Therefore, understanding the intricate relationship between financial constraints and adherence is of paramount importance in developing strategies that reduce economic barriers for patients. Moreover, there is an imperative to determine the cost-effectiveness of interventions aimed at improving medication adherence. Evaluating the economic impact on both individual and societal levels is essential for crafting interventions that not only improve adherence but also generate substantial value for healthcare systems. By addressing the economic dimensions of adherence, we can advance strategies that promote affordability, enhance medication-taking behaviours, and contribute to the overall efficiency of healthcare delivery systems.

Therapy dimension

Advancing the role of digital technology in adherence management and personalised medicine

An important development over the next 20 years will be to engage patients with digital technology to integrate continuous monitoring of treatment adherence, clinical outcomes, and side effects. This will allow for personalised reassessment of treatment recommendations, and thus an opportunity to minimise adverse effects through titration and treatment optimisation. For example, digital inhalers have an integrated electronic module for recording, storing and communicating with a mobile application and dashboard inhaler usage data, which means that they can give patients and their physicians feedback on the patient's inhaler technique as well as their adherence (Kaplan et al., 2023). Additionally, more consideration should also be given to adherence to prescription digital therapeutics (PDTx), which are health software solutions intended to treat or alleviate a disease, disorder, condition, or injury by generating and delivering a medical intervention that has a demonstrable positive therapeutic impact on a patient's health. Several of them have already been approved in both Europe and the U.S. (Wang et al., 2023). However, in the case of PDTx, non-adherence is likely to be an issue, just as it is with traditional medicines.

Appropriate management of adherence in the context of polypharmacy and multimorbidity.

The prevalence of multimorbidity and related polypharmacy are on the rise, mostly due to ageing of the global society. Unfortunately, polypharmacy paves the way to non-adherence (Franchi et al., 2021). Therefore, in the next 20 years more attention should be paid to the management of multiple health conditions rather than single diseases. In parallel, a consensus should be reached on the measurement and optimisation of adherence in patients taking multiple medications. Progress in the measurement and support for adherence in persons with multimorbidity could significantly improve outcomes for individual patients and reduce costs for healthcare systems. It may also address health inequalities, since people of lower socio-economic status, those representing minority ethnic groups and patients with severe mental illnesses are more likely to be affected by multiple health conditions (Álvarez-Gálvez et al., 2023).

Patient dimension

Provision of patient education to enhance their understanding of their illness and medications

Patient having knowledge about their illness and medicines is one of the important patient-centred factors in medication adherence. At the same time, physicians and other healthcare providers claim that they do not have enough time to devote it to adherence support of their patients. Thus, pharmaceutical companies, health insurance and public health programs should be encouraged to become more innovative in providing patient education, enhancing overall health literacy and addressing misconceptions and concerns about illness and treatment. The current patient education methods such as brochures are not adequate. More resources should be spent to understand effective patient education strategies. To respond to adherence challenges successfully, it is crucial to harness advancements in behavioural sciences and health psychology. Exploring options like call centres, supported by pharmaceutical and health insurance companies, in medical, pharmacy, and nursing schools could be a proactive step to offer support to patients and enhance their understanding of medications. Notably, the World Health Organization (WHO) has recently released a dedicated guide on therapeutic patient education for policymakers, health professionals, and educational/training bodies (WHO).

Medication adherence should become one of the vital measures in routine clinical practice

To incorporate it seamlessly into intake procedures, nurses or physician assistants should systematically inquire about patients' adherence to each prescribed medication in non-judgemental way, recording all the information, including reasons for non-adherence, in the Electronic Medical Record (EMR). This detailed documentation can serve as a valuable resource for physicians to engage in meaningful discussions with patients regarding their medication regimen. Recognising it as a vital measure will help keep track of the adherence behaviour with chronic medications (Magid and Ho). As far as patient-related factors are concerned, this meticulous documentation stands as the primary method for monitoring and providing timely interventions, also ensuring a comprehensive approach to healthcare management.

Condition dimension

Implementation of new technologies to support adherence and persistence

Further development is now expected that could contribute to increasing adherence and persistence in several clinical conditions, acting directly on pathogenic mechanisms that contribute to the disease progress. This involves, for example, RNA-based therapies which are currently used in the treatment of dyslipidaemia, and are under development for hypertension and other diseases (Ren et al., 2020). It is hoped that these approaches will help to reduce practical barriers to adherence and persistence, allowing for drug administration once every 6 months or even once a year.

Improved detection of patients at high risk of non-adherence in clinical practice

Detection of patients at high risk of poor adherence and persistence is a major challenge in individuals with chronic health conditions. In recent years, new technologies have been developed to screen patients with chronic treatments for adherence. This includes, for example, the measurement of drug levels in blood or urine using LC-MS technologies, or the introduction of 'digital pills' equipped with ingestible microsensors (Browne et al., 2018). These approaches, which have some limitations, can be applied by research centres but are of limited use in clinical practice (Berra et al., 2016), (Peeters et al., 2024). Therefore, there is a clear need to develop new approaches that would enable physicians or healthcare professionals to detect patients at risk of non-adherence using simple but reliable methods. Notably, the same patient may exhibit different levels of adherence to various drugs, and at different time points throughout their journey (Schulz et al., 2016). Therefore, this approach should be applied to address each condition on a case-by-case basis.

Healthcare system dimension

Using artificial intelligence in medication adherence management

Artificial Intelligence will play a pivotal role in medication adherence management, enabling healthcare systems to anticipate adherence barriers and intervene proactively. AI-powered chatbots and virtual assistants may deliver timely reminders, provide medication education, and offer supportive counselling, thus improving patient engagement and adherence outcomes (Babel et al., 2021). Moreover, real-time monitoring through wearable sensors and other devices will enable continuous assessment of medication adherence and prompt AI-enhanced interventions when deviations occur, with the aim of improving medication management and health outcomes. With the progress of data science and the integration of vast amounts of data from different sources, such as socioeconomic data, patient baseline clinical characteristics, patient-reported perceptual and practical barriers to adherence, and prescribing and dispensing data, it will be possible to predict quite accurately the medication adherence trajectory for an individual and create dynamic intervention plans to improve medication adherence. However, it is important to acknowledge that although application of 'big data' along with machine learning and artificial intelligence holds great promise for identifying patients for which adherence-improving interventions are helpful (Kardas et al., 2020), there also exists a potential risk that these technologies will be wrongly used to limit access to medications and healthcare. Furthermore, there needs to be an evidence-based consideration of which predictor variables should be included in these algorithms so as not to introduce bias and to support equitable decision making. Therefore, in the coming decades, ethical use of these technologies will be important.

Increased access to adherence-enhancing interventions

It is also expected that healthcare systems will significantly increase access to adherence-enhancing interventions by

expanding reimbursement and insurance coverage. This improved access, ideally with reduced or no cost incurred by patients, will be pivotal in ensuring the use of these interventions and delivering comprehensive support to individuals (Kardas et al., 2022). Furthermore, telehealth and remote monitoring technologies will play a transformative role in broadening access to adherence-enhancing interventions beyond conventional healthcare settings. However, achieving equitable access to telehealth services and the necessary technology infrastructure will be paramount.

Conclusion

Results of our study affirm that the WHO adherence report, published 2 decades ago, initiated a cascade of important changes. They have notably influenced both the research and practice of supporting medication adherence. However, despite these strides, we are still confronted with the persistent challenge of non-adherence. Considering the inherent complexities of human behaviour and the intricate network of other factors contributing to non-adherence, this problem is expected to remain in the years to come.

The multifaceted nature of the phenomenon highlights the fact that there is no universal answer or one-size-fits-all solution. To ensure further progress, a step-by-step strategy appears to be the most promising option. Within the spectrum of available approaches, careful selection becomes crucial, thus improving chances of success. While in this paper we have proposed a selection of targets for the future, we acknowledge the inherent limitations of this an approach, particularly due to the non-random selection of invited contributors. Notably, all experts came from high-income countries, which reflects the concentration of studies on this subject in Europe and the United States. However, this limits the diversity of perspectives, leaving low- and middle-income countries (LMICs) underrepresented. The accepted framework allowed for the presentation of only selected items, leaving no room for other issues that may be of significant importance in specific contexts, such as, e.g., drug shortages. For all these reasons, we do not intend to impose an 'adherence Decalogue.' Nonetheless, we believe that offering a carefully chosen set of top-ranked objectives identified by experts may provide a useful starting point for further discussions on the priorities of advances in medication adherence management.

In essence, these ten suggestions fuse together to call for a paradigm shift - a repositioning of adherence on national agendas. What is needed is not only patient support but also an overarching adherence-supportive ecosystem, which starts with accurate assessment of adherence in clinical trials, actively engaging patients and their organisations, and extends throughout every step of the patient's therapeutic journey. In 2003, the WHO report quoted the statement by Haynes et al. (2002): "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". Undoubtedly, this phrase remains a guiding principle for those dedicated to addressing the challenges of medication adherence.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Requests to access the original datasets should be directed to przemyslaw.kardas@umed.lodz.pl.

Author contributions

PK: Conceptualization, Formal Analysis, Methodology, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing. BrB: Writing–original draft, Writing–review and editing. BiB: Writing–original draft, Writing–review and editing. MB: Writing–original draft, Writing–review and editing. CD: Writing–original draft, Writing–review and editing. MH: Writing–original draft, Writing–review and editing. EM: Writing–original draft, Writing–review and editing. AP: Writing–original draft, Writing–review and editing. JS: Writing–original draft, Writing–review and editing. KT: Writing–original draft, Writing–review and editing. EU: Writing–original draft, Writing–review and editing. TA: Conceptualization, Formal Analysis, Methodology, Supervision, Validation, Writing–original draft, Writing–review and editing.

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Medication nonadherence - definition, measurement, prevalence, and causes: reflecting on the past 20 years and looking forwards

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In 2003, Sabate's World Health Organisation report defined medication nonadherence as a phenomenon where individuals' behaviour does not correspond to prescribed treatment recommendations from their healthcare provider. This concept of nonadherence evolved beyond a categorisation of patients as adherent or nonadherent. Rather, nonadherence varies within the same individual and treatment over time, and between treatments and individuals. The type and patterns of nonadherence are key determinants of outcome with individuals with the same percentage nonadherence having different outcomes depending on their pattern of nonadherence. Often the poorest clinical outcomes occur in individuals who do not initiate medication or discontinue early, but much of the nonadherence literature remains focused on implementation. This paper provides a nuanced discussion of nonadherence which has been enabled in part by the growing availability of technologies such as electronic nonadherence monitors, new biomarkers for adherence and greater access to 'big data' (e.g., on prescription refills). These allow granular assessment of nonadherence that can be linked with biophysical markers captured using technologies such as wearables. More validated self-report measures have also become available to profile nonadherence in research and practice. Together, in-depth data on dosing and clinical measures provide an opportunity to explore complex interactions between medications, therapeutic effects and clinical outcomes. This variation in measurement and definition means that there is a more fine-grained understanding of the prevalence of nonadherence and a greater recognition of the prevalence of nonadherence, with growing evidence suggesting that approximately a fifth of patients do not initiate treatment, of those initiating treatment approximately 30%–50% of patients do not implement their treatment as prescribed and that, over long follow-up periods in some conditions 80%–100% of patients discontinue. There is potential too to better understand causes of nonadherence. New behavioural models synthesise determinants of nonadherence previously considered separately. Frameworks like the COM-B (considering individual capability, opportunity, and motivation factors) and MACO (focusing on Medication Adherence Contexts and Outcomes) emphasize the multifaceted nature of nonadherence

determinants. Greater focus on dynamic processes with interplay between individual, social, and environmental influences is needed. Addressing these complexities could lead to more effective and personalised support for patients.

KEYWORDS

medication adherence, measurement, definition, causes, prevalence

1 Introduction

The landmark 2003 World Health Organisation medication nonadherence report (Sabaté, 2003) begins with discussion of the definition of nonadherence, highlighting the need to go beyond medication and to consider patients as active in generating healthcare recommendations. The authors conclude adherence is "*the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider*". This definition locates nonadherence behaviour within a person who is in receipt of recommendations rather than within the healthcare provider or system. It implies nonadherence is continuous, rather than easily categorised into "adherent" vs. "nonadherent" behaviour.

This perspective paper will outline key developments across the areas of definition, prevalence, measurement and causes of nonadherence over the last 20 years and discuss future directions in these areas (see Figure 1).

2 Developments in definitions of nonadherence: going beyond definitions to taxonomies and processes

Since the WHO adherence report, the definition of adherence has continued to be debated with more recent models including elements of health provider behaviour, and, in the case of medication adherence, splitting adherence into multiple behaviours rather than conceptualising this as a single, consistent behaviour [e.g., (Vrijens et al., 2012; Bartlett Ellis et al., 2023; Chan et al., 2020; Xu et al., 2023)]. For example, digital medication packaging and devices can record the number and timing of medication doses accessed by a patient, providing a more detailed picture of medication-taking over time than traditional measures such as dispensing records (Koledova et al., 2020). Together these changes in measurement have highlighted that adherence can be thought of as multiple behaviours, occurring at different times and places. Some of these behaviours may be performed alone, whereas others are reliant on carers, friends, family, healthcare professionals and healthcare systems (Bartlett Ellis et al., 2023).

Nonadherence as a concept has existed since 400BC when Hippocrates wrote "keep a watch. on the faults of the patients, which often make them lie about the taking of things prescribed. For through not taking disagreeable drinks, purgative or other, they sometimes die" (Brown and Bussell, 2011). This quote summarises tenets of nonadherence that are applicable today - nonadherence is common; patients can conceal nonadherence, and nonadherence can negatively affect health including mortality (Simpson et al., 2006). By the 1970s, nonadherence research was established though referred to as non-compliance research (Becker and Maiman, 1975). The importance of involving patients in treatment decisions was recognised further since this time, and the terminology of concordance was developed in the 2000s to reflect the agreement process between the prescriber and patient. However, uptake of the term concordance has not been far-reaching (Hugtenburg et al., 2013). In 2012, Vrijens et al. (2012) established the first taxonomy to describe (non)adherence behaviour and following this, the EMERGE guideline was published to standardise reporting of nonadherence research using this taxonomy (De Geest et al., 2018). These events have shaped the definition of adherence over the last decade. Rather than considering adherence as a static patient characteristic where patients are classified as 'adherent' or "nonadherent" based on an assessment at a single point in time, adherence is now understood to be a behaviour which can differ

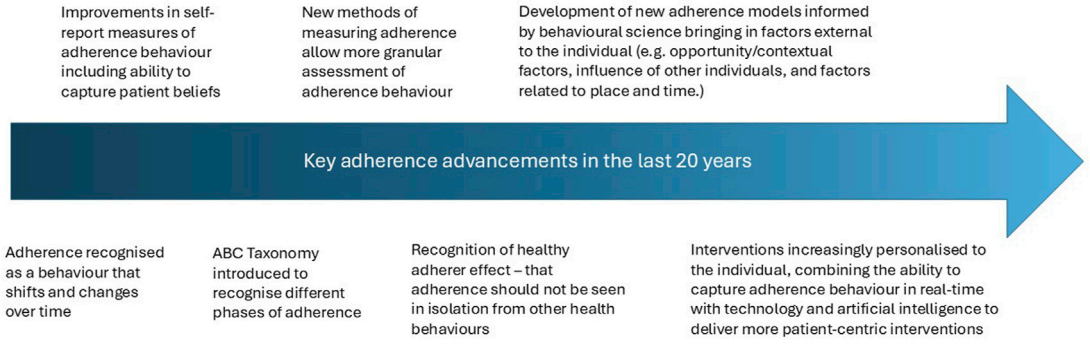

FIGURE 1
Key advancements in medication adherence in the last 20 years.

both between and within the same individual over time (Horne, 2006). Reviews of reviews (Gast and Mathes, 2019) have also shown that it is difficult to use overt stable patient characteristics such as socio-demographic factors, traits, illness or treatment characteristics to predict nonadherence; rather nonadherence is frequently driven by treatment beliefs and illness perceptions (Horne et al., 2013; Foot et al., 2016). For example, being prescribed a treatment which is perceived as a newer medication within the same therapeutic class is associated with a 2.5% reduction in nonadherence for every 10 years increase in medication 'newness' - independent of treatment regimen, condition or patient characteristics (Blankart and Lichtenberg, 2020).

Nonadherence should ideally be viewed holistically considering other health behaviours (Steiner, 2012). Adherence to even placebo medication has mortality benefits (odds of dying 0.56 with adherence to placebo *versus* 0.55 for adherence to medication compared to nonadherence) (Simpson et al., 2006). This is known as the 'Healthy Adherer Effect' (Chewning, 2006). The psychological basis for the Healthy Adherer Effect has been less well-elucidated. Potentially it in part occurs because different health behaviours do not occur in isolation and can interact with one another and be influenced by common factors within and outside of the individual (Steiner, 2012).

Despite increasing research supporting the need to conceptualise nonadherence as a behaviour and not a non-modifiable trait (Horne et al., 2019; Horne et al., 2018), there continues to be research that characterises patients as adherent or nonadherent. With the complexities of nonadherence as a behaviour, we propose that there is a need to move towards more granular conceptualisation of nonadherence and to explore why and how nonadherence changes over time, and whether there are different factors that affect the different stages of nonadherence differently.

3 Prevalence of nonadherence

The widely cited statistic on the prevalence of nonadherence states that approximately 30%–50% of patients do not take their prescribed medication as recommended (Sabaté, 2003). However, the reality is that the rate of nonadherence is likely to vary across patient groups, medications, measurement methods, how strict a definition of nonadherence is used, and the timing and time period an adherence measure covers. Given that increasingly nonadherence is viewed as happening on a continuum (see Section 2 above), estimates of nonadherence prevalence may be inherently flawed as they rely on categorising individuals dichotomously (De Geest et al., 2018). Estimates of the prevalence of nonadherence should therefore refer to the type of nonadherence and the period over which it is assessed. Additionally, it is hypothesised that prevalence estimates that cover a longer period of time or use a stricter cut-off for adherence may be likely to come to the conclusion that a higher proportion of patients are not adherent.

3.1 Prevalence of nonadherence to initiating treatment

Much nonadherence research focuses on implementation once treatment is started despite evidence showing that non-initiation of medication (primary nonadherence) is associated with poorer health outcomes including higher mortality rates (Jackevicius et al., 2008) and emergency department visits (Lee et al., 2016). The limited research that exists exploring reasons for non-initiation suggest that the factors that influence patients' decisions to initiate a medication or not are similar to the factors influencing whether a patient continues to take a medication long-term or stops it prematurely (discontinuation or non-persistence). Part of non-initiation is primary nonadherence, whereby a medication is newly prescribed but then the prescription is not filled at a pharmacy (Fischer et al., 2010). Cheen et al. (2019) systematically reviewed 33 studies and estimated that 17% of patients with six long-term conditions did not collect a newly prescribed medication with rates highest in osteoporosis and hyperlipidaemia (both 25%) and lowest in diabetes mellitus (10%). Studies of patients with a mean age under 65 years old had significantly higher primary nonadherence rates. But, lower primary nonadherence was found in patients aged 19–44 than in children or patients aged over 45 in a recent analysis of 34,243 Canadian primary care patients (Zeitouny et al., 2023) but older patients with polypharmacy were also at increased risk of primary nonadherence. Rates of primary nonadherence are also likely to vary with treatment type and healthcare system factors; Anaba and Arabambi (2022) examined rates at which dermatology patients collected a prescribed medication from a hospital in Lagos, Nigeria, and found 72% topical medications were not collected compared to 23% of oral medications, with more than half of patients who had not collected a medication saying that lack of availability and cost were the reasons for their nonadherence (Anaba and Arabambi, 2022).

Many patients who collect a medication (or have it delivered to them after dispensing) may still not initiate treatment (i.e., take the first dose) (Fischer et al., 2010). Estimates of the number of patients who obtain a prescription but then do not take the first dose are not widely available. Few adherence measures specify whether any dose is taken. Where digital adherence monitors (e.g., MEMs caps) are used to monitor adherence with oral medication in newly treated patients over time, there appear to be low rates of patients with 100% nonadherence (Hebing et al., 2022) but, people participating in research studies in which adherence is monitored may be more likely to initiate treatment than people who are not monitored. Studies of medication waste, such as analysis of medications returned to Dutch community pharmacies (Bekker et al., 2018), report returns of unopened packets, perhaps hinting that not all collected medications may be started. With the difficulties with capturing medication initiation, the true rates of non-initiation may be to accurately measure. Triangulating different data sources such as linking prescribing and dispensing records, along with electronic adherence monitoring, may help provide useful estimates of rates of non-initiation (Figure 2).

3.2 Prevalence of implementation nonadherence

Implementation nonadherence is the most frequently assessed and commonly known form of nonadherence, with rates varying widely across patient groups, contexts and medication (Gast and Mathes, 2019; Foley et al., 2021). Implementation nonadherence is

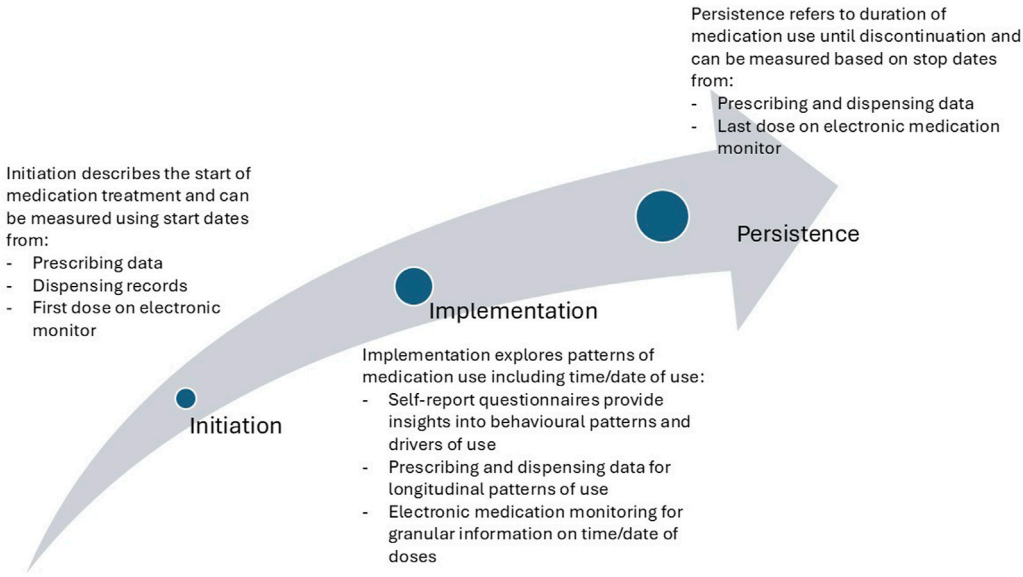

FIGURE 2
Different stages of adherence and data sources to assess each adherence stage.

most often assessed in relation to number of doses taken, but can encompass timing, amount of medication taken, overuse, and adherence to other instructions (e.g., combination with food/fluid) (Nieuwlaat et al., 2014). Helmy et al. (2019) estimated that 37.9% of patients receiving immunosuppressants after heart transplant did not implement their medication as prescribed, within this 26.2% of patients took their immunosuppressant at a different time from that prescribed, while 17.3% did not take all of their immunosuppressant doses.

Rates of nonadherence are also likely to vary depending on the cut-off used to classify participants as nonadherent and the time period evaluated. Davis et al. (2010) estimated that 61% of patients with Parkinson's disease took less than 80% of their medication (based on prescription refill data) over a 7 year period. Whereas, Buh et al. (2023) found 37.7% of patients with HIV at a clinic in Cameroon had missed one or more dose of their medication in the last month. When following up people taking antiretroviral treatment for 20 months using electronic monitoring, Wagner et al., found implementation nonadherence rates increased as time progressed (Wagner et al., 2020).

Rates may vary systematically across different contexts or healthcare systems, for example, Mahmood et al. (2022) reviewed 66 studies assessing implementation nonadherence to antihypertensives in Asia, and estimated an overall prevalence of 48% nonadherence, but found wide variation across regions (Mahmood et al., 2021). Relating to healthcare system factors, rates of antihypertensive implementation nonadherence in one cohort from Islamabad were lower in tertiary care patients than primary and secondary care patients and lower in those who had access to free medical care than those who did not (Mahmood et al., 2020). As with all factors that contribute to medication nonadherence, it is important not to overgeneralise or assume simple causation when considering associations between healthcare system and context factors and implementation nonadherence rates. For example, cost-related implementation nonadherence may occur because of medication unaffordability, but may also occur because groups who experience cost-related medication nonadherence may also be at increased risk of depression, which itself is linked to nonadherence (Briesacher et al., 2007; Gonzalez et al., 2011).

Implementation nonadherence is also likely to be higher for treatments that are more difficult to take or access. Okada et al. (2021) review studies estimating the prevalence of nonadherence to intravitreal ocular therapy for macular degeneration, which requires attendance at regular appointments for injections into the eye, and found rates of implementation nonadherence as high as 95.6% (Okada et al., 2021). There is evidence that treatments that involve multiple doses, or are involve complicated dosing instructions also achieve poor implementation rates (Ingersoll and Cohen, 2008).

Interestingly, there is emerging evidence that suggests there may be time-of-day effects on medication adherence with morning doses achieving greater adherence than evening doses. Phillips et al. conducted a study with electronic medication monitors in patients on twice-daily dosing for type 2 diabetes over 1 month and found that patients overall missed fewer morning pills (Phillips et al., 2021). However, the authors did not find that variability in dose timing differed between morning compared to evening. Thus, better morning adherence may not be due to consistency in the timing *per se* of the medication taking, but perhaps the linking of the morning adherence with a particular consistent routine such as morning coffee, which could vary in timing across different days. In contrast, the evenings may be more disrupted where the medication is either not taken at all, or if remembered, was taken at roughly the same time each evening. More research into the role of behavioural patterns and routines on routine medication taking is warranted to explore time-of-day and seasonal effects. Overall, implementation nonadherence can be said to be common but prevalence estimates are highly variable given the variation in conditions, seasonal and timing effects.

3.3 Prevalence of non-persistence

Non-persistence, whereby patients stop taking a medication before the time agreed with a healthcare professional is generally believed to increase over time. For example, Joret et al. (2022) found that non-small cell lung cancer patients took an estimated 98% of doses at the beginning of tyrosine kinase inhibitor treatment, but that at around 2 months, nearly half of patients had discontinued treatment and at 4 months more than 60% had discontinued. Hardtstock et al. (2022) evaluated non persistence to long-acting asthma treatments over a 12 months follow-up period and estimated non-persistence at 86.7%. There is some suggestion that non persistence increases with experience of adverse effects, with Fleming et al. (2022) finding that a majority of studies included in a review of adjuvant breast cancer treatment persistence found that patients who reported more adverse effects were more likely to discontinue. Alefan et al. (2022) found that adverse effects were particularly strongly linked to rates of discontinuation when the adverse effects were not anticipated by the patient.

Taking the estimated rates of initiation, implementation and persistence together, it is hypothesised that the often-quoted estimate of 30%–50% nonadherence is likely to be an underestimate. Measurement of all three components of nonadherence and longer follow-up times might demonstrate that nonadherence is more common than adherence in many patient populations.

4 Measurement of (non)adherence

There are multiple methods of measurement of nonadherence including self-report, healthcare records analysis, electronic monitoring and biomarker evaluation (discussed elsewhere in this special edition). The consensus remains that there is no universal "gold standard" for medication nonadherence assessment which is universally applicable (Sabaté, 2003) with cross-referencing of multiple methods often identifying more patients who are not adherent. The idea of 'gold standard' also varies depending on the concept that is being explored. For implementation, electronic adherence monitors that can capture the time and date of dosing may be the closest to being a 'gold standard, particularly with some monitors such as digital inhalers that can monitor inhalation (Chan et al., 2013). For medication initiation in an ambulatory setting, pharmacy claims data may be considered the 'gold standard' if the patient can only acquire the prescribed medication from a community pharmacy (Rasmussen et al., 2022). However, what may be considered gold standard will depend on the purpose for measuring adherence and there are an ever-increasing range of methods to assess nonadherence, each with their own advantages and disadvantages (Table 1).

4.1 Self-report measures of medication nonadherence

Despite the potential for harnessing new technologies to map nonadherence, arguably self-report measures are still the dominant technique used to evaluate the extent to which someone is following the recommendations of their healthcare provider (Kamusheva et al., 2024). Often, they are relatively low cost, can be more feasible to use in routine care, can provide an immediate picture of adherence to facilitate intervention and can give insight into elements of nonadherence that may not be accessible from other measurements.

Common critiques of self-report measurement include that it risks over-estimation due to social desirability bias, is reliant on accurate memory of nonadherence, and may be dependent on patients having an accurate understanding of the recommendations that they have been given about how to take their medication (Stirratt et al., 2015). There is reasonably strong evidence that some patients who self-report good adherence are not accurately reporting their behaviour, for example, a recent US study (Hebel et al., 2020) used urine testing for biomarkers for antiretrovirals for pre-exposure prophylaxis of HIV and found that 12%–15% of patients self-reporting full adherence had nonadherence indicated through urine testing.

The COSMIN checklist (Mokkink et al., 2010), arose from a consensus exercise focusing on how to evaluate patient reported outcome measures such as adherence self-report measures. It highlights internal consistency, content validity, hypothesis testing for construct validity, criterion validity and responsiveness as key dimensions on which to evaluate new measures. These criteria have been increasingly applied to evaluate or develop self-report adherence measures. Kwan et al. (2020) found most self-report measures of (non)adherence had good evidence of construct validity, structural validity and content validity. However, there was weak evidence of the test-retest reliability perhaps unsurprising, given that adherence can be a dynamic behaviour, minimal evidence relating to cross-cultural validity of measures, and poor reporting of how measures how been developed. Tegegn et al. (2022) reviewed self-report measures for medication (non) adherence in cardiovascular disease against the COSMIN criteria; no measure assessed all elements of initiation, implementation, and persistence/discontinuation, with most focused on implementation and none on initiation. Few (non)adherence self-report measures have been validated across all target conditions or groups, or in a wide range of languages/cultures, with implications for relevance. For example, Vianna et al. (2021), reviewed the use of self-report measures to assess adherence to warfarin therapy and highlighted that generic measures had been used but that these did not capture adherence to some of the medication-taking recommendations (e.g., changing dose if experiencing bleeding) which patients taking warfarin are asked to follow.

Overall medication nonadherence self-report measures are increasingly robustly validated. For example, Chan et al. (2020), reported on the development of a five-item self-report scale, the Medication Adherence Report Scale (MARS-5) which included items probing intentional and unintentional nonadherence and considered properties including internal reliability, construct validity and hypothesis testing. The Morisky Medication Adherence Scale (MMAS-8) is another commonly used eight-item structured, self-report measure that assesses medication adherence (Morisky et al., 2008). There are also disease specific questionnaires. Wilson et al. (2016) developed a three-item measure for use in patients with HIV based on reported doses taken/missed over the previous 30 days and validated against objective measures.

TABLE 1 Methods to measure nonadherence and their advantages and disadvantages.

	Self-report	Prescribing or dispensing records	Electronic medication monitors
Advantages	• Cheap • Easy to administer • Limited preparation required • Can provide behavioural insights into reasons for nonadherence	• Cheap • Routinely collected • Objective • Can provide information on longitudinal trends and patterns of adherence • Useful for population level analysis • Can be linked easily with other electronic health records	• Granular information on time/date of dosing • Useful for individual level data to tailor adherence strategies to the individual as part of adherence discussions • Can capture diverse range of information as part of predictive analytics • Functions to support adherence • Real-time data can inform early warning alerts
Disadvantages	• Prone to bias • Often only cross-sectional snapshot of adherence	• Requires data cleaning and processing to interpret • Only proxy for medication consumption	• Expensive • Not routinely available • Technical faults possible

Dima et al. (2017) validated a measure of nonadherence in asthma against dispensing records and probed overuse of treatment as well as underuse.

With the rise of 'open science' and increasing concern for access to scientific tools and outputs, there has been an increasing focus on legal and cost implications of self-report adherence measure use Tesfaye and Peterson (2022) highlight that many measures may be infeasible for clinicians and researchers in low resource settings to use due to legal and cost restrictions. In clinical practice there may be additional barriers of time, and uncertainty regarding whether the measure is validated for use that fits with clinical practice (e.g., verbal delivery). Garfield et al. (2011) highlighted that there is limited available data on key factors relevant for clinicians assessing adherence such as how long a measure takes to complete, and suitability for carer completion.

Selection of a self-report adherence measure therefore needs consideration of the psychometric properties of the measure, the aspects of adherence that need to be assessed, consideration of use restrictions and cost, and the available data on relevance to the particular research/clinical context, patient group and medication. The use of validated self-report measures can therefore be used to provide key insights into the behavioural drivers of medication nonadherence.

4.2 Electronic monitoring and technologies to measure nonadherence

As our understanding of nonadherence as a behaviour has advanced, so too have technologies to assess nonadherence. These have been developed to better capture the complexity of nonadherence and medication-related behaviours, whilst at the same time providing opportunities for nonadherence promoting interventions. Electronic medication monitors (EMM) have existed since the 1990s in the form of smart inhalers (Julius et al., 2002), electronic dispensing 'smart' pill boxes/bottles and smart pills. These devices in its simplest form record the number of doses taken over time, though current available devices now routinely capture date/time stamps of each medication dose. A recent meta-analysis showed that individuals receiving EMM has significantly reductions in nonadherence with a large magnitude of effect though this did not always translate to clinical benefit in studies which reported both outcomes (Chan et al., 2022). Whilst EMM capture one aspect of medication taking – which is opening of the medication container or inhaler actuation, EMMs still cannot confirm actual medication consumption, which may explain why EMM studies of adherence do not always correlate with clinical outcomes (Chan et al., 2013). How nonadherence relates to clinical outcomes is a question that requires further exploration outside this review but is worth acknowledging that nonadherence alone is only an intermediate outcome and that changes in clinical outcomes are possible even without associated increases in nonadherence.

More sophisticated EMM can also capture location of dosing, allowing linkage with GPS-related data such as environmental factors, and linkage with other datasets. One example is the Propeller Health adherence monitoring inhaler device which can record the location of reliever inhaler use (Merchant et al., 2016). The ability to track and map the location of medication use has provided insights into where 'hot spots' of asthma attacks are occurring and allowed further investigation into linkage with environmental triggers such as weather and pollen. This is likely to have important benefits as the effects of climate change increase in years to come, with geographic mapping of medication nonadherence offering new insights to inform resource planning, medication access policies and population health management. EMM can link with wearables, health provider portals, patient apps and be used with AI in predictive analytics to see how changes in patterns of medication use can predict outcomes. For example, changes in reliever medication use alone without input from any other predictors has been shown to predict the onset of an asthma exacerbation 5 days before the attack occurs (Lugogo et al., 2022). The availability of real-time medication use data can thus be used to inform early-warning systems and alerts for patients and providers of negative health outcomes.

4.3 Prescription refill database and "big data" analysis of care records

Another method of nonadherence assessment that has exploded in the last 20 years is evaluation of prescription and pharmacy databases to establish patterns of prescription redemption as a proxy for medication-taking. A range of indicators can be calculated. These include whether a prescription is redeemed, indicating primary nonadherence or non-initiation (Cheen et al., 2019). Medication possession ratio whereby the number of doses of redeemed

treatment are evaluated against the number of doses prescribed can also be calculated to indicate potential implementation nonadherence in terms of missed doses (Vink et al., 2009). Finally, the date of last prescription refill can indicate discontinuation or persistence with treatment (Gershon et al., 2021).

Prescription refill data has been validated against nonadherence biomarkers and self-report [e.g., (Osula et al., 2022)], with studies showing moderate correlations between medication possession ratio and other outcomes that would be associated with nonadherence (Hood et al., 2018). Unlike self-report data it is 'objective' and less likely to be influenced by social desirability bias. But, prescription refill rates are known to be affected by factors such as oversupply, and prescribing duration patterns (Galozy et al., 2020). In addition, prescription refill data can only indicate whether a medication is dispensed but not whether or how it is taken such as timing, storage or use (e.g., inhaler technique), so may not correlate with some nonadherence outcomes (Pattock et al., 2024).

Another potentially useful tool to provide system- or population-level analysis of nonadherence is the utilization of patient records. For example, nonadherence discussions and support provided by healthcare providers and recorded in electronic patient notes may provide insight into patterns of nonadherence (Insani et al., 2023). Healthcare records systems may have specific codes or processes for healthcare professional logging of nonadherence, but this data is yet to be widely used in research. Healthcare records are being linked to pharmacy and other data to gain additional insights (Xu et al., 2023). The growth of large language models and artificial intelligence offer potential for data mining of electronic healthcare and pharmacy records to gain insights into nonadherence (Turchin et al., 2024). Offering nonadherence support automatically to certain patients based on healthcare records has been piloted (Bosl et al., 2013) but is under-explored. As dispensing data are often routinely collected, and, depending on access rights and availability, accessible to healthcare professionals they may be a useful cue for provision of nonadherence support within daily practice. Another use of prescription or dispensing records is to track longitudinal medication use and examine how trajectories of treatment initiation and discontinuation relate to outcomes (Hommel et al., 2017).

5 Causes of nonadherence

Nonadherence is widely recognised as a complex behaviour with multifactorial causes (Foley et al., 2021). Kardas et al. (2013) conducted a review of systematic reviews of determinants of nonadherence, highlighting 771 factors that had been linked to nonadherence. This complexity means that for any patient, there are likely to be multiple facilitators and barriers to nonadherence, and that no single intervention is likely to be effective in ensuring nonadherence across all patients, all of the time (Nieuwlaat et al., 2014). Of note, despite the large range of factors identified in the review of reviews, there remained a great deal of unexplained variance in nonadherence behaviour, suggesting that most studies simply cannot test all of the large number of relevant factors that contribute to nonadherence or that untested factors or interactions between factors may drive nonadherence.

To simplify this complexity, there have been classifications of nonadherence determinants. Sabate (2003) stated factors could be patient-, condition-, healthcare system-, therapy-related or socioeconomic, emphasising that causes of nonadherence go beyond individual patients. Several approaches to understanding causes of nonadherence have highlighted factors external to the patient. The Perceptions and Practicalities Approach (Horne et al., 2018), emphasises patients can be nonadherent due to both practical factors, e.g., cost, medicines access, largely leading to unintentional nonadherence and perceptual factors, e.g., beliefs, emotional responses largely leading to intentional nonadherence. Likewise, the COM-B model applied to nonadherence, states patients will not adhere without the physical and psychological Capability (e.g., swallowing capacity, memory), social and physical Opportunity (e.g., support from family, housing) and the reflective and automatic Motivation (e.g., impulses, beliefs) to adhere (Jackson et al., 2014).

Comparatively less focus has been placed on understanding healthcare system or healthcare professional factors that contribute to nonadherence, although the COM-B model could be applied to behaviours of anybody involved in adherence processes including carers and healthcare professionals. The Medication Adherence Contexts and Outcomes Framework (Bartlett Ellis et al., 2023), depicts medication adherence as a series of processes involving different individuals, locations and outcome behaviours. For example, a patient and healthcare provider may interact at a clinic leading to treatment prescription process and the outcome of treatment initiation. Mapping what is known about causes of nonadherence to different processes and individuals involved may enable the development of timely interventions strategies.

All three stages of adherence appear to be strongly influenced by patients' evaluation of the benefits and harms of medication (Pound et al., 2005). At the initiation stage, the decision to start medication is conditioned by memories of past experiences, environmental influences and preconceived ideas possibly to a greater extent than other stages of adherence (Gil-Girbau et al., 2020; Chapman et al., 2024). At treatment initiation, patients' emotional reaction to diagnosis and treatment recommendations is key and the health provider-patient relationship appears central to the patients' experience and decision to initiate the medication (Chapman et al., 2024).

Less is known about factors that affect patients' decisions to discontinue treatment with most of the published work in this area focused on mental health or cardiac conditions (Keogh et al., 2022). Available studies show that the decision to discontinue medication is often a carefully considered one by the patient, rather than an impulsive action, and is influenced by social, environmental and personal factors (Keogh et al., 2022). Experiences of adverse effects and a desire to regain agency and control have been reported to influence discontinuation (Gershon et al., 2021; Keogh et al., 2022; Gameiro et al., 2012).

6 Future directions for research and practice

The WHO states that "adherence is the single most important modifiable factor that compromises treatment outcome" (Sabaté, 2003). With the millions of dollars that are invested yearly into new pharmaceuticals, there is an urgent need to refocus the priorities of clinicians, researchers, funders, and policymakers on addressing nonadherence. Without adherence, there can be no gains made

from new healthcare innovations. Yet despite over 50 years of research into nonadherence, the gains that have been made in practice have been minimal. With the new opportunities offered by big data, electronic healthcare databases, digital technologies and AI, the ability to deliver personalised care tailored to the individual's treatment beliefs, illness perceptions and practical barriers should be a part of routine care. The ability to measure an individual's beliefs and perceptions via validated questionnaires was one of the major breakthroughs in the last 30 years, allowing quantification of patient experiences without needing to rely on qualitative data (Weinman et al., 1996; Horne et al., 1999). This enables practitioners and researchers to rapidly and accurately assess patients' beliefs, which should allow the delivery of tailored interventions. Combined with AI that could be used to 'learn' from the patients' responses to questionnaires about adherence and factors driving adherence and the resulting adherence behaviour, there is potential to detect, measure, intervene and potentially predict future nonadherence within the same intervention.

Because nonadherence can change within and between individuals and over time, the continued focus on reporting nonadherence as a static average percentage is likely a further barrier to advancements in adherence research. Early work suggested that for antihypertensive medication a threshold of 80% of medication taken was sufficient to lower blood pressure (Haynes et al., 1980). However, a recent systematic review of (non) adherence thresholds in relation to clinical outcomes found that reported thresholds used to classify nonadherence status range from 46% to 92% (Baumgartner et al., 2018) meaning the validity of the historical 80% threshold could not be confirmed. With the uncertainty in the 80% threshold and the wide variability across patients and conditions associated with this cut-off, it would be prudent for future studies to move away from a static, binary classification system of seeing adherence as a "yes/no" outcome or a simple percentage adherence. Nonadherence needs to be conceptualised as a complex behaviour that requires sophisticated measurement and reporting.

This call for a more personalised, patient-centric approach is captured by Reach in a recent review of nonadherence where he proposes nonadherence should be viewed as a "syndrome" (Reach, 2023). A new model of nonadherence informed by the humanities, philosophy, and behavioural economics is described. The model emphasises the role of character traits, habit-formation, and trust. How this model can be operationalised in practice is yet to be seen. This novel exploration of the intersection between behavioural science and epidemiological methods could hold the key to future solutions for nonadherence.

7 Summary and conclusion

In summary, the complexity of adherence is increasingly recognised, leading to the development of new frameworks and approaches to define, measure and understand the causes of nonadherence. Rather than a binary concept, adherence is increasingly being seen as a process that happens over time and involves a wide range of individuals. With this change in conceptualisation, a wider range of measurements and causes are being understood. Rates of nonadherence seem likely to exceed the oft-quoted 30%–50% figure once a full range of aspects are considered. New technologies offer the potential to of a more granular understanding of nonadherence and more effective support for patients taking medicines. There is a need for a paradigm shift for all researchers, clinicians and policymakers to use these technologies to their full potential and to see nonadherence as a health behaviour that shifts and changes with time rather than a static characteristic. Only then can we truly address nonadherence in a personalised, equitable and timely manner.

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Clinical and economic consequences of medication nonadherence: a review of systematic reviews

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Background: Medication efficacy observed in clinical trials may differ from its effectiveness during real-world usage. Medication nonadherence is one of the key factors being responsible for this efficacy-effectiveness gap. The World Health Organization estimated that only 50% of chronic medication users is adherent and nonadherence results in both negative health outcomes for the patient and higher societal costs. An overview of the consequences across disease groups may allow some comparison and could contribute to identification of priority clinical areas.

Objective: We aimed to provide an overview the impact of nonadherence on clinical and economic outcomes.

Method: We narratively reviewed systematic reviews published between 2014 and 2024 on the effect of medication nonadherence on clinical and economic outcomes.

Results: Overall, 43 systematic reviews were identified, including over 410 original studies on clinical outcomes and 174 on economic outcomes, covering different clinical areas (e.g., organ transplantation, cardiovascular diseases, diabetes, depression and chronic lung diseases [asthma/COPD]). Beyond diminished treatment effects, medication nonadherence has been associated with elevated mortality, increased healthcare utilization (including hospital admissions), and higher direct (e.g., more healthcare provider visits) and indirect financial cost burden (e.g., work productivity losses due to absenteeism and presenteeism) for patients and society.

Conclusion: Medication nonadherence is associated with poor clinical and economic outcomes across disease areas. Given the significant impact of nonadherence, raising awareness among healthcare professionals and policymakers, early stakeholder engagement in intervention design, and eventually implementation of cost-effective interventions on both health policy, system and individual patient level are urgently required.

KEYWORDS

medication adherence, economic outcomes, clinical impact, burden, cost-effectiveness, chronic diseases, adherence, clinical outcomes

Introduction

Medication is the cornerstone treatment prescribed for most chronic diseases such as asthma, diabetes and osteoporosis. Generally, these medications have been extensively evaluated in randomized clinical trials and have been granted market access based on a positive benefit-risk ratio. However, this positive benefit-risk ratio may not always be observed in daily real-world practice and one the key determining factors for this discrepancy is medication nonadherence.

Medication adherence has been defined by the World Health Organisation (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 healthcare provider." (1) Globally, the WHO estimated that around half of all chronic patients do not take their medicine according to prescription (World Health Organization, 2003). This is not without consequences. The Organization for Economic Co-operation and Development (OECD) estimates that medication nonadherence has been associated with 200,000 deaths and €125 billion avoidable medical expenditures per year in Europe in patients (Khan and Socha-Dietrich, 2018). In the USA, similar figures have been estimated with reported avoidable medical expenditures of $100–300 billion per year due to adverse drug events of which one-third was attributed to medication nonadherence (Cambridge, 2009; Senst et al., 2001). These negative consequences of medication nonadherence for patients have been shown in multiple studies as well. Already in 2002, a meta-analysis demonstrated the overall significant negative impact of therapy and medication nonadherence on treatment outcomes such as pain, risk of cardiovascular events and morbidity in a variety of disease areas (Robin DiMatteo et al., 2002). In the years that followed, multiple additional studies have been published confirming and extending these findings.

However, while overall estimates are essential to raise awareness and shape policy, most of the previous studies focused on the effect of adherence enhancing interventions (Kini and Ho, 2018), on the specific treatment outcomes (Robin DiMatteo et al., 2002), focused only on the economic outcomes (Cutler et al., 2018; Iuga and McGuire, 2014) or both on clinical and economic outcomes but in specific disease groups, e.g., COPD (van Boven et al., 2014), or populations, e.g., aging population (Walsh et al., 2019). More holistic insight into the clinical and economic impact of nonadherence per disease group may however be more informative for policymakers to inform the overall potential of these adherence supporting interventions in terms of cost-effectiveness, budget impact, scale-up and implementation.

We aimed to assess the clinical and economic impact of medication nonadherence by narratively reviewing previously published systematic reviews across chronic diseases.

Materials and methods

Study design

This semi-systematic narrative review was reported according to the Scale for the Assessment of Narrative Review Articles (Baethge et al., 2019).

Search strategy and selection process

Two semi-structured searches were performed in Medline via PubMed using combinations of the following search terms: medication adherence AND burden, economic, impact, outcomes, clinical, AND systematic review. One search focused on the clinical impact of medication nonadherence and the other on the economic impact of medication nonadherence (see Supplementary Material for detailed search strings). The literature search was performed in May 2024. To provide an up-to-date overview, articles were filtered by publication date; only articles published after 1 January 2014 were screened. Reference lists of relevant articles were inspected to identify further relevant systematic reviews.

Study inclusion criteria were (1) the study design was a systematic review and/or meta-analysis, (2) the study assessed the relationship between nonadherence to medication and any clinical and/or economic outcomes in any disease area as main or secondary study outcome, and (3) the study was published in English.

All articles on clinical outcomes were screened for eligibility by one researcher (MA) on title and abstract. In case of doubt, the full-text article was screened or the article's title and abstract were screened by a second researcher (NA). This same process was also performed concerning the articles on economic outcomes, but by two other researchers (GO and DA).

Data items and extraction process

Data from relevant studies were extracted and checked independently by two researchers. Subsequently, data were manually tabulated in a Microsoft Excel file.

The following data items were extracted for each article: last name of first author and year of publication, the number of included original studies, the number of included original studies with a clinical or economic outcome, the clinical area or disease, type of medication, definition of adherence, the clinical or economic outcome, significance of the impact on the clinical or economic outcome (significant or non-significant), and direction of the relation between nonadherence and the clinical or economic outcome (positive or negative). In case of meta-analysis, the overall significance was extracted. In case of missing data or when data were described unclearly, this was reported as not reported.

Reported cost data in the included reviews were adjusted to 2024 US$ using the consumer price index for all urban consumers (CPI-U), applying January values to account for inflation across the specified period. As all relevant cost data in the included reviews were originally reported in USD, no currency exchange adjustments were necessary.

Results

Search results

In total, the searches yielded 43 relevant systematic reviews and meta-analyses ($N = 5$) (Walsh et al., 2019; Altice et al., 2019; Souza et al., 2016; Lee et al., 2022; Shehab et al., 2019). After inspection of

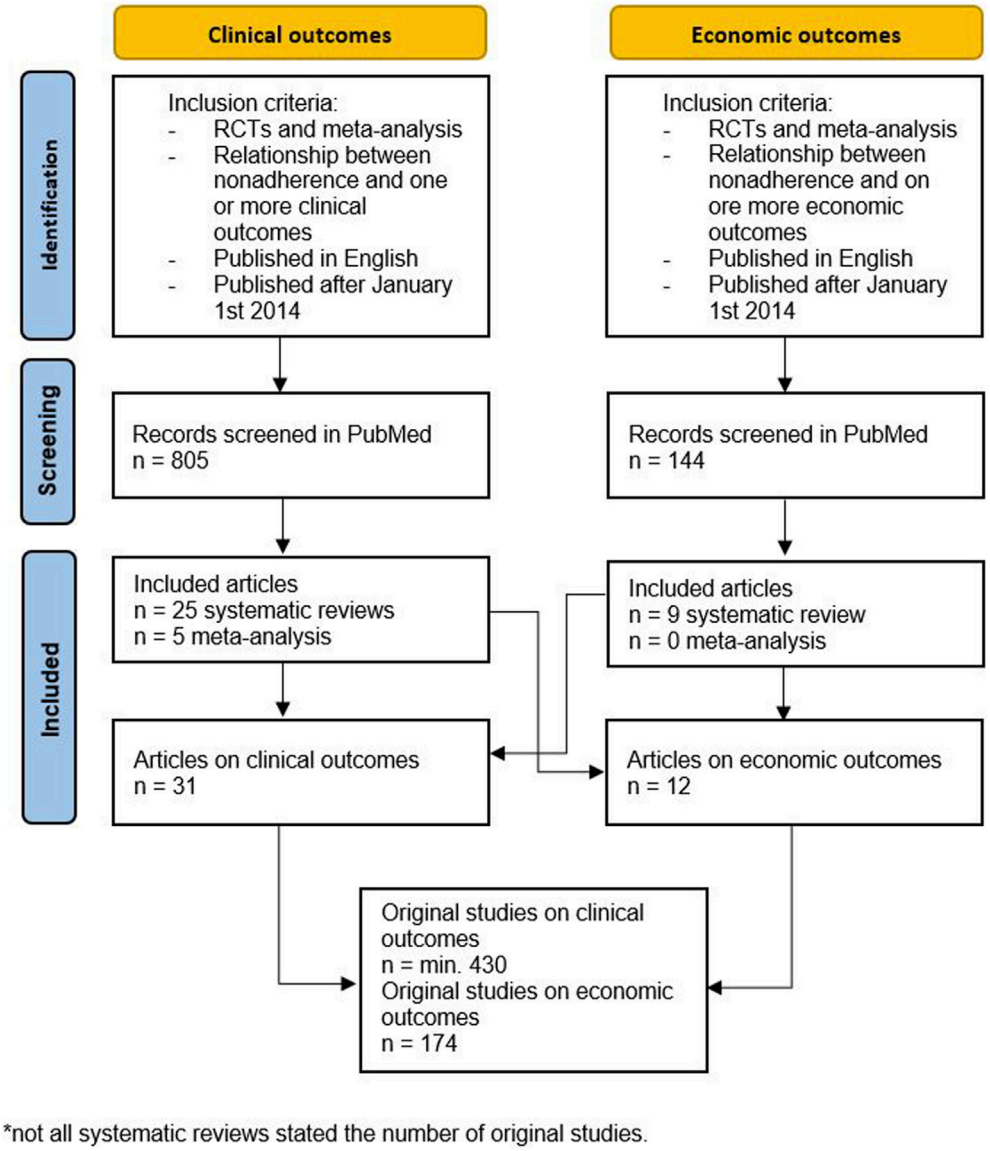

FIGURE 1
Flowchart of included articles.

reference lists, no more relevant studies were identified. In total, 31 systematic reviews reported on the clinical impact of nonadherence (van Boven et al., 2014; Walsh et al., 2019; Altice et al., 2019; Souza et al., 2016; Lee et al., 2022; Shehab et al., 2019; Sussman et al., 2022; Martin-Ruiz et al., 2018; Evans et al., 2022; Deshpande et al., 2017; Parmar et al., 2017; Capoccia et al., 2016; Ho et al., 2016; De Vera et al., 2014a; Nassetta et al., 2022; Bårnes and Ulrik, 2015; Mikyas et al., 2014; Chimeh et al., 2020; Foka and Mufhandu, 2023; El-Saifi et al., 2018; Ágh et al., 2015; De Vera et al., 2014b; Kengne et al., 2024; Lee et al., 2024; Inotai et al., 2021; Eliassen et al., 2023; Maniadakis et al., 2018; Alahmari et al., 2023; Visintini et al., 2023; Hussain et al., 2021), 12 on the economic impact of nonadherence (Cutler et al., 2018; van Boven et al., 2014; Evans et al., 2022; Deshpande et al., 2017; Capoccia et al., 2016; Ho et al., 2016; Chimeh et al., 2020; Kengne et al., 2024; Maniadakis et al., 2018; Noens et al., 2014; Hameed et al., 2014; Pennington and McCrone, 2018), and 8 on both (van Boven et al., 2014; Evans et al., 2022; Deshpande et al., 2017; Capoccia et al., 2016; Chimeh et al., 2020; Kengne et al., 2024; Maniadakis et al., 2018; Noens et al., 2014) (Figure 1).

Not all studies that were included in the original systematic reviews and meta-analyses focused on both the clinical or economic outcomes. In total, these systematic reviews covered at least 430 unique studies on clinical outcomes and 174 studies on economic outcomes.

The clinical focus of the systematic reviews included mostly patients with cardiovascular disease including atrial fibrillation (N = 6) (Shehab et al., 2019; Sussman et al., 2022; Martin-Ruiz et al., 2018; Deshpande et al., 2017; De Vera et al., 2014a; Hameed et al., 2014), hypertension (N = 3) (Souza et al., 2016; Kengne et al., 2024; Lee et al., 2024), transplantation (N = 4) (Parmar et al., 2017; Nassetta et al., 2022; Visintini et al., 2023; Hussain et al., 2021), and chronic

TABLE 1 Overview of systematic reviews on the clinical consequences of medication nonadherence.

First author, year	Clinical area	Definition of (non) adherence	Medication	Included studies with clinical outcomes/included studies (n/N)	Clinical outcomes	Direction (-/+)* and signficance S, NS, NR)** on outcome	Effect size***
Walsh et al. (2019)	Ageing population	"Medication adherence is defined as the process by which patients take their medication as prescribed, consisting of 3 main components: initiation, implementation and discontinuation."	medication in general, not specified	11/66	hospitalization (all cause)	+ S	OR 1.17 [95% CI, 1.12-1.21) Z=7.65 (p<0.0001)
					hospitalization (disease-specific)	+ NS	OR 1.07 [95% CI, 0.98-1.17)Z=1.47 (p<0.143)
					ED visits	+ NS	OR 1.05 [95% CI, 0.90-1.22] Z=0.57 (p=0.566)
					physician office visits	+ S and NS	
					utilization of outpatient services	+ NS	OR 1.09 (95% CI: 0.87–1.36), (p=0.46)
					quality of life	+ S and NS	
					mortality	+ S and NS	HZ 0.79 95% CI, 0.63-0.98)Z= 2.12 (p=0.034)
					depression	+ NS	
Shehab et al. (2019)	Atrial fibribilation (AF)	-	novel oral anticoagulants (NOACs), not specified	6/6	bleeding events	+ S	7.5% (95% CI, 0.2-14.8] (p=0.045)
Sussman et al. (2022)	Atrial fibrilation non-vulvar (NVAF) and stroke risk	-	oral anticoagulants, (OACs), not specified	6/16	İschemic events[1]	+ S	
					mortality	+ S and NS	
					bleeding events [2]	+ S	
Barnes and Ulrik (2014)	Asthma	-	ICS (in combination with long-acting β2 agonists), not specified	6/19	number of rescue courses of oral corticosteroids	+ NS	
					hospitalization	+ NS and NR	
					FEV1	- S and NS	
					% eosinophils	- S and NS	
					mortality	+ NR	

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10.3389/fphar.2025.1570359

TABLE 1 (*Continued*) Overview of systematic reviews on the clinical consequences of medication nonadherence.

First author, year	Clinical area	Definition of (non) adherence	Medication	Included studies with clinical outcomes/included studies (n/N)	Clinical outcomes	Direction (-/+)* and signficance S, NS, NR)** on outcome	Effect size***
Eliassen et al. (2023)	Breast cancer	"In breast cancer, treatment non-adherence occurs when a patient fails to take the treatment as prescribed throughout the treatment period (ie, frequently missing doses), whereas non-persistence to AET occurs when a patient stops treatment continuously for a prolonged period of time."	adjuvant endocrine medication, tamoxifen and aromatase inhibitors	14/14	event-free survival	+ S	
					overall survival	+ S	
Inotai et al. (2021)	(nonmetastic) Breast cancer	"... refers to the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen."	endocrine therapies, not specified	12/12	distant metastasis	+ S	
					recurrence of breast cancer	+ S	
					worse disease free survival	+ S	
					mortality	+ S and NS	
Deshpande et al. (2017)	Cardiovascular disease (CVD)	-	statins, not specified	20/139	cardiovascular events [3]	- S and NS	
					mortality	+ S	
					hospitalization	+ S	
					ED visits	+ S	
Martin-Ruiz et al. (2018)	(risk on) Cardiovascular disease (CVD)	-	statins, not specified	17/17	mortality	+ S	
					cardiovascular events [4]	+ S and NS	
					hospitalization	+ S and NR	
De Vera et al. (2014a)	Cardiovascular disease (CVD)	"Medication adherence is a complex construct that encompasses the following distinct problems: (i) poor execution of the dosing regimen, such that doses are delayed or omitted, which may lead to transient interruptions in drug action; and (ii) discontinuation of the medication, which may lead to intermittent or permanent loss of drug effects."	statins, not specified	19/28	cardiovascular events [5]	+ S	
					mortality	+ S	
					hospitalization	+ S	

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10.3389/fphar.2025.1570359

TABLE 1 (*Continued*) Overview of systematic reviews on the clinical consequences of medication nonadherence.

First author, year	Clinical area	Definition of (non) adherence	Medication	Included studies with clinical outcomes/included studies (n/N)	Clinical outcomes	Direction (-/+)* and signficance S, NS, NR)** on outcome	Effect size***
Maniadakis et al. (2018)	Chronic inflammatory disease (CID)	-	biologic therapy (TNF)	7/17	disease activity	+ S and NR	
					disease relapse	+ NR	
					disease duration	+ NR	
					hospitalization	+ NR	
Noens et al. (2014)	Chronic myeloid leukemia (CML)	-	BCR-ABL inhibitor therapy, imatinib	6/19	suboptimal response	+ S	
					event-free survival	- S	
Ágh et al. (2015)	Chronic obstructive pulmonary disease (COPD)	"Medication adherence 'refers to the act of conforming to the recommendations made by the provider with respect of timing, dosage and frequency of medication taking'."	COPD medication, not specified	7/7	quality of life	- S and NS	
Van Boven et al. (2014)	Chronic obstructive pulmonary disease (COPD)	". . . the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen"	COPD medication, not specified	7/12	hospitalization	+ S, NS and NR	
					ED visits	+ NS and NR	
					outpatient visits	+ NS and NR	
					symptoms [6]	+ NR	
					FEV1	- NS	
					PC20	- S	
					mortality	+ S and NS	
					quality of life	- S and NS	
Ho et al. (2016)	Depressive disorder	-	antidepressants, not specified	9/11	relapse or recurrence	+ S	
					ED visits	+ S and NR	
					hospitalization	+ S	
					depression severity	+ S	
					response and remission	- S	

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10.3389/fphar.2025.1570359

TABLE 1 (*Continued*) Overview of systematic reviews on the clinical consequences of medication nonadherence.

First author, year	Clinical area	Definition of (non) adherence	Medication	Included studies with clinical outcomes/included studies (n/N)	Clinical outcomes	Direction (-/+)* and signficance S, NS, NR)** on outcome	Effect size***
El-Saifi et al. (2018)	Dementia	-	not specified	1/20	institutionalisation	+ NR	
					mortality	+ NR	
Capoccia et al. (2016)	Diabetes mellitus (DM)	-	glucose-lowering agents, not specified	12/98	HbA1c	- S	
					diabetic complications	+ S	
					ED visits	+ S	
					hospitalization	+ S	
Evans et al. (2022)	Diabetes mellitus (DM) type 2	-	antidiabetic medications, not specified	81/92	HbA1c	- S and NS	
					hypoglycaemia	- S and NS	
					hospitalization	+ - NR	
					ED visits	+ - NR	
					outpatient visits	+ - NS or NR	
					microvascular events [7]	+ S and NS	
					macrovascular events [8]	+ S and NS	
Vera, 2014	Gout	-	allopurinol and uric acid lowering agents, not specified	1/16	sUA concentration	- NR	
Visintini et al. (2023)	Haematopoietic stem cell transplantation (HSCT)	"...the late or non-initiation of the prescribed treatment, sub-optimal implementation of the dosing regimen, or early discontinuation of the treatment."	immunosuppressents, not specified	5/14	GvHD	+ NS	
					mortality	+ NS	
Hussain et al. (2021)	Heart transplantation (HTx)	-	immunosuppresents, not specified	3/23	transplant coronary artery disease	+ S	
					acute late rejection	+ NS	
					mortality	+ S and NS	
Nassetta et al. (2022)	(pediatric) Heart transplantation (HTx)	-	İmmunosuppressents, not specified	11/14	transplant rejection	+ S and NS	
					hospitalization	+ S	
					mortality	+ S	
					quality of life	- S	
					mental health	- S and NS	

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10.3389/fphar.2025.1570359

TABLE 1 (*Continued*) Overview of systematic reviews on the clinical consequences of medication nonadherence.

First author, year	Clinical area	Definition of (non) adherence	Medication	Included studies with clinical outcomes/included studies (n/N)	Clinical outcomes	Direction (-/+)* and signficance S, NS, NR)** on outcome	Effect size***
Altice et al. (2019)	Human immunodeficiency virus (HIV)	-	antiretroviral therapies (ARTs), not specified	18/29	viral suppresion	- S and NS	
Foka and Mufhandu (2023)	Human immunodeficiency virus (HIV)	-	antiretroviral therapies (ARTs), not specified	NR/176	virologic failure	+ NR	
Souza et al. (2016)	Hypertension, arterial	-	antihypertensive medication, not specified	4/20	quality of life	- S	MD 9.24 [95% CI, 8.16-10.33], Z=16.71 (p<0.00001)
Lee et al. (2022)	Hypertension	-	antihypertensive medication, not specified	53/162	systolic BP control	- S	MD 3.76 mm Hg [95% CI, 2.23–5.28 mm Hg] (p<0.001)
					diastolic BP control	- S	MD 3.11 mm Hg [95% CI, 2.24–3.99 mm Hg] (p<0.001)
					BP control	- S	OR 2.15 [95% CI, 1.84–2.5] (p<0.001)
					complications from hypertension	+ S	OR 2.08 [95% CI, 0.99–4.35] (p<0.001)
					hospitalization	+ NS	OR 1.38 [95% CI, 1.35–1.41] (p=0.64)
					mortality	+ NS	OR 1.38 [95% CI, 1.35–1.41] (p=0.509)
Kengne et al. (2024)	Hypertension and/or dyslipidemia	-	antihypertensives and lipid-lowering medications, not specified	45/45	BP control LDL	- S - S	
					cardiovascular events [9]	+ S and NS	
					mortality	+ S and NR	
Parmar et al. (2017)	(pediatric) Liver transplantation (LTx)	-	tacrolimus	3/25	quality of life	- S	
Alahmari et al. (2023)	Osteoporosis	"Adherence is sometimes used interchangeably with compliance or as a more general term to refer to both compliance and persistence."	osteoporotic medication, not specified	14/14	fracture risk	+ NR	
					bone mineral density	- NR	

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10.3389/fphar.2025.1570359

TABLE 1 (*Continued*) Overview of systematic reviews on the clinical consequences of medication nonadherence.

First author, year	Clinical area	Definition of (non) adherence	Medication	Included studies with clinical outcomes/included studies (n/N)	Clinical outcomes	Direction (-/+)* and signficance S, NS, NR)** on outcome	Effect size***
Mikyas et al. (2014)	(male) Osteoporosis	-	bisphosphonates, not specified	3/18	fracture risk	+ NR	
Lee et al. (2024)	Thalassaemia	-	İron-chelation agents, not specified	20/20	serum ferritin	- S and NS	
					liver disease	+ S	
					liver iron overload	+ S and NS	
					cardiac disease	+ S	
					cardiac iron overload	+ S and NS	
					endocrinologic morbidity	+ S	
					hepatic morbidity	+ S	
					quality of life	- S sand NS	
Chimeh et al. (2020)	(drug-susceptible) Tuberculosis (TB)	"Adherence is defined as "the extent to which a person's behavior to take medicines, to follow a diet, and/or to execute lifestyle changes corresponds with agreed recommendations from a healthcare provider."	TB medication, not specified	12/14	unsuccessful treatment	+ S and NS	
					successful treatment	- NS and NR	
					mortality	+ S and NS	

*+ = positive relation between clinical outcome and nonadherence; - = negative relation between clinical outcome and nonadherence.

**S = significant, NS, nonsignificant; NR, not reported.

*** in z-score (p-value), mean-difference (p-value) or odds ratio (p-value).

[1] ischemic events = central and non-central nervous system embolism, ischemic strokes, TIA, tromboembolism

[2] bleeding events = hemorraghic stroke, major bleeding, gastrointestinal hemorrhaging.

[3] cardiovascular evenets = IHD, non-fatal CAD, AMI.

[4] cardiovascular events = i.e., AMI, ACS, CAD, CeVD, CHD, CHF, CVD, HF, IHD, MI, stroke.

[5] cardiovascular events = ACS, AMI, CVD, CAD, CHF, CeVD, VTE.

[6] symptoms = cough, phlegm, dyspnea.

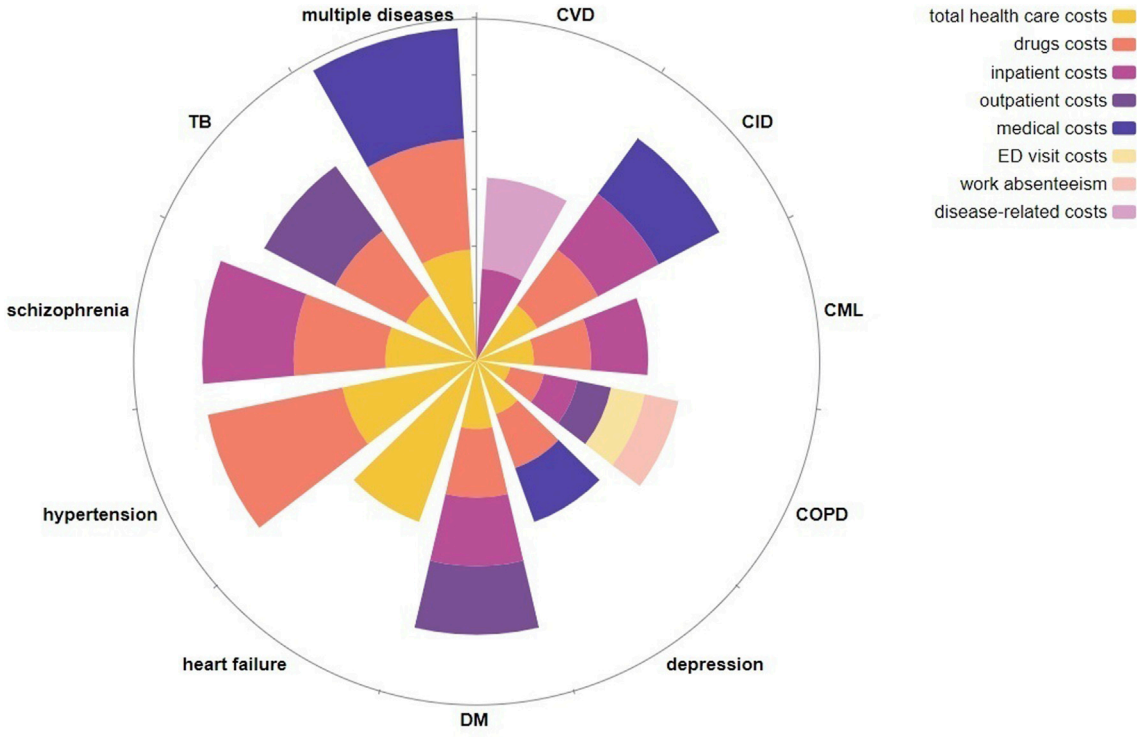
[7] microvascular events = amputations/ulcers nephropathy, neuropathy, renal failure, retinopathy, PVD.

[8] macrovascular events = angina, angioplasty, CABG, CeVD, CeV complications, CVD, CV, complications, CHF, HF, IHD, MI, stroke, TIA.

[9] cardiovascular events = CAD, overall CVD, acute CVD, CeVD, HF, CHF, IHD, AMI, stroke TIA.

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; ART, antiretroviral therapy; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CeV complications, cerebrovascular complications; CeVD, cerebrovascular disease; CHD, chronic heart disease; CHF, chronic heart failure; CV, complications, cardiovascular complications; ED, visits, emergency department visits; GvHD, graft versus host disease; HF, heart failure; HSCT, haematopoietic stem cell transplantation; ICS, inhaled corticosteroids; IHD, ischemic heart disease; MI, myocardial infarction; sUA, serum uric acid; TIA, transient ischemic attack; PVD, peripheral vascular disease; VTE, venous thromboembolism.

10.3389/fphar.2025.1570359



CVD = cardiovascular disease; CID = chronic inflammatory disease; CML = chronic meyloid leukemia; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ED visit costs = emergency department visit costs; TB = tuberculosis

FIGURE 2
Overview of the clinical consequences of medication nonadherence by clinical area with ray length representing the relative amount of identified studies in each clinical area.

lung diseases ($N = 3$). Importantly, this is not the same as the amount of individual studies in a clinical area. For example, only two systematic reviews on diabetes mellitus were included, but these reviews included about 110 individual studies (Evans et al., 2022; Capoccia et al., 2016), whereas the three reviews on chronic lung disease included maximally 23 individual studies (Bårnes and Ulrik, 2015; Ágh et al., 2015; van Boven et al., 2024). In all studies, the outcomes were compared between nonadherent and adherent patients, or outcomes were compared between different levels of adherence.

Overall, no consistent definition of medication (non)adherence within the included studies was found and in some studies (non) adherence was not defined at all. Also, the adherence measurement methods and thresholds for nonadherence varied greatly within the studies.

Clinical impact of nonadherence

In Table 1, an overview of the systematic reviews on the clinical impact of medication nonadherence is provided. Clinical outcomes were often disease specific, but also more generic outcomes (e.g., hospital admissions, all-cause mortality) were reported to be associated with, and mostly negatively impacted by, medication nonadherence. In Figure 2, the clinical outcomes are summarized by clinical area.

Generic clinical outcomes

The generic clinical outcomes (mostly) significantly impacted by nonadherence that were identified within the systematic reviews were quality of life ($N = 7$) (van Boven et al., 2014; Souza et al., 2016; Parmar et al., 2017; Nassetta et al., 2022; Bårnes and Ulrik, 2015; Chimeh et al., 2020; Ágh et al., 2015), hospitalization ($N = 12$) (van Boven et al., 2014; Walsh et al., 2019; Lee et al., 2022; Martin-Ruiz et al., 2018; Evans et al., 2022; Deshpande et al., 2017; Capoccia et al., 2016; Ho et al., 2016; De Vera et al., 2014a; Nassetta et al., 2022; Bårnes and Ulrik, 2015; Maniadakis et al., 2018), emergency department (ED) visits ($N = 5$) (van Boven et al., 2014; Walsh et al., 2019; Evans et al., 2022; Capoccia et al., 2016; Ho et al., 2016), outpatient visits ($N = 2$) (van Boven et al., 2014; Evans et al., 2022) and mortality ($N = 15$) (van Boven et al., 2014; Walsh et al., 2019; Lee et al., 2022; Sussman et al., 2022; Martin-Ruiz et al., 2018; Deshpande et al., 2017; De Vera et al., 2014a; Nassetta et al., 2022; Bårnes and Ulrik, 2015; Chimeh et al., 2020; El-Saifi et al., 2018; Kengne et al., 2024; Inotai et al., 2021; Visintini et al., 2023; Hussain et al., 2021).

In patients with arterial hypertension (Souza et al., 2016), asthma (Bårnes and Ulrik, 2015), COPD (van Boven et al., 2014; Ágh et al., 2015), thalassemia (Lee et al., 2024), and in (pediatric) patients with a heart or liver transplantation (Parmar et al., 2017; Nassetta et al., 2022), quality of life was overall negatively associated with medication nonadherence. However, whether a lower quality of

TABLE 2 Overview of systematic reviews reporting on the economic consequences of medication nonadherence.

First author, year of publication	Clinical area	Definition of (non)adherence	Medication	Included studies with economic outcomes/ included studies (n/N)	Economic outcomes	Direction (-/+)* and significance (S, NS, NR) ** on outcome
Deshpande (2017)	Cardiovascular disease (CVD)	"Adherence is usually defined as the extent to which a patient acts in accordance with the prescribed interval and dosing regimen." "Persistence is defined as the duration of time from the initiation to discontinuation of therapy."	statins, not specified	3/151	inpatient costs	- NR
					other CVD related costs	- NR
Maniadakis (2018)	Chronic inflammatory disease (CID)	"Compliance: The extent to which a patientacts in accordance with the prescribed interval and dose of a dosing regimen." "Persistence: The duration of time from initiation to discontinuation of therapy."	biologic therapy	7/129	drug costs	+ NR
					inpatient costs	- S
					medical costs	- NR
					total healthcare costs	- S
Noens (2014)	Chronic myeloid leukaemia (CML)	-	BCR-ABL inhibitor (imatinib)	3/19	drug costs	+ NR
					inpatient costs	- NR
					total healthcare costs	- NR
van Boven (2014)	Chronic obstructive pulmonary disease (COPD)	"the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen"	COPD medication, not specified	4/12	drug costs	+ NR
					inpatient costs	- NR
					outpatient costs	+ - NR
					ED visits costs	- NR
					total healthcare cost	- NR
					work absenteeism	- S
Ho (2016)	Depressive disorder	-	antidepressants, not specified	3/11	drug costs	+ S
					medical costs (physician, emergency room, hospital, laboratory, or any other medical charges)	- S and NS
					total healthcare costs	+ - NS
Capoccia (2015)	Diabetes mellitus (DM)	-	glucose-lowering agents, not specified	4/98	inpatient costs	- S
					total healthcare costs	- S and NR

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10.3389/fphar.2025.1570359

TABLE 2 (*Continued*) Overview of systematic reviews reporting on the economic consequences of medication nonadherence.

First author, year of publication	Clinical area	Definition of (non)adherence	Medication	Included studies with economic outcomes/ included studies (n/N)	Economic outcomes	Direction (-/+)* and significance (S, NS, NR) ** on outcome
Evans (2021)	Diabetes mellitus (DM), type 2	"adherence as the extent to which a person's antidiabetic medication-taking behaviour corresponds with recommendations from their healthcare provider" "Persistence was estimated based on the fill time between prescriptions or medication insurance claims."	antidiabetic medications, not specified	20/92	drug costs	+ S and NS, - NS
					inpatient costs	- S and NS
					outpatient costs	- S and NS
					other costs	+ - NS
					total healthcare costs	+ - S and NS
Hameed (2014)	Heart failure	"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"	not specified	3/9	total healthcare costs	- NR and NS
Kengne (2024)	Hypertension and/or dyslipidaemia	-	antihypertensives and lipid-lowering medications, not specified	18/45	drug costs	+ NR
					total healthcare costs	- S
Pennington (2018)	Schizophrenia	-	antipsychotics, not specified	28/28	drug costs	- S and NS, + S
					inpatient costs	+ - S and NS
					total healthcare costs	+ - S and NS
Chimeh (2020)	(drug-susceptible) Tuberculosis (TB)	"Adherence is defined as "the extent to which a person's behaviour to take medicines, to follow a diet, and/or to execute lifestyle changes corresponds with agreed recommendations from a healthcare provider."	TB medications, not specified	2/14	drug costs	+ NR
					outpatient costs	+ NR
					total healthcare costs	+ - NR
Cutler (2018)	Multiple diseases	"the extent to which the patients' behaviour matches agreed recommendations from the prescriber"	not specified	79/79	drug costs	+ NR
					medical costs	+ - NR
					total healthcare costs	+ - NR

*+ = positive relation between clinical outcome and nonadherence; - = negative relation between clinical outcome and nonadherence, ? = direction of relation between clinical outcome and nonadherence not stated or unclear

** S= significant, NS= nonsignificant, NR= not reported

Abbreviations: CID=chronic inflammatory disease; CML=chronic myeloid leukaemia; COPD=chronic obstructive pulmonary disease; CVD= cardiovascular disease; DM= diabetes mellitus; ED visit= emergency department visit

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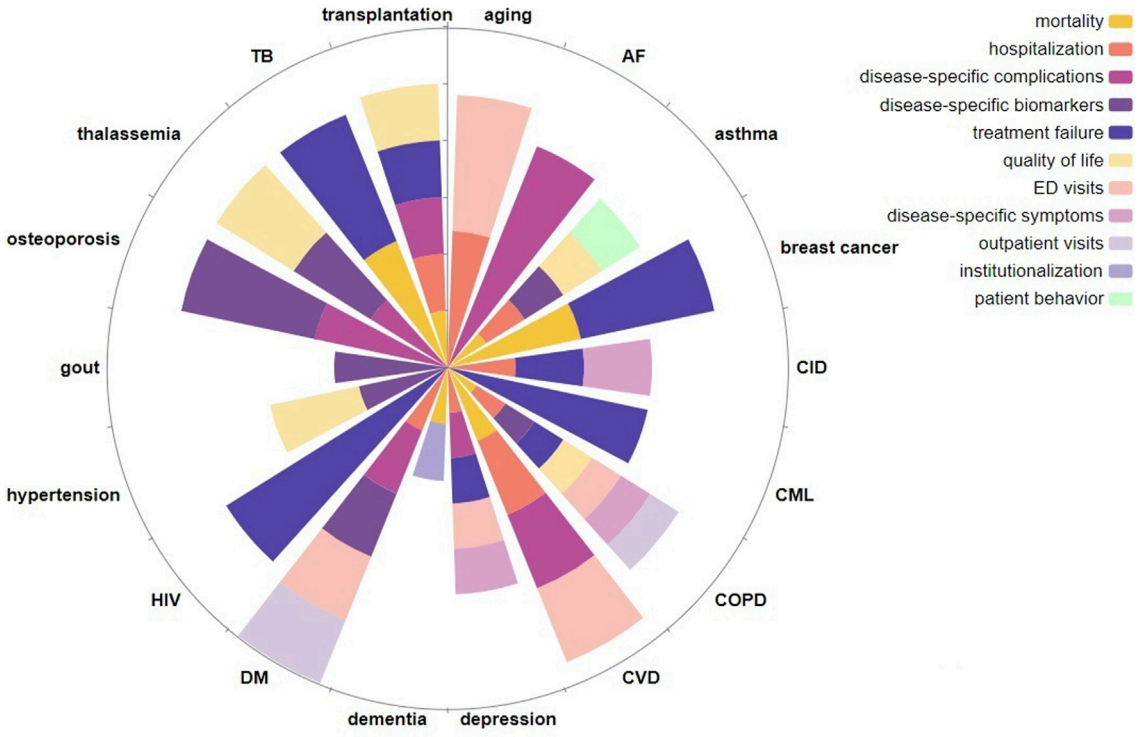

AF = atrial fibrillation; CID = chronic inflammatory disease; CML = chronic meyloid leukemia; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DM = diabetes mellitus; ED visits = emergency department visits; HIV = human immunodeficiency virus; TB = tuberculosis

FIGURE 3
Overview of the economic consequences of medication nonadherence by clinical area with ray length representing the relative amount of identified studies in each clinical area.

life resulted in more medication nonadherence or *vice versa* was not always clear. Besides, although all the reviews focused on health related quality of life (HRQoL) it was measured variously over the included studies and in some studies and reviews a distinction was made between different components of quality of life. For example, in the review concerning patients with hypertension, both the total scores on quality of life as well as the mental and physical component were presented (Souza et al., 2016). In table 1, this differentiation has not been made and only the overall impact on quality of life is presented.

A higher risk of hospitalization due to nonadherence was found in more patient populations, that is, in patients with asthma (Bårnes and Ulrik, 2015), chronic inflammatory disease (Maniadakis et al., 2018), COPD (van Boven et al., 2014), cardiovascular disease (Martin-Ruiz et al., 2018; Deshpande et al., 2017; De Vera et al., 2014a), depression (Ho et al., 2016), diabetes (Capoccia et al., 2016), pediatric heart transplantation (Nassetta et al., 2022), hypertension (Lee et al., 2022), and in a general aging population (Walsh et al., 2019). Hospitalization was also operationalized variously, i.e., hospital admissions, duration of being hospitalized, or specified as being disease-specific or all-cause hospitalization. The latter differentiation was also found in relation to the outcomes "outpatient visits" and Emergency Department (ED) visits. The systematic reviews that covered these clinical outcomes showed an increase in ED visits (van Boven et al., 2014; Walsh et al., 2019; Evans et al., 2022; Capoccia et al., 2016; Ho et al., 2016) and outpatient visits (van Boven et al., 2014; Walsh et al., 2019; Evans et al., 2022) in nonadherent patients with COPD (van Boven et al., 2014), diabetes (Evans et al., 2022; Capoccia et al., 2016), depression (Ho et al., 2016) and in the general aging population (Walsh et al., 2019). Notably, one systematic review on patients with type 2 diabetes demonstrated less outpatient visits in patients being less nonadherent to their medication compared to patients that were more adherent (Evans et al., 2022). One systematic review found a higher risk on institutionalization in nonadherent patients with dementia (El-Saifi et al., 2018).

Furthermore, it was found that mortality rates, all-cause or disease specific, were higher in nonadherent patients with non-vulvar atrial fibrillation (Sussman et al., 2022), asthma (Bårnes and Ulrik, 2015), breast cancer (Inotai et al., 2021; Eliassen et al., 2023), COPD (van Boven et al., 2014), cardiovascular disease (Martin-Ruiz et al., 2018; Deshpande et al., 2017; De Vera et al., 2014a), dementia (El-Saifi et al., 2018), heart and stem cell transplants (Nassetta et al., 2022; Visintini et al., 2023; Hussain et al., 2021), hypertension (Lee et al., 2022; Kengne et al., 2024) and tuberculosis (Chimeh et al., 2020). In patients with breast cancer, it was also found that the probability of disease-free survival was higher among more adherent patients (Inotai et al., 2021).

Disease specific clinical outcomes

Some studies included disease specific outcomes such as disease-specific health risks or complications, disease-related symptoms or disease-specific biomarkers.

In patients with COPD (van Boven et al., 2014), chronic inflammatory diseases (CID) (Maniadakis et al., 2018) and depression (Ho et al., 2016) and the aging population (Walsh et al., 2019), disease-specific symptoms, such as experienced depression severity, were used as a clinical outcome. Overall, these patients reported either more symptoms or more severe symptoms when they were not adhering to their medication regimen. One review reported an association between patient medication behavior as clinical outcome and nonadherence (Bårnes and Ulrik, 2015). That is, in patients with asthma, a higher number of rescue courses of oral corticosteroids (a proxy for asthma exacerbations) was positively associated with nonadherence, although nonsignificant (Bårnes and Ulrik, 2015).

Disease-related health risks and complications were mostly reported in patients with cardiovascular disease. Generally, these patients had a significant higher risk for cardiovascular events such as acute myocardial infarction (AMI), cerebrovascular disease (CeVD), and ischemic stroke, when being nonadherent compared to patients being adherent (Martin-Ruiz et al., 2018; Deshpande et al., 2017; De Vera et al., 2014a; Kengne et al., 2024). On the contrary, in patients with AF being adherent to anticoagulants, this was significantly and positively associated with bleeding events (Shehab et al., 2019; Sussman et al., 2022). In patients with heart, liver or stem cell transplantation (Nassetta et al., 2022; Visintini et al., 2023; Hussain et al., 2021), patients with breast cancer (Inotai et al., 2021; Eliassen et al., 2023), HIV (Foka and Mufhandu, 2023), hypertension (Lee et al., 2022; Kengne et al., 2024), thalassemia (Lee et al., 2024), tuberculosis (Chimeh et al., 2020) and DM (Evans et al., 2022; Capoccia et al., 2016), being nonadherent was mostly significantly related to severe and life-threatening disease-specific complications as well. Furthermore, recurrence or worsening of disease was more common in nonadherent patients with breast cancer (Inotai et al., 2021), CID (Maniadakis et al., 2018) and depression (Ho et al., 2016). Lastly, it was demonstrated that patients with osteoporosis have a significantly higher risk of fractures (Mikyas et al., 2014; Alahmari et al., 2023) and patients with hypertension have significantly worse blood pressure control (Lee et al., 2022; Kengne et al., 2024) due to medication nonadherence.

Biomarkers have been associated with nonadherence such as bone mineral density in osteoporosis (Alahmari et al., 2023) or forced expiratory volume in 1 s (FEV1) (van Boven et al., 2014), eosinophil percentage (Bårnes and Ulrik, 2015) in asthma and additionally histamine determination (PC20) (van Boven et al., 2014) in COPD. Other biomarkers that have been negatively influenced by nonadherence are glycohemoglobin (HbA1c) (Evans et al., 2022; Capoccia et al., 2016) and hypoglycaemia (Evans et al., 2022) in DM, serum urine acid (sUA) in gout (De Vera et al., 2014b; Lee et al., 2024), serum ferritin in thalassaemia (Lee et al., 2024), and blood pressure control (Lee et al., 2022; Kengne et al., 2024) and cholesterol levels (LDL) (Kengne et al., 2024) in hypertension.

Economic impact of nonadherence

In Table 2, an overview of the economic impact of medication nonadherence is provided. Economic outcomes were often direct healthcare costs, though only one systematic review provided data on the impact of medication nonadherence on indirect costs. In Figure 3, the economic outcomes are summarized by clinical area.

Direct healthcare costs

Direct healthcare cost outcomes identified within the included systematic reviews were inpatient costs ($N = 7$), outpatient costs ($N = 3$) (van Boven et al., 2014; Evans et al., 2022; Chimeh et al., 2020), ED visit costs ($N = 1$) (van Boven et al., 2014), medical costs (healthcare costs excluding drug costs) ($N = 2$) (Ho et al., 2016; Maniadakis et al., 2018), drug costs ($N = 8$) (van Boven et al., 2014; Evans et al., 2022; Ho et al., 2016; Chimeh et al., 2020; Kengne et al., 2024; Maniadakis et al., 2018; Noens et al., 2014; Pennington and McCrone, 2018), and total healthcare costs ($N = 11$) (Cutler et al., 2018; van Boven et al., 2014; Evans et al., 2022; Capoccia et al., 2016; Ho et al., 2016; Chimeh et al., 2020; Kengne et al., 2024; Maniadakis et al., 2018; Noens et al., 2014; Hameed et al., 2014; Pennington and McCrone, 2018).

In most reviews, nonadherent patients had higher medical costs and lower drug costs. However, the overall impact of medication nonadherence on total healthcare costs was found to be mixed, mostly varying between increased costs and no significant change. This variation depended on whether the higher medical costs were balanced by the lower spending on drugs. Similar trends could be observed across all investigated disease areas, including DM (Evans et al., 2022; Capoccia et al., 2016), tuberculosis (Chimeh et al., 2020), cardiovascular disease (Deshpande et al., 2017), heart failure (Hameed et al., 2014), hypertension and dyslipidaemia (Kengne et al., 2024), depressive disorder (Ho et al., 2016), schizophrenia (Pennington and McCrone, 2018), chronic inflammatory disease (Maniadakis et al., 2018), chronic myeloid leukaemia (Noens et al., 2014), and COPD (van Boven et al., 2014).

The economic impact of medication nonadherence across multiple disease groups was evaluated in one systematic review (Cutler et al., 2018) only. This review revealed that medication nonadherence was generally associated with higher total healthcare costs, with significant variability in the economic impact across different diseases. Specific estimates for the mean (SD) adjusted total cost of medication nonadherence per annum per person were as follows: DM at $8,327 ($2,335), respiratory disease at $8,584 ($469), cardiovascular disease at $12,146 ($5,320), mental health conditions at $14,585 ($5,315), gastrointestinal disease at $30,771 ($8,270), and osteoporosis at $43,372 ($14,266) (all costs adjusted to 2024 US$). Despite the fact that cost data across various disorders were compared after being converted to the same currency and year, and were extrapolated to annual costs, there was a wide range between disease-specific estimates. This variability can be partly attributed to the various cost indicators used by the individual studies and other heterogeneity in study design, not allowing meaningful cost comparisons between diseases.

Indirect costs

Only one systematic review (van Boven et al., 2014) reported data on the association between medication adherence and indirect costs, specifically productivity. Based on a retrospective analysis of US administrative healthcare claims, adherent patients with asthma/COPD had significantly fewer days absent from work, with potential annual savings of around $2,504 (adjusted to 2024 US$) per employee. Cutler et al. (2018) also investigated indirect costs, but did not report any information on the impact of medication nonadherence on indirect costs, only which study assessed them and which types of indirect cost outcomes were included (e.g., short-term disability, workers' compensation, paid time off costs, productivity costs, absenteeism costs, and presenteeism costs).

Discussion

Main findings

This narrative review of systematic reviews demonstrates the many negative, and sometimes even fatal, consequences of medication nonadherence. Thirty-one systematic reviews on the association between nonadherence and clinical outcomes were found across 17 different clinical areas and 12 systematic reviews on the association with economic outcomes in 11 clinical areas. Most studies on clinical outcomes demonstrated a positive and significant association between nonadherence and mortality, hospitalization and ED visits. Areas covered were mostly organ transplantation, cardiovascular diseases, and chronic lung diseases. Almost all studies on economic outcomes showed higher costs in patients with lower levels of adherence to medication. These costs were mostly related to total healthcare costs, drug costs and inpatient costs.

Interpretation of findings

Nonadherence demonstrated to negatively impact most identified outcomes significantly over multiple studies and clinical areas, and with respect to both economic and clinical outcomes. Given this broad impact, there are some important considerations that need to be highlighted.

Medication nonadherence was regularly not (clearly) defined and measurement methods varied greatly within and between outcomes and clinical areas. This is a well-known described issue in both research and daily clinical practice (Jimmy and Jose, 2011; Lam and Fresco, 2015; Stirratt et al., 2015). Besides, each measurement method is known for its unique strengths and limitations, e.g., the questionable reliability of patient self-reports and the limited informational value but more objectiveness of pharmacy records (Jimmy and Jose, 2011; Lam and Fresco, 2015). Because of these limitations, it has been recommended to combine two different measurement methods for optimal and reliable information on patients' medication use (Lam and Fresco, 2015). To obtain more detailed and objective data, digital adherence technology such as electronic pill bottles or digital inhalers could be used. Yet, most studies used only one measurement method. Remarkably, one study used clinical outcomes itself (i.e., reduction or control of blood pressure) as (indirect) measurement method of level of adherence (Souza et al., 2016). Furthermore, two studies differentiated between medication adherence and persistence (Evans et al., 2022; Maniadakis et al., 2018). Even though persistence always includes the element of time in its measurement method and adherence measurement methods do not, we did not use this differentiation in our review. When we referred to adherence in this review, this also included persistence. Altogether, the variety in measurement methods of medication adherence is both a strength and a limitation. On the one hand, even when measured differently, similar findings are demonstrated across studies, confirming and strengthening the evidence regarding the negative impact of nonadherence. On the other hand, due to this variety in measurement methods, comparisons within the same clinical area but across different studies, is challenging and meta-analysis was often not possible. Note that also outcome definitions varied, i.e., hospitalization was measured as rehospitalization, duration of hospitalization, all-cause hospitalization and disease-related hospitalization.

With this review, we aimed to provide an overview of the consequences of medication nonadherence. However, it was not always possible to clearly distinguish between the consequences and the associated factors of medication adherence. Causality is difficult to establish, even in clinical trials. Where most criteria for demonstrating a causal relation are integrated in randomized controlled trials, it is not bulletproof, especially when it concerns patient behavior or experiences. An example of a clinical outcome for which causality with adherence is questionable, is quality of life. If medication adherence improves quality of life–due to, e.g., less symptoms as consequence of medication adherence–or if a higher quality of life results in more medication adherent behavior–because patients with a higher quality of life, for example, receive more social support to be adherent.

Related to the topic of causality, an absence of treatment effect–seen in, e.g., patients with HIV, tuberculosis, COPD and asthma–and negative consequences of pharmaceutical treatment–e.g., in patients with AF–can also be caused by individual differences in pharmacokinetics and pharmacodynamics. For example, some studies identified a lower probability of virologic suppression in nonadherent HIV patients compared to adherent HIV patients (Altice et al., 2019; Foka and Mufhandu, 2023). In another study, no significant difference in improvement in lung function–FEV1 in COPD and asthma, and % eosinophils in asthma–was found between adherent and nonadherent COPD and asthma patients (van Boven et al., 2014; Bårnes and Ulrik, 2015). The treatment failure in these studies could indeed be attributed to medication nonadherence, however treatment failure could potentially also be (partially) explained by the absence of a biological response in these patients. Regarding these individual differences in biological response, in some clinical areas relatively little is known yet, e.g., asthma and depression (Drevets et al., 2022; Vijverberg et al., 2018; Norbury and Seymour, 2018), and this variability is

not accounted for in medication effectiveness and adherence studies. However, an increase in interest is seen in, e.g., studies on the biological response differences between men and women (Soldin and Mattison, 2009; Madla et al., 2021; Franconi et al., 2007).

The relevance of medication adherence differs greatly between diseases and there seems to be relatively limited attention for these characteristics. The forgiveness of a drug concerns the amount of deviation in adherence that is allowed to still gain the intended effect of that drug (Assawasuwannakit et al., 2015). This pharmaceutical forgiveness of nonadherence, and the threshold of medications' treatment effect varies by disease and drug (McAllister et al., 2022; Osterberg et al., 2010). For example, the forgiveness of nonadherence for immunosuppressants in patients with organ transplantation is much lower than the forgiveness of statins in patients with (a risk for) cardiovascular diseases (Osterberg et al., 2010). Although we identified mostly severe to fatal consequences of nonadherence, also the clinical and economic consequences of medication nonadherence can be more or less severe, and therefore more or less relevant, across clinical areas. The relevance–forgiveness and consequences–of medication nonadherence for a disease is an essential consideration when comparing medication nonadherence over multiple clinical areas (McAllister et al., 2022). The same is true for the feasibility to achieve good medication adherence. Medication plans or schedules can be more or less complex and extensive within and between both individual patients and diseases. The higher the impact and likelihood of nonadherence in any particular disease area, the higher the likelihood that interventions that focus on enhancing adherence will be clinically effective and cost-effective.

Strengths and limitations

With this semi-systematic narrative review, we have aimed to provide an up-to-date overview of the overall impact of medication nonadherence across disease areas. However, given the pragmatic nature of this narrative review, we possibly missed some relevant articles with our search strategy as we only included articles published in English, and focused on systematic reviews published in the last decade. Also, some studies could have been overlooked given only one researcher included the studies on clinical outcomes and one researcher included the studies on economic outcomes. Also, we do not provide a detailed overview of the included studies. These details, such as the medication adherence measurement methods, are important for the interpretation of our findings. However, we do provide an extensive overview of all the clinical outcomes together with how these outcomes are associated with nonadherence and its significance. In addition, the context–such as specific patient characteristics (e.g., health literacy) or the organization of healthcare in a specific population (e.g., accessibility) – could potentially moderate the relation between nonadherence and the clinical and economic consequences. This was however beyond the scope of this review. Notably, we also categorized negative consequences as reported in the included reviews. However, whether the consequence is indeed always negative or positive depends on its context. For example, in one study on patients with diabetes, it was found that nonadherence was related to less outpatients visits. Whether less frequent outpatient visits are however negative for the patient depends on the nature of these visits. That is, if the outpatient visits concern pro-active or preventative disease and medication patient behaviors, more outpatient visits could not be interpreted as negative. This should be considered when interpreting the these study's findings. Furthermore, although we only included systematic reviews and meta-analysis published in the last decade, these studies mostly included original studies that were published before. Another strength is that we included different clinical specialties instead of focusing on one clinical area as in most previous reviews. This allows some comparison across diseases, and could contribute to identify priority clinical areas in which nonadherence should be addressed and tackled.

Recommendations

The clinical consequences for patients and the financial burden of medication nonadherence has been established once more, demonstrating the necessity to invest in interventions detecting and managing nonadherence. However, it remains a challenge for healthcare providers to identify and manage treatment nonadherence (Jimmy and Jose, 2011; El Halabi et al., 2022). More use of (a combination of) validated and objective adherence measurement instruments and the implementation of effective interventions in policy and in daily clinical practice is recommended (Jimmy and Jose, 2011; Lam and Fresco, 2015). However, implementation often turns out to be challenging given studies typically report limited details necessary for implementation (Zullig et al., 2019). We recommend contacting study teams of relevant literature on effective interventions to provide this necessary information. In reporting, implementation science and frameworks can be used to determine what information is needed (Bauer and Kirchner, 2020). Most importantly, the interventions should consider the implementation process from the start, i.e., including stakeholders in the whole process and report more details on the context. Furthermore, concordance of patients' and physicians' treatment goals) and simplification of treatment regimens–where possible–are highly recommended for managing nonadherence (El Halabi et al., 2022). Yet most importantly, the reasons for nonadherence should be used as guide for selecting the most suitable intervention. The communication skills of healthcare professionals are demonstrated to be crucial in this and are often demanded to execute interventions effectively (Haskard Zolnierek and DiMatteo, 2009). Educational programs and intervention trainings should therefore emphasize verbal and nonverbal

communication skills. In this review, several inconsistencies and gaps in the literature were identified and this provides guidance for further research. Primarily, there is a need for more disease-specific differentiation between adherence and nonadherence and its measurement methods. Future studies on the impact of medication nonadherence should consider the pharmaceutical forgiveness of each specific pharmaceutical treatment–including the threshold for the treatment effect–to create a more meaningful differentiation between adherence and nonadherence. This together with a unified definition of medication nonadherence will also allow for a more meaningful comparison between studies and clinical areas, and could provide essential insights to inform treatment guidelines. Besides, a more in depth understanding of some disease-specific causes and its influences on nonadherence is required, e.g., on the possible influence of heterogeneity in biological response on medication nonadherence and its clinical consequences. Lastly, although many interventions for nonadherence have been developed over the years, there is still a need for more precise and usable adherence measurements that can be integrated into daily clinical practice (Jimmy and Jose, 2011; Lam and Fresco, 2015). The more specific and valid medication nonadherence measures, the more relevant these measures are for daily practice and therefore the higher the change of uptake of these measure in guidelines and practice. Evidently, though some of the chronic diseases with the highest disease burden are covered–i.e., cardiovascular disease, diabetes mellitus and chronic lung diseases COPD and asthma–there are also clinical areas that were less covered. Although a worldwide increase is found in, e.g., mental health diseases, cancers and substance use, relatively little or no studies concerning these clinical areas were identified and covered in this narrative review (United Nations, 2023; Roser et al., 2024). More research in needed in these clinical areas. Moreover, contextual factors such as population specific characteristics (e.g., health beliefs) or healthcare organizational factors (e.g., accessibility of healthcare) could potentially also moderate the relationship between nonadherences and the consequences differently in various disease groups. This was beyond the scope of this study and seems to be an underexposed although potentially relevant topic for further comparison between disease groups.

Despite the amount of studies demonstrating the serious consequences of medication nonadherence, the rates of nonadherence do not seem to have declined although it is estimated that medication use and costs will keep increasing the next years (IQVIA Institute, 2024). A positive remark is that adherence issues have been integrated more and more in guidelines, e.g., in the GINA 2023 report on asthma and the ESC 2024 guidelines on hypertension (McEvoy et al., 2024; Global Initiative for Asthma, 2023). Still, we should bring nonadherence to the top of the agenda of stakeholders. We should focus particularly on the implementation of nonadherence measurement instruments and interventions thereby taking into account the socioeconomic and cultural factors associated with nonadherence. The socioeconomic and cultural factors such as lack of access to medicines due to lack of financial capacity or reachability of healthcare facilities, but also the reluctance of patients to embrace medication regimes because of, e.g., cultural differences, are crucial (Ágh et al., 2024). In many African countries and in Traditional Chinese Medicine, spirituality and herbal products have a more prominent healthcare and the patients' health beliefs. Therefore, the negative consequences of medication nonadherence observed in this review could be worse in developing regions and regions with different beliefs and customs concerning healthcare such as Sub-Saharan Africa (Kagee et al., 2011; Macquart de Terline et al., 2019). Lastly, both in designing and implementing nonadherence interventions, the context should be considered thoroughly and measurement instruments and interventions should be adjusted culturally appropriate.

Conclusion

Across disease areas, medication nonadherence in patients with chronic diseases has been associated with elevated disease burden and mortality, increased healthcare utilization (including hospital admissions), and higher direct (e.g., more healthcare provider visits) and indirect financial cost burden (e.g., work productivity losses due to absenteeism and presenteeism). Given this significant impact, interventions on both policy, health system and individual patient level are required. For the greater implementation of measurement instruments and interventions in daily practice, stakeholders such as healthcare professionals, patients and insurers need to be involved from the start. Current available evidence to improve nonadherence could be used more effectively by considering the context and content of both the studies and the targeted population more thoroughly. Furthermore, the development and more frequent and precise use of adherence measurement tools, the provision of personalized interventions based on nonadherence behavioral phenotypes and adequate reimbursement of cost-effective adherence enhancing interventions in daily practice are recommended.

Author contributions

MA: Data curation, Formal Analysis, Investigation, Software, Visualization, Writing – original draft, Writing – review and editing. NA: Data curation, Investigation, Methodology, Writing – original draft, Writing – review and editing. GO: Data curation, Investigation, Writing – original draft, Writing – review and editing. DA: Data curation, Investigation, Writing – original draft, Writing – review and editing. TÁ: Conceptualization, Investigation, Methodology, Supervision, Writing – review and editing. JvB: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review and editing.

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Supplementary material

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Healthcare provider interventions to support medication adherence: state-of-the-science overview

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Medication adherence remains a global health issue and healthcare providers (HCPs) play an important role in supporting patients to adhere to treatment. This article provides a state-of-the-science overview of the evidence for: i) the effectiveness of HCP-delivered interventions on medication adherence outcomes; and ii) the types of implementation approaches targeting evidence-to-practice gaps among HCPs supporting medication adherence. Hundreds of randomized controlled trials and dozens of systematic reviews on the effectiveness of HCP-delivered interventions have been conducted to date. HCP-delivered interventions typically produce small-to-medium effect sizes on adherence outcomes, however, there is considerable heterogeneity in effects and few interventions that show promise are implemented into routine practice. Some key features of potentially effective HCP-delivered interventions include: moving beyond education-only, using multiple behaviour change strategies, tailoring interventions to different determinants of non-adherence, incorporating pharmacists and nurses to deliver interventions, providing ongoing support to patients, and addressing health system-level barriers and inequities. To improve the uptake of evidence into adherence-related clinical practice, it is likely that health systems must adapt to enable HCPs to better support adherence over time and in a patient-centered way. Such approaches include, improving routine screening of adherence issues, making adherence-related clinical guidelines more actionable, using routinely collected data to identify patients with adherence challenges, enhancing HCP incentivization models, and establishing quality indicators for adherence monitoring and support. Concepts and evidence from implementation science should be leveraged to support these types of system-level approaches to address evidence-to-practice gaps. In conclusion, despite an extensive evidence base for the effectiveness of HCP-delivered interventions - and a growing body of evidence for approaches targeting practice change among HCPs - we have identified several areas that could help advance the field. These include optimizing the content and delivery of adherence interventions, understanding how to implement effective strategies, and reaffirming the need for health system-level solutions.

KEYWORDS

medication adherence, behaviour change, healthcare providers, implementation science, health systems, state-of-the-science

1 Introduction

Medication adherence is a global health problem which has been extensively researched over the past 60 years. Taking medication as prescribed is crucial for the full benefits of the therapy to be realized, yet many patients face challenges in this regard which can lead to poorer clinical outcomes, increased healthcare utilization, and additional cost to health systems (Khan and Socha-Dietrich, 2018; Sabaté, 2003). Medication non-adherence is considered a major problem across all chronic conditions with myriad factors associated with poor adherence identified from the literature (e.g., patient-, disease-, therapy-, socioeconomic-, and healthcare system-related factors (Sabaté, 2003; Kardas et al., 2024)). Not only does this reflect the complexity of medication-taking as a behaviour (i.e., there are many potential barriers to taking medication as prescribed), it also means that it can be difficult to identify the key issues among individual patients having difficulties with their regimen (Kardas et al., 2013).

Medication adherence is defined as the extent to which a patient takes a medication in line with the treatment regimen agreed upon with their healthcare provider (HCPs) (Sabaté, 2003). Medication-taking behaviour can be difficult to measure in routine practice and often relies on self-report from patients which is associated with potential social desirability and recall bias that may underestimate the extent of the problem. Moreover, HCPs have been shown to underestimate rates of non-adherence among their patients (MacIntyre et al., 2005; Miller et al., 2002) meaning that patients who may need support can often go undetected. Researchers have posited three stages of medication adherence: initiation (e.g., starting a medication), implementation (e.g., fitting medication-taking into one's routine), and persistence (e.g., maintaining medication-taking over time) (Vrijens et al., 2012). Barriers to medication-taking may look very different depending on the stage of adherence. For example, understanding how to take a medication correctly is particularly important during the initiation phase, understanding where a medication best fits into one's daily routine is important during the implementation phase, and connecting with a HCP if there are concerns about side effects may be a necessary action during the maintenance phase.

Several behaviour change theories, models, and frameworks have been applied to better our understanding of medication-taking behaviour (Conn et al., 2016a). One such prominent theory of medication adherence is the Perceptions and Practicalities Approach (PAPA) developed by Horne and colleagues (Horne et al., 2019). The PAPA posits that individuals taking medication can experience both perceptual (e.g., patients' beliefs and preferences about their medication regimen–intentional non-adherence) and practical barriers (e.g., patients' capacity and resources to follow their medication regimen–unintentional non-adherence) and that any support provided to patients should match the types of barriers they are experiencing (National Institute for Health and Care Excellence, 2009). For example, if a patient is weighing up whether a medication is going to help their condition (necessity beliefs) versus the risk of problematic side effects (concerns about adverse effects), this would be considered a perceptual barrier. Where a patient is having difficulty following a medication regimen due to an inconvenient dosing schedule, this would constitute a practical barrier. The type of patient-centered supports offered by HCPs are likely to differ markedly depending on the type of barrier identified with some designed to make adherence easier and more convenient and others to enhance motivation by addressing the perceptions that influence motivation (National Institute for Health and Care Excellence, 2009).

HCPs play a crucial role in supporting patients to take their medications as prescribed. HCPs are the gatekeepers for prescribed medications and their interactions are central for setting patients up for success with their treatment regimens. Different HCPs are involved in the prescribing process and supporting medication-taking over time. Physicians, nurses, and pharmacists can all play key roles to support adherence across a patients' journey, however, there are inconsistencies in how such roles are fully realized in routine practice and multiple barriers in medication adherence management continue to be surfaced in the literature (Hafez et al., 2024). In particular, issues can arise when medication adherence is not seen as a shared goal and responsibility between HCP and patient which can undermine efforts to help patients take medication correctly over time (Bosworth et al., 2011).

HCPs can be considered as either intervention deliverers (e.g., a pharmacist providing a standardized counselling session to a patient about the importance of adherence) or intervention recipients (e.g., conducting an audit of practice among pharmacists and providing feedback (i.e., audit and feedback) to identify opportunities to improve practice), which is a subtle but important distinction. This perspective can also be extended to consider the 'dual' role of HCPs within the same intervention study. For example, in studies where HCPs are intervention deliverers, they should also be considered as intervention recipients and work should be done to understand their barriers to change and what can then be done to support implementation. We believe it is crucial to identify the supports that HCPs themselves need to change their clinical behaviour to increase the likelihood that patients receive evidence-based care to support medication-taking. To achieve this, we can draw upon concepts and evidence from implementation science which is a discipline focused on understanding why evidence-to-practice gaps occur in healthcare and how such gaps can be addressed in the real world (Grimshaw et al., 2012).

2 Aims

The aim of this state-of-the-science overview is two-fold. First, we will summarize evidence from a suite of systematic reviews looking at the effectiveness of HCP-delivered interventions on medication adherence outcomes. Second, we will take concepts and evidence from implementation science and summarize evidence on approaches targeting evidence-to-practice gaps among HCPs supporting medication adherence. In this overview, we focus mainly on data from randomized controlled trials, systematic reviews, and meta-analyses rather than individual studies or other types of intervention study designs.

3 Impact of HCP-delivered interventions on medication adherence outcomes

There have been dozens of systematic reviews (and systematic review of reviews) looking at the effectiveness of HCP-delivered

interventions on medication adherence outcomes (Wilhelmsen and Eriksson, 2019; Anderson et al., 2020; Ryan et al., 2014). As an exploratory exercise, we conducted a search of the Cochrane Library - considered the gold standard for evidence synthesis studies - to identify systematic reviews of interventions targeting medication adherence which likely reported features of HCP-delivered interventions (note, given this was an informal scan of a singular evidence repository, we do not report key information such as inclusion/exclusion criteria and PRISMA flowchart as per systematic review guidance). A total of 68 systematic reviews from the Cochrane Library had the term "medication adherence" listed in the title/abstract or as a keyword. Among this suite of systematic reviews, we screened for findings related to features of HCP-delivered interventions on medication adherence outcomes. We found 10 studies which reported key features of interventions which are summarized in Table 1. Among such studies, a range of clinical and health system outcomes were found including mortality, morbidity, healthcare utilization, healthcare costs, patient satisfaction, and quality of life (Conn et al., 2016b).

Across systematic review studies, HCP-delivered medication adherence interventions typically produce small-to-medium effect sizes for adherence outcomes (e.g., pharmacy-led interventions to support medication adherence in diabetes, standardized mean difference effect size = −0.68; 95% CI -0.79, −0.58; $p < 0.001$ (Presley et al., 2019); HCP-led interventions to support medication adherence in acute coronary syndrome, odds ratio = 1.54, 95% CI 1.26, 1.88, $p < 0.001$ (Crawshaw et al., 2017)), however, there is considerable heterogeneity in terms of sample population, intervention type, and study outcomes. Moreover, few interventions that show promise in improving adherence are powered to test their effect on clinical outcomes (Nieuwlaat et al., 2014) or are implemented into routine practice which contributes to evidence-to-practice gaps. Wilhelmsen and Eriksen conducted a systematic review of reviews around this topic which included 32 systematic reviews of varying methodological quality (Wilhelmsen and Eriksson, 2019). A total of eight systematic reviews, five of which were Cochrane systematic reviews, were rated as high-quality and were further analyzed. Some key findings from their analysis revealed that patient education and counselling (e.g., information to help patients understand what the medication is doing in the body, are addressing patient concerns that commonly occur such as worries about side effects or long-term impacts of taking a medication) showed some positive effects on medication adherence. Simplifying medication dosing was shown to have some benefit on morbidity and patient satisfaction. Interventions delivered by pharmacists and nurses were more effective than interventions delivered by primary care physicians. Similar findings were reported by Ryan and colleagues who conducted a Cochrane systematic review of 75 reviews evaluating the effects of interventions to improve medication adherence. In relation to features of HCP-delivered interventions, there was evidence that simplifying medication dosing and interventions involving pharmacists had generally positive effects on medication adherence (Ryan et al., 2014).

In the next section, we posit some key features of potentially effective HCP-delivered interventions to support medication adherence.

3.1 Moving beyond education-only

Patient education is a commonly used strategy to support adherence and HCPs are in a good position to deliver these types of interventions due to their established trusting relationship and ongoing contact with patients. However, whilst education is necessary for behaviour change (the individual needs to know about what they are meant to do and why it is important to do it), it may not be sufficient on its own to support meaningful behaviour change over time. Education can certainly help support a patient make sense of their medication regimen by addressing beliefs about their illness and/or treatment (perceptual barrier) yet other considerations may be required if a patient is experiencing practical barriers to adherence. A systematic review of reviews by Anderson and colleagues identified several adherence intervention components beyond education (focusing on practical barriers to medication-taking) that include simplifying medication dosing (e.g., reducing the number of medications or instances per day which medications are taken), electronic and non-electronic reminders, incentives to reduce out-of-pocket costs, monitoring and feedback, habit-focused interventions, and specialized medication packaging. Notably, interventions were found to be more effective when they included multiple strategies (Anderson et al., 2020). Whilst education may often be seen as the 'default' strategy (it is clearly important), it is crucial that HCPs have a variety of tools in their professional 'toolbox' to meet the needs of their patients.

3.2 Using multiple behaviour change strategies

It is expected that HCPs should have multiple behaviour change strategies at their disposal to support patients to be adherent over time (see medication adherence clinical practice guideline from the UK's National Institute for Health and Care Excellence (NICE) (National Institute for Health and Care Excellence, 2009)). In line with the PAPA outlined above, patient education and counselling (e.g., telling a patient about what medication they will be prescribed and answering any questions or concerns they might have) may be a helpful strategy for patients that report ambivalence towards their medications or have concerns about potential side effects (i.e., perceptual barrier, intentional non-adherence (Horne et al., 2019)). However, other strategies may be required for individuals who are motivated but experience other barriers to adherence, such as forgetting to take treatment regularly or having complex drug regimens to manage (i.e., practical barrier, unintentional non-adherence (Horne et al., 2019)). It should, however, be noted that intentional barriers (e.g., medication beliefs) and unintentional barriers (e.g., forgetting) may not be mutually exclusive, with some evidence that intentional non-adherence mediates unintentional non-adherence (Gadkari and McHorney, 2012).

3.3 Tailoring interventions to different determinants of non-adherence

In addition to the need for multiple behaviour change strategies to be available for HCPs, it is also probable that tailoring the strategy to the patient and the issues they are facing is required for the best

TABLE 1 Select studies from the Cochrane Library reporting features of HCP-delivered interventions to support medication adherence.

Author	Population	Intervention	Comparison	Outcome	Number of studies	HCP group	Key features of HCP-delivered interventions	Effect sizes	Certainty of evidence (based on GRADE criteria)
Nieuwlaat et al. (2014)	Various	Interventions of any sort intended to affect adherence with prescribed, self-administered medications	Group not receiving the intervention	Medication adherence Clinical outcomes	182 RCTs	Allied health providers	"The RCTs at lowest risk of bias generally involved complex interventions with multiple components, trying to overcome barriers to adherence by means of tailored ongoing support from allied health professionals such as pharmacists, who often delivered intense education, counseling (including motivational interviewing or cognitive behavioural therapy by professionals) or daily treatment support (or both), and sometimes additional support from family or peers"	Not conducted due to high heterogeneity	Not reported
Cross et al. (2020)	Older adults	Interventions to improve medication-taking ability or medication adherence	Usual care or receiving a different intervention	Medication adherence Medication-taking ability	50 studies	Pharmacists (31 studies) Nurses (17 studies) Physicians (15 studies)	"When considered separately by subgroups based on health professional delivering the intervention, there was no difference in adherence between those interventions delivered by pharmacists, nurses, or two or more health professionals when measured either as a dichotomous outcome"	Dichotomous outcome (risk ratio 1.21 versus 1.19 versus 1.38; test for subgroup differences $p = 0.83$; $I^2 = 0\%$) Continuous outcome (standardized mean difference = 1.38 versus −0.13 versus 0.42; test for subgroup differences $p = 0.08$; $I^2 = 61.4\%$)	Low
Al-Aqeel et al. (2020)	Epilepsy	Effectiveness of interventions aimed at improving adherence to antiepileptic medication in adults and children with epilepsy	Usual care or no intervention	Medication adherence	20 RCTs	HCPs	Educational interventions led by HCPs (13 RCTs)	Not conducted due to high heterogeneity	Moderate
van Driel et al. (2016)	CVD	Effects of interventions aimed at improving adherence to lipid-lowering medications	Usual care	Medication adherence Clinical outcomes	35 RCTs	HCPs	7 studies compared adherence rates of those in an intensification of a patient care intervention (e.g., electronic reminders, pharmacist-led interventions, healthcare professional education of patients) versus usual care	7 studies Participants in the intervention group had better adherence than those receiving usual care (odds ratio = 1.93, 95% CI 1.29 to 2.88	Moderate

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10.3389/fphar.2025.1567967

TABLE 1 (*Continued*) Select studies from the Cochrane Library reporting features of HCP-delivered interventions to support medication adherence.

Author	Population	Intervention	Comparison	Outcome	Number of studies	HCP group	Key features of HCP-delivered interventions	Effect sizes	Certainty of evidence (based on GRADE criteria)
Ryan et al. (2014)	Various	Interventions to improve safe and effective medicines use	Unrestricted	Medication use, medication adherence, adverse events and clinical outcomes	75 systematic reviews	Pharmacists	"Simplified dosing regimens: with positive effects on adherence" "Interventions involving pharmacists in medicines management, such as medicines reviews (with positive effects on adherence and use, medicines problems and clinical outcomes) and pharmaceutical care services (consultation between pharmacist and patient to resolve medicines problems, develop a care plan and provide follow-up; with positive effects on adherence and knowledge)" "Education/information as part of pharmacist-delivered packages of care"	Not conducted due to high heterogeneity	Moderate
Brown et al. (2019)	Depression	Pharmacy-led interventions to support patients with depression	Usual care	Depression Medication adherence	12 studies	Pharmacists	6 studies did show that people who received support from their pharmacy were more likely to take their antidepressants as prescribed	Risk ratio = 0.73, 95% CI 0.61–0.87)	High
Mateo-Urdiales et al. (2019)	HIV	effects of interventions for rapid initiation of antiretroviral therapy (defined as offering antiretroviral therapy within 7 days of HIV diagnosis)	Usual care	Medication uptake Clinical outcomes	7 studies	HCPs	"The rapid antiretroviral therapy intervention was offered as part of a package that included several cointerventions targeting individuals, health workers and health system processes delivered alongside rapid antiretroviral therapy that aimed to facilitate uptake and adherence to antiretroviral therapy"	4 studies Better antiretroviral therapy uptake at 12 months (risk ratio = 1.09, 95% CI 1.06 to 1.12	Moderate
Weeks et al. (2016)	Various	To assess clinical, patient-reported, and resource use outcomes of non-medical (nurses, pharmacists, allied health professionals, and physician assistants) prescribing for managing acute and chronic health conditions in primary and secondary care settings compared with medical prescribing (usual care)	Medical prescribing	Medication adherence Clinical outcomes	46 studies	HCPs	4 studies - continuous outcome data showed an effect favoring patient adherence in the non-medical prescribing group	(Mean difference = 0.15, 95% CI 0.00–0.30)	Moderate

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TABLE 1 (*Continued*) Select studies from the Cochrane Library reporting features of HCP-delivered interventions to support medication adherence.

Author	Population	Intervention	Comparison	Outcome	Number of studies	HCP group	Key features of HCP-delivered interventions	Effect sizes	Certainty of evidence (based on GRADE criteria)
Smith et al. (2021)	Various	-oriented interventions designed to improve outcomes in people with multimorbidity in primary care and community settings	Usual Care	Medication adherence Clinical outcomes Healthcare utilization HCP behaviour	17 RCTs	HCPs	"In 11 studies, the predominant intervention element was a change to the organization of care delivery, usually through case management or enhanced multidisciplinary team work. In six studies, the interventions were predominantly patient-oriented, for example, educational or self-management support-type interventions delivered directly to participants"	4 studies, slightly improve medication adherence	Low
Gordon et al. (2023)	Inflammatory bowel disease	Different types of educational interventions, how they are delivered, and to determine their effectiveness and safety in people with inflammatory bowel disease	Usual care	Medication adherence Clinical outcomes	14 studies	HCPs	HCP-led training programs	Medication adherence, patient knowledge and change in quality of life showed conflicting results that varied between no major differences and differences in favor of the educational interventions	Low

Notes. CVD, cardiovascular disease; GRADE, grading of recommendations assessment, Development and Evaluation; HCP, healthcare provider; RCT, randomized controlled trial.

possible results. As highlighted by Bosworth and colleagues (Bosworth et al., 2011), given the myriad factors associated with medication adherence, it is unreasonable to think that a one-size-fits-all approach would be appropriate. It should be acknowledged that adding in aspects of tailoring to HCP-delivered adherence intervention undoubtedly increases complexity of such interventions, however, this is likely the price to pay in order to maximize effectiveness. Allemann and colleagues suggested that medication adherence interventions should target current modifiable factors and be tailored to unmodifiable factors (Allemann et al., 2016). For example, a HCP-delivered intervention targeting medication beliefs posing barriers to adherence (a potentially modifiable factor) tailored to the individuals level of education and ethno-cultural background (an unmodifiable factor), may be a more suitable approach versus a standardized, non-tailored approach.

3.4 Involving pharmacists and nurses as intervention deliverers

Multiple HCP groups such as physicians, nurses, and pharmacists could conceivably be integrated into delivering adherence interventions, which is reflected in the literature (Nieuwlaat et al., 2014; Crawshaw et al., 2019) There is evidence to suggest that some HCPs may be better placed than others to deliver adherence interventions. Two systematic reviews of reviews by Wilhelmsen and Eriksen (Wilhelmsen and Eriksson, 2019) and Ryan and colleagues (Ryan et al., 2014) found that interventions delivered by pharmacists and nurses showed a better result in improving adherence and outcomes than interventions delivered by primary care physicians. Reasons may include more frequent and sustained patient contact among allied HCPs versus physicians, greater involvement in follow-up care, and specific training in techniques such as motivational interviewing (Nieuwlaat et al., 2014). Pharmacists have seen a shift in practice in recent years in an attempt to increase patient-facing activities (e.g., spending more time talking to patients about their medication regimen). This enhanced role of pharmacists to interact with patients directly patient directly using education and counselling methods, provides an opportunity for better supports to be in place for patients over time (Kini and Ho, 2018). Importantly, the effectiveness of HCP-delivered interventions may also vary by care setting. Community pharmacists, for example, often have more frequent and informal contact with patients, which facilitates timely adherence discussions and follow-up. In contrast, hospital-based teams may benefit from access to multidisciplinary support and clinical data, but have fewer opportunities for sustained patient engagement post-discharge. These contextual differences should inform how adherence interventions are designed and which HCPs are best positioned to deliver them. Successful integration of pharmacists, nurses, and physicians into multidisciplinary adherence teams depends on factors such as clearly defined roles, effective communication workflows, and shared accountability. According to the Interprofessional Collaboration Model (Orchard et al., 2010), high-functioning teams require mutual respect, common goals, and structured coordination mechanisms. However, practical barriers can undermine collaboration, including hierarchical dynamics and reimbursement models that may undervalue the contributions of

certain HCP groups. As discussed in Section 5, addressing these system-level challenges is critical to enabling scalable, team-based adherence support.

3.5 Providing ongoing support to patients across stages of adherence

Medication-taking for chronic conditions is often long-term/lifelong behaviour. As such, it is likely that HCPs need to be available to provide ongoing support for patients at various timepoints which requires synchrony across acute, primary, and community care settings. It may be that different HCPs are more involved at different times (and at multiple timepoints) during the patient's journey, when acute hospital events transition into primary and community care. For example, HCPs working in primary care settings are well-placed to identify patients who do not initiate treatment. Care mechanisms should be in place to support patients as they transition between services (Tyler et al., 2023; Daliri et al., 2021). This is particularly pertinent in the post-discharge period from hospital when issues around medications (e.g., side effects) can arise and can lead to premature discontinuation. Odeh and colleagues address this issue nicely as part of a pharmacist-led, post-discharge intervention study to support medication use among polypharmacy patients (Odeh et al., 2019). The intervention comprised multiple telephone touchpoints between pharmacist and patient within three-months of hospital discharge with tailored conversations informed by the PAPA. The study found that patients receiving the intervention had better adherence and lower readmission rates versus those in a propensity score matched control group. Moreover, the intervention was associated with greater cost-effectiveness. This study demonstrates several features discussed so far, namely, tailoring intervention content using a theory such as the PAPA, using pharmacists to deliver interventions, and providing post-discharge at multiple timepoints.

3.6 Addressing health system-level barriers and inequities

Many of the points detailed above speak directly to the practice of HCPs. However, HCPs operate as part of a health system where other macro-level challenges sometimes make it difficult for HCPs to adequately support patients with their medication-taking. Health system barriers such as access to services, available resources, time, and cost associated with clinical practice can all potentially impact how HCPs support patients with their treatment which can also exacerbate health inequities among patients. Moreover, given the multitude of factors relating to adherence (e.g., patient-, disease-, therapy-, socioeconomic-, and healthcare system-related factors (Sabaté, 2003)), it seems likely that multifaceted interventions are most appropriate, despite the inherent difficulty of implementing complex interventions into routine practice. Much of this multi-layered and multi-component intervention thinking speaks to the use of models, theories, and frameworks from the literature to better inform the development, evaluation, and implementation of complex adherence interventions (Conn et al., 2016a) (a topic discussed further in Section 6).

4 Implementation approaches targeting evidence-to-practice gaps among HCPs supporting medication adherence

We conceptualize a HCP-targeted adherence intervention as one that is focusing on HCP clinical practice (i.e., implementation intervention), to essentially help HCPs to help their patients to be more adherent to treatment. The key feature here is the primary focus on HCP behaviour rather than a patient, given that HCPs are considered the recipient of the intervention itself. Identifying such gaps in clinical practice and focusing on behaviour change among HCPs speaks directly to the field of implementation science (Grimshaw et al., 2012). As such, we can use learnings and evidence from implementation science to help understand why evidence-to-practice gaps occur and how such gaps can be addressed in real world settings. To date, there have been several systematic reviews conducted in this area focusing on HCP practice change interventions and implementation strategies to support knowledge uptake (e.g., Clinical practice guidelines).

A systematic review of 218 HCP-targeted intervention studies found small improvements in patient adherence (mean difference effect size = 0.23; 95% CI 0.19, 0.29; $p < 0.001$) (Conn et al., 2015). Specific types of HCP-targeted interventions included improving HCP medication adherence skills (e.g., teaching HCPs how to uncover patients' barriers to adherence and generate solutions), integrating healthcare processes (e.g., strategies designed to improve care coordination between HCPs), improving HCP communication skills, providing feedback to HCPs about patients' adherence, HCPs monitoring adherence, shared decision-making, increasing time with patients, and reducing distance between patients and their HCP (mean difference effect sizes ranged from 0.01–0.30 between types of interventions). Subgroup analyses did not find certain types of interventions to be superior than others, however, mediation analysis revealed that interventions were more effective when they included multiple strategies. A limitation of these data were that most intervention studies did not measure or report actual changes to HCP clinical practice which limits our understanding of how these types of interventions work (i.e., in conceptualizing pathways to change, it would be expected that such interventions change HCP behaviour which then leads to patient behaviour change (Toomey et al., 2020)).

In the next section, we posit some key features of potentially effective HCP-targeted adherence interventions and offer some system-level implementation approaches for addressing known evidence-to-practice gaps (see Table 2 for a summary of key features of HCP-delivered versus HCP-targeted adherence interventions).

4.1 Early identification and routine screening of adherence issues

A systemic issue within health systems is the lack of streamlined processes to recognize adherence issues early (e.g., patients not initiating treatment) and to routinely screen for poor adherence. If HCPs are unaware of adherence issues, then it remains difficult to initiate supports for patients to reduce the likelihood of treatment discontinuation. In the simplest terms, screening might involve HCPs asking patients about their medication-taking behaviour in an honest and open way (as indicated in the UK's NICE guidelines

TABLE 2 Key features of potentially effective HCP-delivered interventions (Section 4) and HCP-targeted implementation approaches (Section 5) to support medication adherence.

Feature	HCP-delivered interventions (Section 4)	HCP-targeted implementation approaches (Section 5)
Primary Aim	Improve patient medication adherence	Improve HCP practice related to adherence support
Intervention recipients	Patients	HCPs
Intervention delivery agents	Physicians, pharmacists, nurses	Health systems, implementation teams
Intervention examples	Education, counselling, simplified dosing, reminders, pharmacist-led post-discharge support	Audit and feedback, educational meetings, clinical reminders, local champions
Design features	Use of multiple behavior change strategies; tailoring to perceptual/practical barriers (PAPA); ongoing patient contact	Based on implementation science strategies; often includes multifaceted approaches requiring system changes
Key barriers	Patient-level barriers (e.g., ambivalence, forgetfulness, complex regimens)	HCP-level barriers (e.g., lack of knowledge, workflow challenges, lack of feedback)
Key facilitators	Trust, personalization, repeated contact	Role clarity, actionable guidelines, interprofessional collaboration, technology support
System-level supports	Coordination across care settings; inclusion of pharmacists and nurses	Integration into workflows; electronic medical record alerts; adherence screening tools; incentive and remuneration models

for medication adherence (National Institute for Health and Care Excellence, 2009)), normalizing challenges with adherence (e.g., "many people find it difficult to take meds regularly . . . "), and referring to specific time periods when discussing medication use (e.g., 'over the past month . . .). Specific issues relating to early identification/screening include a lack of valid screening tools, inadequate integration of existing tools into electronic medical record systems, as well as time pressure and a lack of expertise, all of which reduce the likelihood that adherence issues are screened for and then discussed in an open and honest way (Garfield et al., 2011; Engel et al., 2017). Medication adherence screening tools along with more general patient-reported outcome/experience measures should be embedded into routine practice and HCPs should be trained on their use and provided opportunities to practice using them (Stirratt et al., 2015; Gleeson et al., 2016). Advances in health technology may offer promising solutions to some of these issues: for instance, artificial intelligence (AI)-driven risk prediction algorithms can flag patients likely to experience adherence issues using electronic medical records or pharmacy data (Babel et al., 2021). Digital tools such as mobile applications with HCP dashboards (e.g., Medisafe) also provide real-time monitoring capabilities, allowing HCPs to track missed doses and initiate timely support (Babel et al., 2021; Hartch et al., 2024) These digital tools may also help address systemic barriers by automating parts of the adherence screening process, reducing the time-burden on HCPs, and potentially improving scalability of routine adherence monitoring across large patient populations.

4.2 Making adherence-related clinical practice guidelines more actionable

Clinical practice guidelines are crucial to identify evidence-to-practice gaps to inform the clinical practice of HCPs. Ruppar and colleagues conducted a systematic review of 23 clinical practice guidelines to identify recommendations relating to medication adherence (Ruppar et al., 2015). Key recommendation categories included assessment strategies, educational strategies, behavioural strategies, therapeutic relationship strategies, and outside influences/co-morbidities. The authors called for additional rigor for developing these types of guidelines and also suggested that the strategies listed in the guidelines were too vague and lacked specific, workable examples to guide HCPs; thus, making recommendations in the guidelines hard to operationalize in practice. Moreover, dissemination plans across the guidelines were often suboptimal or missing entirely, meaning that engagement with target HCPs may be impacted.

Clinical practice guidelines are only useful if they are adopted by those they are targeting. Thus, it may be useful to embed a behaviour change perspective into the guideline development process, or into the development of an implementation intervention that is intended to support the integration of an existing guideline into practice. In a critical appraisal of guideline recommendations which identified behavioural specification as the foundational element for implementation, none of the included recommendations were fully behaviourally specific, and there was a lack of consistency on required behaviours across guidelines for the same topic (Graham et al., 2023). Multiple systematic reviews identify lack of specificity of guideline recommendations as a key barrier to their uptake (Wang et al., 2023). Additional work could be done to specify individual guideline recommendations in behavioural terms (i.e., clarify the specific clinical action to be undertaken along with who should do it, when, where, and how (Michie and Johnston, 2004)). This could be achieved using the Action, Actor, Context, Target, Time (AACTT) Framework, developed to support behavioural specification in implementation studies (Presseau et al., 2019), but which could be applied to help improve how clinical practice guideline recommendations are written (Michie and Johnston, 2004). The framework defines five components that should be specified to fully describe a behaviour that is being targeted for change in healthcare contexts, namely,: the "Action" (a discrete observable behaviour);

"Actor" (the individual or group of individuals who perform (or should/could perform) the action; 'Context' (the physical setting in which the actor performs (or should/could perform) the action; "Target" (the individual or group of individuals for/with whom the actor performs the action; and "Time" (the time period and duration that the actor performs the action in the context with/for the target) (Presseau et al., 2019). In addition, clinical practice typically doesn't change based on guideline dissemination alone; active implementation strategies are typically required to encourage the desired change (Grimshaw et al., 2012; Crawshaw et al., 2025).

4.3 Using routinely collected data to identify patients with adherence issues

The widespread and persistent issue of poor medication adherence lends itself to large scale, population-based research methods and the harnessing of 'big data'. Patients reliant on medications are tied to a range of care settings and stakeholders including the prescriber's clinic, the dispensing pharmacy, their health plan, prescription drug plan, and pharmacy benefit management, which requires system-level synergy to reduce gaps in care (Bosworth et al., 2016). From the perspective of a HCP, having up-to-date medication-related information and data linkages between prescribing and dispensing services may help to identify patients at risk of non-adherence. Again, this provides an example of the context and systems infrastructure in which HCPs work which can enhance or inhibit their ability to address medication adherence issues among their patients.

4.4 Enhancing HCP incentivization models to support adherence

Incentivization for providing services (e.g., pay-for-performance) is commonplace in health systems, however, HCP activities related specifically to medication adherence are not routinely incentivized, and for those that are, may be unbalanced to favor certain HCP groups over others. Established prescribing services such as the "New Medicines Service" and "Medicines Use Review" programs in the United Kingdom have shown to add clinical value in primary care and community pharmacy contexts (Elliott et al., 2020), however, activities targeting medication adherence specifically are yet to be established across the board (Khan and Socha-Dietrich, 2018). As such, there have been calls to expand HCP remuneration models to capture activities focused on identifying and addressing adherence issues and capturing adherence data over time, which may encourage practice change and improved medication adherence management.

4.5 Establishing quality indicators for adherence monitoring and support

In addition to incentivizing adherence-related activities among HCPs, there may also be an argument to develop care quality indicators around medication adherence (i.e., adherence as a performance measure). In practice, this would involve setting evidence-based benchmarks around the delivery of adherence-related services in routine practice (e.g., screening rates for non-adherence, community pharmacy referrals to discuss adherence issues). This could potentially set the stage to leverage knowledge from the audit and feedback literature to support medication adherence-related clinical targets and improve processes of care (Zaugg et al., 2018).

4.6 Drawing on what is already known about supporting practice change from implementation science

There are opportunities to draw on the broader implementation science literature to inform the design and evaluation of HCP behaviour change-focused interventions to better support patient medication adherence. For example, numerous systematic reviews have been produced which have established the effectiveness of specific implementation strategies such as educational meetings, audit and feedback, clinical reminders, and local champions who drive change (Ivers et al., 2012; Pantoja et al., 2019; Forsetlund et al., 2021). Systematic reviews tend to show that such implementation interventions lead to small-to-medium improvements in clinical practice, and these can be a good place to start when considering which implementation strategy to pursue. The variation in effectiveness often identified indicates that more work needs to be done to determine how to maximize the effectiveness of such interventions. Such work is ongoing across the field and is relevant to the development of adherence-focused interventions. For example, evidence indicates that audit and feedback is more likely to be effective when the feedback is provided more than once, when it is relayed by a supervisor or colleagues, is delivered in a written format accompanied by verbal feedback, and when it includes both explicit targets for change and an action plan for achieving those targets (Ivers et al., 2012, 2025). A recent systematic review focusing on the pharmacist role in primary care found that involving pharmacists in the delivery of audit and feedback interventions can lead to improvements in prescribing outcomes, providing both verbal and written feedback enhances effectiveness, and also determined that the addition of computerized decision support for prescribers led to greater practice improvements (Carter et al., 2023).

Similar to patient behaviours, the determinants of HCP behaviours are wide-ranging and their relative importance as targets for change may vary depending on several factors including the nature of the behaviour under focus and the wider context in which it is enacted. Previous research has identified several important factors which can influence HCP behaviour, including knowledge of guideline recommendations (Beenstock et al., 2012); social influences, professional roles and identities, and power dynamics (Etherington et al., 2021); having multiple goals for care delivery which may facilitate or conflict with one another (Presseau et al., 2009); the strength of intention to perform specific clinical behaviours (Godin et al., 2008); and the extent to which clinical behaviours are habitual or can be

performed relatively automatically (Presseau et al., 2014; Potthoff et al., 2019). Many clinical behaviours become highly routinized over time, and there have been several calls in the literature for more studies that incorporate dual process models and seek to understand the role of automatic determinants of HCP behaviour alongside reflective determinants (Nilsen et al., 2012). To develop appropriately-targeted interventions for HCPs, further work is needed to understand which HCP behaviours are key for supporting medication adherence and the factors that influence these behaviours in the various contexts in which HCPs work.

Drawing on existing evidence such as this when developing interventions can help to maximize the impact of HCP-focused strategies to improve medication adherence. A key tenet of implementation science is the importance of developing a detailed understanding of the problem before selecting and implementing an intended solution. This can help to ensure that the selected strategy is fit-for-purpose and adequately addresses existing barriers to or facilitators of change. For instance, time constraints (opportunity-related issue), guideline familiarity (knowledge issue), and habitual prescribing patterns (automaticity issue) are known barriers to practice change, yet each would require markedly different strategies to support HCPs to change their behaviour. Frameworks such as the Theoretical Domains Framework (Cane et al., 2012) or the Consolidated Framework for Implementation Research (Damschroder et al., 2022) can be used to systematically identify the barriers and facilitators for a specific medication adherence-related practice issue to form the basis for intervention development and increase the chances of success.

5 Future directions and recommendations for research and practice

Given the complexity of medication adherence as a behaviour, it is perhaps unsurprising that there is considerable heterogeneity across HCP adherence interventions in terms of sample population, intervention type/content/delivery, and study outcomes, thus making it difficult for adherence researchers to navigate through the evidence landscape. In recent times, there has been progress to improve the reporting of the content, delivery and other features of behaviour change interventions using theory-informed tools such as the Behaviour Change Technique Taxonomy version 1 (BCTTv1) (Michie et al., 2013) and more recently the Behaviour Change Intervention Ontology (BCIO) (Norris et al., 2019) to aid intervention development, evaluation, and optimization. Another useful approach is Intervention Mapping (IM) (Kok et al., 2016). This approach involves: conducting a needs assessment to identify target behaviours and behavioural determinants (Sabaté, 2003); identify determinants to target for change by mapping behaviours to their determinants to create matrices of change objectives (Kardas et al., 2024); select and operationalize theory-based intervention components to address identified determinants (Kardas et al., 2013); develop an organized program based on the intervention components (MacIntyre et al., 2005); plans for adoption, implementation, and sustainability (Miller et al., 2002); develop a plan for outcome and process evaluation. The IM approach provides a taxonomy of behaviour change techniques and a process within which theory can be integrated. It has been used to develop adherence interventions targeting both intentional and unintentional non-adherence (Moon et al., 2021). One of the overarching goals of using frameworks such as the BCTTv1, BCIO, or an IM approach is to ensure a higher success rate of behaviour change interventions. Can we get the point where we can empirically state 'which behaviour change techniques work for whom in which contexts delivered by what means' (Armitage et al., 2021)? This line of questioning closely relates to 3Cs reported by Horne and colleagues (Content–what is being delivered?; Channel–how is it being delivered?; and Context–what is the setting/circumstance in which delivery happens (Horne et al., 2019; Stewart et al., 2023)). In terms of medication adherence research, this line of work has the potential to help develop HCP interventions that are more behaviourally intelligent because their content is based on sound understanding of adherence and based on evidence rather than rolling out the same ideas which have been shown to be generally ineffective.

There is encouraging work progressing in relation to medication adherence study outcomes with the recent development of a core outcome set for medication adherence trials in primary care (Bhattacharya et al., 2024). Whilst green shoots of progress are most welcomed in this space, there remains a persistent challenge, namely, that few interventions that show promise are implemented, scaled, and costed within health systems. Therefore, additional emphasis must focus on the cost-effectiveness of effective HCP adherence interventions and their scalability. Moreover, we reiterate the need for medication adherence research to consider the dual roles of HCPs as both deliverer and target of behaviour change interventions. Work should be done to understand the barriers to behaviour change among HCPs and what can then be done to support implementation. This should involve working closely with HCPs to understand their perspectives about what factors might impede implementation efforts and generating ways around such barriers. We have highlighted a number of areas where HCP practice can directly support patients to adhere to treatment (e.g., moving beyond education-only strategies to a 'toolbox' of distinct, tailorable strategies), however, it is imperative that HCPs are supported at a system-level to allow them to improve their practice. Developing and integrating adherence screening tools, improving clinical practice guidelines, adapting health technology infrastructure, and generating quality indicators are just some examples of system-level solutions which are probably needed to shift the needle to improve both medication adherence and clinical outcomes and support implementation efforts in the real world.

6 Conclusion

There is an extensive evidence-base for the effectiveness of HCP-delivered interventions to support medication adherence, and a growing evidence-base for approaches targeting practice change

among HCPs. We have identified several areas that could help advance both research and clinical practice with a particular focus on the content and delivery of HCP adherence interventions, the implementation of effective strategies, and the need for system-level approaches to support HCPs. We believe there is opportunity to leverage learnings and evidence from implementation science to help support the uptake and scale of effective adherence interventions into routine practice.

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Clinicians' view on non-adherence: sharing expert opinion

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Introduction: Medication non-adherence (NA) remains a persistent challenge across all medical specialties, contributing to adverse patient outcomes and increased healthcare burdens. While numerous studies have explored patient-related factors influencing adherence, the perspectives of healthcare professionals remain underrepresented in literature. This study aims to document the individual experiences of seven international physicians across diverse medical fields, highlighting barriers, detection methods, and strategies employed to address NA in their daily practice.

Methodology: A structured qualitative approach was employed, incorporating semi-structured interviews and written questionnaires to capture expert insights. Seven physicians from specialties including family medicine, gastroenterology, otolaryngology, otology and neurotology, obstetrics and gynecology, endocrinology and cardiology participated in the study. Data were analyzed thematically to identify recurring patterns, specialty-specific challenges, and practical solutions implemented by clinicians.

Results: Clinicians reported that NA detection primarily relied on patient self-reporting, clinical markers, and medication reconciliation. Barriers to adherence varied by specialty but commonly included polypharmacy, treatment complexity, patient skepticism, socioeconomic constraints, and asymptomatic conditions. Strategies to enhance adherence encompassed patient education, shared decision-making, therapeutic simplification, digital tools, and team-based care models. Despite proactive efforts, clinicians cited systemic limitations such as time constraints, fragmented healthcare records, and inadequate adherence-tracking mechanisms.

Conclusion: Addressing NA requires a patient-centered, interdisciplinary approach integrating education, digital innovations, and structured follow-up strategies. The study underscores the necessity for larger-scale research to validate adherence interventions and refine multidisciplinary frameworks.

Given the study's qualitative nature and small sample size, future research should incorporate broader datasets and diverse healthcare perspectives to develop more comprehensive adherence solutions.

KEYWORDS

non-adherence, medication adherence, patient compliance, adherence strategies, expert opinion

1 Introduction

Medication adherence is defined as the degree to which patients follow medical instructions. It ranges from taking their medication as prescribed to complying with diets and lifestyle changes (Brown and Bussell, 2011; Vrijens et al., 2012; Aljofan et al., 2023). The World Health Organization (WHO) categorizes adherence factors into patient, treatment, disease, socio-economic, and healthcare system-related influences (World Health Organization, 2003; Gast and Mathes, 2019; Kvarnström et al., 2021; Peh et al., 2021). Despite these insights, medication non-adherence (NA) remains a widespread challenge that affects patients across all medical specialties and care settings. NA is recognized as a multifactorial and persistent challenge across nearly all medical specialties and conditions, whether acute (e.g., malaria), chronic (e.g., hypertension), symptomatic (e.g., cystic fibrosis), or asymptomatic (e.g., dyslipidemia). Its complex causes contribute to a substantial burden on patient health, clinical practice, and the overall healthcare system (Hommel et al., 2019; Burnier et al., 2021; Lopes and Santos, 2021; Santos et al., 2022).

Although many recent studies have investigated patient adherence, the way healthcare professionals (HCPs) individually experience and address this issue varies significantly and has not yet been fully investigated in the literature (Panahi et al., 2022). The challenges they encounter are influenced by multiple factors, including healthcare setting, disease characteristics, and the individual circumstances of each patient. For example, in chronic conditions, HCPs often struggle to keep patients engaged in long-term treatment, while in acute care, the challenge may be ensuring that patients understand and follow urgent medical instructions. Beyond the medical aspects, factors like health literacy, financial constraints, and cultural beliefs about medication play a crucial role in shaping adherence.

This study aimed to document, to our knowledge for the first time in the literature, the individual perspectives of seven international physicians on medication NA in their daily practice across various medical specialties, including family medicine and primary care, gastroenterology, otolaryngology, otology and neurotology, obstetrics and gynecology (OB-GYN), endocrinology and diabetes, and cardiology. Their insights offer a nuanced understanding of how NA manifests across different fields, highlighting both common challenges and specialty-specific concerns. By examining their experiences, this study seeks to uncover the complexities of NA and explore practical strategies that HCPs can implement to enhance adherence in their respective practices, ultimately providing valuable guidance for optimizing patient adherence in routine care.

2 Methodology

2.1 Study design and interview framework

This study used a qualitative semi-structured approach to ensure a comprehensive recall of all authors' insights and analyze their perspectives on NA. A combination of individual interviews and written questionnaires served as the primary data collection method. This dual approach preserved the authenticity of expert perspectives while capturing a diverse and well-rounded view of their clinical experiences and cultural backgrounds. Data from the semi-structured interviews and written questionnaires were collected by an independent third party to ensure objectivity.

The study design followed a multi-step process:

- Initial meeting: A preliminary meeting was held with all seven international authors to define the study objectives and key areas of interest. The experts were selected based on their interest in NA (e.g., through publications, clinical practice, or congress presentations) within their respective fields: family medicine and primary care, gastroenterology, otolaryngology, otology and neurotology, OB-GYN, endocrinology and diabetes, and cardiology.
- Preliminary data collection: Before conducting the interviews, an open-ended, free-text questionnaire was distributed via email to all authors to gather initial reflections and perspectives (a copy of the questionnaire is available in Supplementary Appendix 1).
- Development of the interview guide: Based on insights from the initial meeting and questionnaire responses, a draft interview guide was developed (a copy of the interview guide is available in Supplementary Appendix 2). The guide included open-ended questions designed to elicit in-depth responses on clinical experiences, opinions, and perspectives.
- Pilot testing: The interview guide was tested with three clinicians to assess clarity, relevance, and potential ambiguities. Revisions were made based on their feedback.
- Individual interviews: Interviews were conducted online, each lasting approximately 1 hour.

2.2 Data analysis

The collected data was analyzed thematically to identify common patterns and unique insights. First, the responses were

Abbreviations: EHR, Electronic health record; ENABLE, European Network to Advance Best Practices and Technology on Medication Adherence; HCPs, Healthcare professionals; LDL, Low-density lipoprotein; NA, Non-adherence; OB-GYN, Obstetrics and gynecology; WHO, World Health Organization.

synthesized into a cohesive narrative that accurately represented the collective viewpoints of the clinicians. The independent third party involved in conducting the interviews and questionnaire was also responsible for data analysis, ensuring objectivity and minimizing bias. Three individuals worked independently and simultaneously on the narrative construction and identification of key themes based on the raw data. Their reports were then shared within the group, compared, and consolidated through an iterative process to arrive at the most accurate and coherent narrative. No software was used in this analysis. This narrative was used to extract key themes and structure the manuscript, accordingly, ensuring the inclusion of all relevant perspectives. Additionally, direct quotes from physicians were incorporated to highlight individual viewpoints and provide a nuanced representation of their experiences.

Experts were informed that the meetings would be recorded and that the discussions would be used for the purposes of this manuscript. All experts agreed to these terms and provided formal consent prior to the interviews. For the questionnaire, experts were likewise informed that their responses would be used, and all provided consent to the privacy policies before proceeding.

3 Results: Insights from clinicians across specialties

This section explores insights from the seven physicians on NA, each offering perspectives shaped by their respective medical specialties. Their experiences highlight approaches to detecting NA, its impact on clinical practice, and the challenges associated with managing it, including specialty-specific considerations. Additionally, broader discussions address strategies to improve adherence, alongside the identified needs for enhanced training and access to robust data to support clinical decision-making.

3.1 Family medicine and primary care: addressing polypharmacy and aging populations

3.1.1 Detection of non-adherence

Associate Professor Ngiap Chuan Tan (Singapore), specializing in family medicine, frequently encounters NA in patients with multi-morbidities. It is flagged during consultations and through pharmacist-led medication reconciliation. Discrepancies between prescribed and dispensed medications indicate adherence issues. *"Pharmacists will consult the doctors if they suspect that the patients are not taking the medication. This is an opportunity for intervention."*

3.1.2 Impact on clinical practice

NA in aging populations leads to poor health outcomes and additional physician workload. *"Patients may not fully understand the function or the purpose of taking each of the tablets,"* Prof. Tan noted, emphasizing therapeutic clarity. Limited consultation time and language barriers further complicate adherence management.

3.1.3 Challenges and specialty-specific considerations

In family medicine, where continuity of care is key, NA presents unique challenges. Unlike specialists who focus on a single condition, family physicians manage a wide array of conditions simultaneously, requiring a holistic approach. Prof. Tan noted that NA in polypharmacy patients is often selective, with patients adhering to some medications while neglecting others. Furthermore, fragmented electronic health record (EHR) systems exacerbate these challenges. Limited integration between public and private HCPs hinders comprehensive tracking of patient medications and adherence. *"We do not have a clear picture of what the patients are receiving from different HCPs,"* he remarked.

3.2 Gastroenterology: emphasizing patient interaction and long-term monitoring

3.2.1 Detection of non-adherence

Professor Enrique de Madaria (Spain), a specialist in gastroenterology with a focus on exocrine pancreatic insufficiency, emphasized the critical role of direct patient interaction in identifying NA. According to his experience, early detection often hinges on assessing the patient's initial reaction to prescribed treatment. He highlighted that reluctance or apprehension about side effects frequently signals a higher risk of NA. "When you tell the patient the treatment you are going to start, the reaction to that information is very important to detect a risk of NA," he noted.

Routine follow-up visits also provide opportunities to identify adherence challenges. Simple, open-ended questions such as *"Do you have problems taking the treatment?"* or *"Do you experience any issues with the medication?"* are integral to uncovering hidden barriers. Professor de Madaria stressed the importance of observing biological markers and patient-reported symptoms during follow-ups. For instance, in the context of pancreatic enzyme replacement therapy, NA may manifest unexpected symptoms such as persistent diarrhea or constipation. Such observations prompt deeper inquiries to verify whether patients are adhering to the prescribed regimen.

3.2.2 Impact on clinical practice

Managing NA requires significant time investment during outpatient consultations. Professor de Madaria views this as an essential effort to ensure effective treatment outcomes. *"It's an investment; you have to spend time, but it's good for the physician and the patient,"* he explained. While this added responsibility increases the daily workload, it is seen as a necessary step to address the root causes of NA and improve patient care.

The long-term impact of NA varies based on the specific treatments prescribed. In the case of exocrine pancreatic insufficiency, NA may not result in immediate complications but contributes to chronic nutritional deficiencies and the potential for severe consequences over time. Professor de Madaria emphasized the importance of framing these long-term risks in discussions with patients to underline the necessity of adherence.

3.2.3 Patient profiles and challenges

Professor de Madaria identified three primary patient profiles that are more likely to struggle with adherence:

- Skeptical patients: Individuals who harbor negative beliefs about medications often perceive them as harmful despite their therapeutic benefits. Such patients frequently state that medications may *"solve some issues but harm others."*
- Patients with social or addiction issues: Those dealing with socioeconomic challenges, addiction, or unstable living conditions face unique barriers to maintaining adherence.
- Symptomatic patients blaming medications: Patients who attribute all symptoms, whether related or not, to their prescribed treatment, often express reluctance to continue the regimen.

To address these challenges, Professor de Madaria employs tailored communication strategies, emphasizing the benefits of treatment and the consequences of NA. He strives to foster a nonjudgmental environment, encouraging patients to share their genuine concerns and barriers.

3.3 Otolaryngology: addressing complex cases and socioeconomic barriers

3.3.1 Detection of non-adherence

Professor Badr Eldin Mostafa (Egypt), a specialist in otolaryngology with a focus on head and neck malignancies, highlighted several key indicators for detecting NA in his clinical practice. These include direct questioning of patients, missed follow-up appointments, unexpected recurrence of symptoms, and, in some cases, the development of complications. He often initiates conversations about adherence by asking direct but non-confrontational questions, such as whether patients encountered difficulties finding medication or why they missed their last appointment, sometimes using a light-hearted approach to ease the dialogue.

Professor Mostafa systematically identifies non-adherent patients and has noted several at-risk profiles. These include patients with low educational status, those with very high education levels (including HCPs), individuals with low socioeconomic backgrounds, and family breadwinners who cannot afford time off work. *"The highly educated patients often delay treatment while searching for a physician who confirms their preconceived management plan,"* he noted, emphasizing how this behavior can exacerbate adherence issues.

3.3.2 Impact on clinical practice

From a clinical perspective, NA significantly impacts Professor Mostafa's day-to-day practice. It often necessitates time-consuming consultations to restart investigations and follow-ups, usually under less favorable circumstances due to disease progression. At an institutional level, NA can distort clinical data, misguide decision-making, and hinder the effective implementation of guidelines.

Professor Mostafa expressed personal frustration when dealing with non-adherent patients, especially when complaints persist or diseases progress despite available treatment options. He remarked, *"it is frustrating to restart investigations and follow-ups under less favorable circumstances due to disease progression,"* highlighting the emotional and practical toll of NA on clinicians. However, he remains vigilant and focused on early detection and proactive management to mitigate the challenges posed by NA.

3.3.3 Challenges and needs in managing non-adherence

While Professor Mostafa acknowledges the universality of NA, he recognizes that its manifestations can vary by specialty. For example, in otolaryngology, adherence challenges often involve managing complex surgical and medical cases, necessitating tailored interventions. He also noted that logistical, cultural, and socioeconomic factors can significantly influence adherence patterns.

Professor Mostafa believes that addressing NA requires the involvement of adherence specialists to guide HCPs in setting up frameworks and implementing evidence-based strategies. He advocates for disease-specific studies to raise awareness among practitioners about adherence issues relevant to their specialties.

3.4 Otology and neurotology: addressing long-term conditions and patient motivation

3.4.1 Detection of non-adherence

Professor O. Nuri Özgirgin (Turkey), an expert in otology and neurotology, focuses primarily on the treatment of chronic vestibular problems such as vertigo and equilibrium disorders. He highlighted the importance of regular follow-up visits and clinical evaluations in detecting NA. In his practice, NA often becomes evident through unexpected lab results or electrophysiological tests that reveal discrepancies in the patient's progress. *"The follow-up process gives clues about a patient's consistency with the treatment, providing an opportunity to directly address adherence,"* he explained.

Patients with chronic conditions that lack immediate symptoms, such as diabetes mellitus, often show higher rates of NA. However, in otology and neurotology, the earlier clinical alerts—such as worsening vertigo or balance issues—facilitate timely identification of adherence problems.

3.4.2 Impact on clinical practice

NA presents significant challenges in Professor Özgirgin's practice, especially in managing chronic vestibular conditions where adherence is crucial for effective treatment. Non-adherent patients often experience worsening symptoms, such as unsteadiness or social isolation, which require additional interventions to restore their quality of life. *"It is not easy to catch up once the breaking point has been reached. Restoring the situation comes at a financial and emotional cost for both the patient and the healthcare team,"* he noted.

Patients dealing with disabling symptoms like vertigo are generally more motivated to adhere to their prescribed treatment. However, rebuilding trust and adherence after a lapse remains a time-consuming and multifactorial process.

3.4.3 Challenges and needs in managing non-adherence

While adherence is a universal issue in medicine, Professor Özgirgin pointed out that the specific challenges and interventions vary by specialty. In otology and neurotology, adherence to long-term treatments like vestibular rehabilitation or chronic dizziness therapies requires sustained effort. He noted that adherence often improves following surgical interventions, as patients anticipate short-term postoperative recovery rather than prolonged medical regimens.

He also emphasized the need for increased awareness and training among HCPs to better detect and manage NA. *"There is always something new to learn, whether it's better detection, response strategies, or tools to intervene,"* he stated. Additionally, he advocates for scientific societies to promote adherence education through masterclasses and meeting plans.

3.5 Obstetrics and gynecology: overcoming fears and misconceptions

3.5.1 Detection of non-adherence

Professor Tommaso Simoncini (Italy), a specialist in OB-GYN, identifies NA primarily by observing persistent symptoms despite the prescription of effective therapies. His approach includes direct inquiries with patients about potential challenges they faced with the treatment, including inconvenience, lack of perceived benefit, or fears about side effects. Given the frequent use of hormonal therapies in his field, he pays particular attention to whether patients are influenced by external advice or concerns about potential risks such as weight gain or cancer.

Although Professor Simoncini does not systematically identify NA, he becomes vigilant when he perceives resistance or skepticism from patients. Certain patient profiles are particularly challenging, including those with preconceived doubts about treatment and heightened fears about side effects.

3.5.2 Impact on clinical practice

From a clinical perspective, NA significantly impacts Professor Simoncini's practice by contributing to the chronicization of conditions that could otherwise be resolved. Over time, these conditions become less treatable, representing a lost opportunity for effective care. He observed that re-initiating treatment after prolonged NA often yields diminished results despite intensive efforts to educate and reassure patients.

For Professor Simoncini, addressing NA requires strong communication skills to help patients understand the consequences of NA. He emphasized the frustration of not being able to effectively convey reliable messages to patients, as it undermines their trust and engagement with the prescribed therapy.

3.5.3 Challenges and needs in managing non-adherence

Professor Simoncini highlighted the pervasive challenge of miscommunication in OB-GYN. He noted that lingering fears and misconceptions about common treatments—ranging from contraception to menopause management—undermine adherence across various subspecialties. Addressing these challenges requires targeted education and evidence-based resources.

He expressed a need for structured strategies and materials to share with patients, such as physical handouts or digital aids that explain the importance of adherence and its consequences. Additionally, he called for more scientific studies documenting the impact of NA in OB-GYN to strengthen the evidence base for patient education.

3.6 Endocrinology and diabetes: managing chronic conditions and behavioral factors

3.6.1 Detection of non-adherence

Professor Shashank R. Joshi (India), an endocrinologist and diabetologist, identifies NA through a combination of patient, caregiver, and healthcare team feedback. Patients often disclose their NA out of guilt, or caregivers report it during consultations. Additionally, healthcare assistants, such as diabetes nurses or educators, may flag inconsistencies when patient records indicate suboptimal outcomes.

Professor Joshi systematically addresses adherence during each consultation, ensuring that all patients are directly questioned about their medication, diet, and exercise adherence. He uses structured questionnaires, administered by HCPs, to document adherence patterns. While laboratory tests are occasionally used to suspect NA, their application is limited to clinical trials or specific contexts.

In Professor Joshi's practice, certain patient profiles are more prone to NA, including those with addictive behaviors (e.g., smokers or alcohol users), individuals who are overly reliant on lifestyle modifications, and patients experiencing economic hardships. Interestingly, highly committed lifestyle adherents may neglect prescribed medications, believing that lifestyle changes alone suffice. *"We have observed a peculiar phenotype where patients committed to lifestyle changes sometimes neglect their medications, believing they can cure their diabetes solely through lifestyle modifications."*

3.6.2 Impact on clinical practice

NA significantly impacts Professor Joshi's clinical workload, with approximately 30% of his patients exhibiting adherence issues. In his opinion, managing these patients requires 25% more consultation time compared to adherent patients. This increased burden extends to his healthcare team, particularly his assistants and nurses, who are actively involved in identifying and addressing NA.

The repercussions of NA include complications, worsened conditions, and additional healthcare interventions. This creates a vicious cycle, increasing both patient hardships and the workload of the caregiving team. From a personal perspective, Professor Joshi has evolved from feeling frustrated and agitated by NA to adopting a more constructive approach focused on addressing its underlying causes and implementing proactive solutions.

3.6.3 Challenges and specialty-specific considerations

In endocrinology, NA often arises due to the asymptomatic nature of chronic conditions like diabetes and thyroid disorders. Patients may stop medications once biological markers normalize, failing to recognize the long-term necessity of treatment. Professor

Joshi emphasizes the importance of measurable outcomes, such as blood sugar levels or thyroid markers, as motivators for adherence.

Despite the measurable benefits of adherence, chronic care specialties face unique challenges compared to acute care, where adherence is often higher due to immediate supervision. The long-term, unsupervised nature of chronic disease management requires more persistent efforts to engage patients and ensure adherence.

3.7 Cardiology: managing chronic disease and long-term commitment

3.7.1 Detection of non-adherence

Professor Lale Tokgözoğlu (Turkey), an experienced cardiologist, highlights that the detection of NA in her practice is primarily facilitated by clinical markers. In cardiology, expected improvements in blood pressure, lipid levels, and other biomarkers typically serve as clear indicators of adherence. When these markers fail to improve as anticipated, it raises suspicion of NA. *"The likelihood of being refractory to a medicine is extremely low,"* she states, emphasizing that deviations are often a result of missed doses or incomplete adherence rather than therapeutic ineffectiveness.

Initiating a conversation about adherence is approached delicately and without blame. Professor Tokgözoğlu explains, *"I systematically say, 'You are taking this regularly, right?'"* before proceeding to further discussion. This gentle inquiry often leads patients to admit to lapses in adherence, such as forgetting doses or failing to refill prescriptions. By framing the issue as a shared problem and discussing potential solutions, patients feel less defensive and more willing to disclose.

Patients more prone to NA include those who exhibit reluctance toward lifelong medications, individuals with polypharmacy, or those influenced by misinformation—a growing challenge in the age of social media. Additionally, younger patients who question the need for long-term treatments and older adults facing challenges with regimen complexity are at higher risk.

3.7.2 Impact on clinical practice

NA presents a significant burden on Professor Tokgözoğlu's clinical practice. Addressing NA requires additional time and effort, particularly for shared decision-making and patient education. She notes, *"it certainly needs more time and more convincing,"* as it often involves understanding patient concerns, managing potential side effects, and tailoring interventions.

The consequences of NA are often severe and lead to complications such as strokes, ventricular hypertrophy, or elevated blood pressure. These complications not only affect patient health outcomes but also increase the complexity of subsequent medical management. Despite these challenges, Professor Tokgözoğlu remains pragmatic: "I feel it's my duty to align them with scientific facts," she explains, emphasizing the importance of providing evidence-based guidance amidst widespread misinformation.

3.7.3 Challenges and specialty-specific considerations

Professor Tokgözoğlu underscores that the challenges of NA in cardiology are influenced by the asymptomatic nature of many conditions. For instance, patients may not perceive immediate benefits from taking statins, as high cholesterol does not present obvious symptoms. She highlights, *"When you do not take your cholesterol medication, nothing happens,"* making it difficult to sustain adherence. In contrast, the acute symptoms of other conditions, such as hypertension-related headaches, may serve as a natural motivator for adherence.

Additionally, she notes that the effectiveness of adherence strategies varies based on individual patient profiles. Educational materials, whether print or digital, must be adapted to the patient's age, literacy level, and access to technology.

3.8 Needs for training and data

Some of the interviewed physicians emphasized the need for enhanced training and data-driven approaches to optimize the management of medication NA. A unified national EHR system was identified as crucial for tracking prescriptions and dispensed medications across healthcare providers, improving coordination and adherence monitoring. Digital solutions, including mobile applications, AI-driven risk assessments, and smart pillboxes, were highlighted as promising tools, particularly for elderly patients with cognitive challenges. However, effective integration of these technologies requires standardized training for HCPs to ensure their appropriate use.

In addition to technological advancements, the need for team-based care models was underscored, advocating for the active involvement of pharmacists, nurses, and administrative staff in adherence management. Training programs should focus on equipping HCPs with skills to detect and address NA, incorporating motivational techniques and behavioral strategies. Furthermore, generating robust scientific data on the clinical consequences of NA is essential to raise awareness and drive systemic improvements. Time constraints, particularly in high-volume clinical settings, were recognized as a major challenge, reinforcing the need for structured training programs, particularly for younger clinicians. Providing guidance on evidence-based digital tools would further support clinicians in integrating technology effectively into patient care. A multidisciplinary, data-driven, and technology-enhanced approach was recommended to strengthen adherence management strategies.

3.9 Strategies to improve adherence

The seven physicians interviewed outlined a range of strategies to enhance medication adherence, tailored to their respective specialties and patient populations. Common themes emerged across their approaches, emphasizing patient education, behavioral interventions, and system-level improvements. Shared decision-making and proactive communication were widely endorsed, ensuring that patients understand their conditions, treatment benefits, and potential consequences of NA. Many physicians employed tailored regimens, deprescribing where possible, and leveraging behavioral techniques such as linking medication intake to daily routines. Practical tools, including pill organizers and digital reminders, were frequently recommended, though their suitability

varied by patient demographics, particularly among older populations. Several physicians highlighted the importance of multidisciplinary involvement, integrating pharmacists, nurses, and social workers to reinforce adherence strategies. Economic and logistical barriers were also addressed through customized solutions, including financial assistance programs and simplified treatment regimens. Additionally, therapeutic education, both in clinical settings and through public awareness campaigns, was recognized as a critical component in fostering long-term adherence. While digital solutions, such as adherence-tracking applications, were identified as promising, their effectiveness remained contingent on patient familiarity with technology. Overall, a multifaceted, patient-centered approach—combining education, behavioral reinforcement, tailored interventions, and multidisciplinary support—was advocated to optimize adherence outcomes.

4 Discussion

The findings of this study illustrate the complexity of NA, its diverse manifestations, and the strategies clinicians employ to mitigate its impact across different specialties. Key barriers to adherence include patient-related factors such as cognitive decline, skepticism, and socioeconomic constraints, alongside disease and treatment-related challenges like polypharmacy, regimen complexity, and asymptomatic conditions. Healthcare system inefficiencies, including fragmented electronic health records and limited consultation time, further complicate adherence management.

A recent study by the European Network to Advance Best Practices and Technology on Medication Adherence (ENABLE) identified major challenges in NA, including low patient awareness, insufficient time for HCPs, inadequate digital solutions, and poor interprofessional collaboration (Hafez et al., 2024). While these systemic issues are significant, they do not fully encompass the multifaceted nature of NA, particularly within the clinical contexts explored in our study. Although ENABLE advocates for enhanced education and digital interventions, our findings emphasize the need for individualized, patient-centered approaches. NA is often driven by specific patient profiles—such as individuals skeptical of medications or those facing complex social challenges—necessitating tailored interventions. This underscores the limitations of purely technological solutions and highlights the importance of culturally aware, context-sensitive care strategies to improve adherence outcomes.

HCPs employ various strategies to assess the risk of NA upon a first consultation. Beginning with simple inquiries, they identify at-risk groups and adherence barriers. Interviewing patients about adherence is the most used method despite its low reliability, as it relies on the patient's honesty and is subjected to the white coat effect (Hamrahian et al., 2022; Burnier, 2024). Observing patients' reactions to discussions about new treatments is key, especially if the treatment is long term; reluctance may signify potential NA. To prevent NA, thorough explanations of the disease and the prescribed treatments are essential. Unfortunately, the physician's time is limited during a consultation, with only about 5 minutes allocated to discussing treatment adherence (Burnier, 2024). However, during follow-ups, detection of NA often relies on voluntary disclosures from patients or caregivers, direct questioning, inquiring about the patients' current satisfaction with the treatment. Nonetheless, not all physicians investigate NA systematically, some of them rely on their connection with the patient to assess NA and inquire only when they feel it necessary. Sometimes, laboratory analysis could be more reliable for doctors to assess their patient's adherence whether it is by detection of the compound or through biological markers.

While biological markers are not definitive indicators in every specialty, lack of medication efficacy can suggest NA and more specifically in asymptomatic conditions. For instance, the use of statins should result in a decrease in the patient's blood cholesterol. If the low-density lipoprotein (LDL) cholesterol levels remain identical, NA should be investigated (Lansberg et al., 2018). The same principle can be applied to antihypertensive medication with the blood pressure measure. Some comorbidities such as dementia, anxiety, or diabetes can also lead to lower adherence whereas hypertension is associated to a higher adherence to lipid lowering drugs. These identifiable factors can help physicians tailor their approach when facing potentially non-adherent patients (Lopes and Santos, 2021).

Persisting symptoms or complications, missed appointments, and unexpected return of symptoms also flag potential NA. The conversation with patients, initiated with sensitivity, should balance direct questions with gentle questioning into adherence barriers including medication cost, management of side effects and the psychological impact of a lifetime treatment. Using a valid, reliable, cost-effective, straightforward, and readily accessible objective method would be the gold standard in NA detection. However, simpler and less expensive methods often come with lower reliability. In contrast, methods with higher reliability tend to be more expensive and require more infrastructure (Hamrahian et al., 2022). HCPs are forced to rely on clues given by their patients to identify those at risk of poor adherence. Recognizing these profiles and employing tailored approaches can enhance adherence and optimize patient outcomes.

Clinicians often find themselves allocating considerable extra time to address the needs of non-adherent patients, which can amount to a 25% increase compared to adherent peers. Non-adherent patients typically need three extra consultations annually compared to their adherent counterparts (Cutler et al., 2018). This investment is not merely a matter of convenience but a critical component of effective patient care; neglecting it risks exacerbating patients' conditions and complicating treatment pathways. In cardiology alone, poor adherence to cardiovascular medication is directly linked to an increase in cardiovascular events and mortality. An improvement of 20% in adherence is associated with 140 fewer deaths from all-causes per 1 million per year (Chen et al., 2022). This highlights the significant role of the clinicians taking the time to address NA.

The consequences of NA ripple through the healthcare system, leading to worsening conditions, increased reliance on medication, and a shift from manageable to chronic illnesses. Despite the hidden nature of some immediate consequences, the long-term impacts are palpable, both in terms of patient outcomes and the strain placed on healthcare providers. Addressing NA requires not only clinical acumen but also patience and persistence in conveying the importance of treatment compliance. Failure to address this issue not only undermines the quality of care but also represents a missed opportunity to alleviate future complications and enhance patient wellbeing.

5 Limitations

The study is limited by its qualitative nature and the relatively small sample size, which may not fully capture the perspectives across the different clinical settings and specialties, thereby limiting the generalizability of our findings. While the findings provide valuable insights into clinicians' individual views on medication NA future research should aim to incorporate larger datasets, potentially through broader surveys, to provide a more comprehensive and representative understanding of the factors influencing NA. Expanding the scope of investigation to include additional HCPs and patient perspectives could also enrich the findings and contribute to a more holistic view of adherence challenges and potential solutions.

6 Conclusion

Medication NA is a widespread challenge requiring patient-centered, tailored interventions to improve outcomes. The insights from clinicians emphasize the critical role of personalized strategies in detecting and addressing adherence issues. By prioritizing tailored communication, regular follow-ups, and a deeper understanding of individual patient challenges, clinicians can more effectively manage NA. While systemic barriers such as limited patient awareness, time constraints for HCPs, and technological limitations persist, our findings suggest that a flexible, individualized approach is most effective. A team-based model that integrates direct patient-clinician interaction with systemic support and digital innovations holds promise for enhancing adherence and improving patient outcomes. Future research should prioritize validating digital adherence tools, exploring psychological determinants of NA, assessing the impact of multidisciplinary care models, and investigating policy-level changes to enhance adherence support.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

NT: Writing – review and editing, Writing – original draft. SJ: Writing – review and editing, Writing – original draft. ED-M: Writing – original draft, Writing – review and editing. BM: Writing – review and editing, Writing – original draft. OÖ: Writing – original draft, Writing – review and editing. TS: Writing – original draft, Writing – review and editing. LT: Writing – review and editing, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Supplementary material

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Digital interventions in medication adherence: a narrative review of current evidence and challenges

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Non-adherence to prescribed treatments remains a major challenge facing the healthcare system. Despite decades of research, interventions to improve adherence typically have not shown large or sustained effects on adherence and are rarely implemented. Digital technologies provide a potential platform to increase the reach and cost-effectiveness of adherence interventions, allowing them to be widely rolled out. Current evidence suggests that digital interventions can increase adherence, but results are mixed with many interventions failing to improve adherence. This is likely because whilst the included interventions all utilise digital platforms, they vary significantly in their design, content and delivery. Many interventions are not theory or evidence based, do not include patient or healthcare practitioner involvement or focus simply on providing reminders. Evidence suggests that well-designed interventions which are evidence-based, are personalised and maximise interactivity are more likely to be successful. These well-designed interventions hold promise for improving adherence at scale. This narrative review discusses the current challenges facing digital adherence interventions and describes barriers to implementation or adoption which need to be resolved. These include considering reach, accessibility, and acceptability, to avoid increasing existing health inequalities. It is also critical to consider the quality, safety and regulation of available apps and other digital tools, as well as investigating ways to enhance engagement and retention. Finally, some digital tools may require integration into existing systems or may necessitate training of relevant staff. Overall, digital interventions appear to be a promising tool for improving medication adherence, but further work is needed to optimise these tools.

KEYWORDS

adherence, interventions, digital, eHealth, mHealth

1 Introduction

The World Health Organization has classified treatment adherence as a major global problem (Burkhart and Sabaté, 2003). It is estimated that 20%–50% of patients do not take their medication as prescribed (Bosworth et al., 2016). The reasons patients do not take their medication correctly can be either unintentional, such as confusion or simple forgetfulness (Mira et al., 2015), or intentional, where the patient makes a deliberate decision not to take their treatment (Horne et al., 2019). Support to improve adherence therefore needs to foster both motivation and ability to adhere (Horne et al., 2019).

Digital technologies are increasingly being used to deliver these interventions, due to the proliferation of smart phones and other technology developments globally. Internet access continues to grow, with an estimated 5.44 billion internet users worldwide in 2024, accounting for two-thirds of the global population (Statista, 2024b). 69% of the global population have access to a smart phone (Statista, 2024c), with very high levels of penetration in the United Kingdom (84% (Statistics, 2020)) and US (90% (Center, 2024)). Engagement with and implementation of digital healthcare has also been rising over the past 10 years, particularly since the COVID-19 pandemic in 2020 (Mahajan et al., 2021; Mosnaim et al., 2020).

These figures highlight the potential for delivering health programs such as adherence interventions through a mobile phone, computer or similar device. These technologies are often very cost-effective and can reach large numbers of patients with little effort, as well as enhancing the potential for personalisation and automation of interventions.

This narrative review will first provide an overview the current evidence base for digital interventions to improve adherence, followed by an outline of issues in the field and factors associated with the success of digital health adherence tools.

2 Current evidence base for digital interventions

2.1 Text messaging

Several systematic reviews of studies including both randomised and non-randomised designs have shown that Short Message Service (SMS) text interventions can improve medication adherence in patients with diabetes, hypertension and/or dyslipidemia (Belete et al., 2023; Bingham et al., 2021). However, other systematic reviews including just Randomised Controlled Trials (RCTs) with a greater number of studies show more mixed results (Bond et al., 2021; Redfern et al., 2024). For example, a recent Cochrane review of RCTs evaluating text messaging for medication adherence in secondary prevention of cardiovascular disease concluded that the evidence was very uncertain, with only 10 out of 18 studies showing a beneficial effect on adherence compared to usual care (Redfern et al., 2024). Furthermore, any effects tend to be very short term, or do not persist past the end of the intervention (Mulawa et al., 2018; Gautier et al., 2021), and issues have been raised with study quality, such as issues with blinding and selective reporting (Palmer et al., 2021; Adler et al., 2018). Despite these mixed effects, one review found that of the studies (13 of 18) who reported user feedback, satisfaction and interest was very high (Bond et al., 2021).

Some studies have attempted to identify the best ways of optimising text message interventions. Whilst no studies have directly compared tailored vs generic messaging to enhance medication adherence, text message interventions which go beyond simple reminders and are tailored to the individual's beliefs have shown success in improving adherence (Petrie et al., 2012; Riaz and Jones Nielsen, 2019) and tailored messages have been shown to be more effective in changing other health behaviours (Head et al., 2013). Interventions lasting 6 months or longer were more effective than those that are shorter term (Belete et al., 2023), and tapering for an additional 3 months has also shown to be useful in maintaining adherence after the initial intervention (Belzer et al., 2025).

2.2 Apps and web-based programs

Many health behaviour change interventions are now being delivered through mobile applications (apps) or other web-based programs. These allow for the delivery of content direct to the user, along with enhanced options for personalisation, interaction and reminders. A review in 2015 found 681 available adherence apps on the Apple App Store or Google Play Store (Ahmed et al., 2018). The number of adherence apps has grown since then, with a 2017 review estimating 800 medication management apps available (Dayer et al., 2017), and a 2024 review finding 53 available health apps in asthma alone (Robinson et al., 2024). However, despite this proliferation of available apps, there is little consistent evidence for their efficacy (Chong et al., 2023; Cao et al., 2024). Clinical studies evaluating the impact of apps on improving adherence have shown mixed results (Aungst, 2021). A 2020 review of 9 trials of mobile medication adherence apps across a range of health conditions found a significant pooled effect, but five of the nine included studies did not report a significant effect on adherence (Armitage et al., 2020), potentially due to variability in adherence measurement, techniques used and the extent of the tailoring within the included apps.

This lack of consistent evidence for apps is likely due to the significant variation in design, content and delivery (Ng et al., 2020). Few of the publicly available apps meet relevant criteria for quality, content or functionality (Masterson Creber et al., 2016) and most lack a sufficient evidence base. Reviews of trials suggest those that include more interactive features, such as interaction with medical providers, social networking and gamification features, tended to be more effective (Unni et al., 2018; Cazeau, 2021), yet these features are often lacking from publicly available apps (Wang et al., 2024). Similarly, it has been suggested that tailoring intervention content to the individual user will also be associated with positive effects on adherence (Armitage et al., 2020; Goradia et al., 2021; Stewart et al., 2023). For example, several digital interventions which tailor the content to the individual's medication beliefs have shown success in improving adherence (Lakshminarayana et al., 2017; Chapman et al., 2020; Hughes et al., 2022). In the 2020 review mentioned above, the authors highlight examples of successful highly tailored interventions and state their results may support the hypothesis that level of tailoring is associated with the effectiveness of adherence apps (Armitage et al., 2020).

Recent innovations include the use of gamification in medication adherence apps, including features such as social connectivity, avatars, alternate realities, leaderboards, points and badges. These features are proposed to enhance medication adherence as well as adherence to the app itself (Ahonkhai et al., 2021). A review of five studies using gamification features (e.g., leaderboards, levelling up, quests) to improve medication adherence across a range of conditions, found that three of the five studies showed significant improvements in adherence (Tran et al., 2022). Overall, the evidence base for adherence apps is mixed with many poor quality studies, making it difficult to draw conclusions on their

effectiveness (Ng et al., 2020). Reported issues with quality include small sample sizes, self-presentation bias, potential conflicts of interest, lack of appropriate control arms and self-reporting of adherence outcomes (Ng et al., 2020).

2.3 Monitoring and smart products

Over the last decade, the popularity of digital medication adherence systems has surged, with both healthcare providers and patients acknowledging their role in enhancing adherence and overall health results. A recent review by Mason et al. (2022) identified a variety of technology applications for monitoring medication adherence, including electronic pill bottles or boxes, ingestible sensors, video-based technology, and motion sensor technology. The common expectation is that these technologies accurately monitor medication adherence and can easily be adopted in patients' daily lives owing to their unobtrusiveness and convenience of use.

Sensor technologies have been increasingly used to track the medication-taking behaviours of patients. For example, the Medication Event Monitoring System (MEMS) can record every time the patient opens the pill bottle via a sensor embedded in the pill cap. These medication monitors are increasingly used as part of strategies to improve adherence. Despite this, there is limited consensus on how to determine or select the appropriate medication adherence monitoring technology for use. There is a growing need for technology assessment criteria to guide the development and selection of appropriate technologies for monitoring medication adherence to improve patient outcomes (Basu et al., 2019).

Some recent studies have shown promising findings for the use of smart technologies to improve medication adherence. A systematic review by Chan et al. (2022) found that patients receiving an electronic adherence monitoring (EAM) intervention (most commonly devices which record pillbox being opened and sent reminders) had significantly better adherence than those who did not. In this review, data from 27 studies (n = 2,584) were extracted for the adherence outcome, Most studies were conducted on adults (87%) and the most common conditions were in asthma (21%) or human immunodeficiency virus (HIV) (19%), or hypertension (13%). The authors concluded that improved adherence did not consistently translate into clinical benefits (Chan et al., 2022). Acceptability data were mixed, with perceptions of the device being negative in nearly half of the included studies. Issues with acceptability included the reminder beeps, the size of the device and concerns about disclosure. Feedback on the intervention itself was more positive, with patients looking forward to receiving their adherence data. The authors conclude that further research is required to assess patient acceptability and explore effects on clinical outcomes and. A study by van de Hei et al. (2023) found that digital inhaler–based interventions can yield long term cost-savings by optimising medication adherence and inhaler technique and reducing additional biologic prescriptions in patients with difficult-to-treat asthma (van de Hei et al., 2023).

Stakeholders' expectations regarding the use of health information technology for monitoring medication adherence can also vary. From a clinical practice perspective, a user-friendly interface and the accurate monitoring of adherence are considered when selecting appropriate monitoring technologies. From the technological development perspective, although system accuracy and data fidelity remain high priorities, developers also need to consider the feasibility of technical engineering of the system, such as energy consumption and battery lifetime (Aldeer et al., 2018). Human interactions with these technologies can be complicated owing to the comprehensive medical and pharmacological contexts, as well as multidimensional patient medication adherence behaviours.

2.4 Artificial Intelligence and adaptive interventions

Artificial Intelligence (AI)-powered mobile applications are those that apply logical algorithms which are capable of learning from data and making autonomous decisions based on generalizable rules (Zavaleta-Monestel et al., 2025). These have proven to be valuable tools in monitoring and improving medication adherence (Zavaleta-Monestel et al., 2025). In a study conducted by Labovitz et al. (2017), an AI-based smartphone app was developed for stroke patients on direct oral anticoagulant therapy. The app used a neural network to identify the patient and the prescribed drug, confirm ingestion through the phone's camera, and provide medication reminders. The study found a 100% adherence rate among patients using the app compared to 50% in the control group, and identified positive patient feedback. However, the study was small (n = 28), and therefore further research with larger sample sizes is needed to determine long-term effectiveness. Similarly, Bain and colleagues (Bain et al., 2017) used an AI platform incorporating facial recognition and drug verification for real-time monitoring of schizophrenia patients in a 24-week clinical trial. The study demonstrated 17.9% higher adherence in the AI-monitored group compared to a control group receiving modified direct observation therapy. Another clinical trial used a voice-based conversational AI application to support type 2 diabetes patients (Nayak et al., 2023). The results showed that insulin adherence rates were 32.7% higher in the AI-voice application compared to the standard care group.

AI-driven reminder systems have been developed to encourage medication adherence by sending timely reminders to patients. Brar Prayaga et al. (2018) explored the use of "mPulse Mobile," an SMS-based AI reminder system in older patients with non-communicable diseases. They observed significantly higher medication refill rates in the group that received AI-generated SMS reminders compared to a control group that did not receive any reminders. A study by Chaix et al. (2019) found that AI can also play an important role in indirectly improving adherence by empowering patients (Chaix et al., 2019). In their study they used "Vik," a chatbot designed for breast cancer patients to provide personalised health information, including medication reminders. The study showed that patients who engaged more with Vik were observant when using a treatment reminder function, and that medication adherence improved by more than 20% in this group.

AI-assisted technology could also be used to optimise prescriptions by prioritising medications that match the insurance/preferred pharmacy of the patients and check

FIGURE 1
Factors associated with the success of digital adherence tools.

drug–drug interactions. AI has already been shown to be useful for medication reconciliation, which is a procedure often used to reduce medication errors (Long et al., 2016). One of the major contributions that AI-assisted technologies has had in recent years in disease management is through machine learning (ML) and big data analytics. For example, Koesmahargyo and colleagues (2020) used ML to predict medication non-adherence based on real-time dosing data collected from smartphone videos of patients taking their medications (Koesmahargyo et al., 2020). This approach provided highly accurate predictions of adherence across both the trial period and subsequent days or weeks. A systematic review of literature on AI highlighted that machine learning is currently the most commonly used AI technology in healthcare (Guo et al., 2020). In general, however, this field is still in its infancy; there are currently 100 FDA-approved AI/machine learning-based medical devices and algorithms, which are constantly updated on an online database (Medicalfuturist, 2025). A recent review examined the use of AI tools for patient support to enhance medication adherence, with results showing that although the evidence supporting AI tools to assist patients is weak, smart systems using AI tools are promising in helping patients use prescribed medications (Reis et al., 2025). Based on current evidence, AI-powered, personalised approaches are best suited to complex behavioral barriers to intentional adherence, whereas basic digital tools can serve as reminders and educational aids to improve unintentional adherence by providing real-time feedback and tracking.

3 Factors associated with success of digital health adherence tools

As described above, evidence on the effectiveness of digital adherence interventions is mixed, with many interventions failing to improve adherence. In order to develop interventions which will successfully engage participants and improve adherence, the following factors need to be considered (see Figure 1 for a summary).

3.1 Patient acceptability and engagement

Engaging patients in an intervention and retaining them throughout is one of the biggest challenges facing any e-health intervention (Eysenbach, 2005), including adherence interventions, with many participants declining, dropping out of or not fully engaging with adherence interventions (Habib et al., 2021; Ping et al., 2022; Côté et al., 2020). For example, a web-based intervention to support medication adherence in people with HIV found that only 69% accessed the intervention, and of these only 36% completed more than one session. Only four of the initial 45 participants reached session four (Côté et al., 2020).

Reasons for this lack of engagement are complex and multi-faceted. Barriers to e-health in general include concerns about privacy and confidentiality, limited access to the relevant device or the internet, and lack of perceived need for digital support (Moecke et al., 2024; Morrissey et al., 2018). With regards to adherence interventions, concerns around privacy and data

ownership are particularly relevant in interventions involving monitoring or any form of AI, with participants reporting concerns that this data could be used against them (e.g., with insurance companies) (Klugman et al., 2018). Technical issues or lack of user-friendly designs may also impede engagement to digital interventions (Ping et al., 2022; Grindrod et al., 2014). Older adults may face physical difficulties such as issues using small buttons on smartphones, reading small fonts or hearing notifications (van Acker et al., 2023). To overcome these issues, it is essential to involve the target population in intervention development and identify barriers relating to engagement and trust. For example, a survey of medication reminder app users in Singapore suggested that highlighting how apps protect personal data or offering anonymous usage should increase app usage (Ping et al., 2022). Another study found that people were more likely to agree to use an app if a clinical staff member would help them (Morano et al., 2019).

Usability testing and stakeholder feedback can help to develop interventions which are easy to understand and use for the target population (Grindrod et al., 2014; Hosszú et al., 2024). For example, Blixen et al. (2018) collected user feedback as part of the development of a text messaging intervention to improve adherence in people with bipolar disorder and hypertension (Blixen et al., 2018). Results highlighted key areas to increase patient acceptability, such as customising messages, writing out in full instead of abbreviated text speak and a focus on positive rather than negative messages. Similarly, user testing of a web-based diabetes adherence intervention identified several errors and provided recommendations on how to improve the site's user interface (Nelson et al., 2016). Applying user experience (UX) principles, such as clear instructions and user-friendly error messages is also essential in developing apps which are intuitive and that people do not get frustrated with and stop using (Omaghomi et al., 2024). Gamification features such as rewards systems, points and leaderboards may also increase engagement (Omaghomi et al., 2024), as does the overall aesthetic and appearance of the app (Michie et al., 2017). Users also report engaging more with apps that appear to be credible, that are personalised and that allow communication with other users or HCPs (Michie et al., 2017). For example, a personalised smartphone based tracker app in Parkinsons disease showed significant improvements in adherence (Lakshminarayana et al., 2017). Analysis of usage found that 72% of participants in the intervention group continued to use and engage with the application across the 16 week period, with most using the app almost every day. However engagement with apps does not always lead to improved adherence. For example, a gaming app to improve medication in rheumatoid artritis found no significant improvements in adherence, despite the fact that 79% installed the game and 65% of these were active for at least 30 days out of 90 (Pouls et al., 2022).

3.2 Stakeholder engagement

Engaging end-users and wider stakeholders in the early design of interventions is essential to ensure participant acceptability, engagement and retention. Participatory approaches to digital health research have received increasing attention over the past 2 decades, particularly with regards to their role in developing effective digital interventions to promote medication adherence. Public and patient involvement (PPI) refers to the process of involving members of the public or patient groups in the research or design process. This involvement can occur at different stages of the research or design process. One of the driving motivations behind participatory approaches such as PPI is the idea that, in the case of public health research, members of the public have a right to input into designs and decisions in the context of research which may affect them (Bagley et al., 2016). Involving stakeholders who will interact directly or indirectly with the outcomes of research, tool design, or interventions, serves to ensure that the research is relevant, conducted in an ethical and acceptable manner, and that the research is designed in a participant-friendly or user-friendly manner.

In the past, mHealth tools have commonly been designed with consideration only given to existing healthcare systems and protocols, with little or no involvement of the end-users (Schnall et al., 2016). Increasingly however it is recognised that, in order for mHealth tools and applications to be effective, careful consideration needs to be given to the needs, requirements, and capacities of the end-users. Some reported barriers and enablers such as the importance of data privacy and security appear to be unique to PPI in digital innovation and these need to be addressed as part of this process (Baines et al., 2022).

A strong emphasis on participatory research and user-centred design, are said to play a key role in overcoming the uptake and retention issues described previously (Morton et al., 2020). While PPI focuses primarily on the involvement of patients in research and design, participatory approaches may involve engagement with stakeholders across various levels of healthcare delivery, depending on the purpose of the research design. Involving stakeholders, such as community health workers, nurses, administrators, and data managers in the design of mHealth tools allows for the gathering of valuable input in relation to various factors in effective design, including relevance, usability, and acceptability (de Beurs et al., 2017; Brewer et al., 2020). Effective eHealth interventions for self-management involve multidisciplinary teams harnessing diverse expertise. Systematic frameworks for intervention design and evidence-based user-centred methods, such as the person-based approach and Public and Patient Involvement (PPI) (Baines et al., 2022) facilitate this teamwork.

The WHO underscores involving end users in initial design phases to inform critical elements like perceived benefits and barriers to behaviour change, aligning interventions with community characteristics (WHO, 2021). Recognising this, increased emphasis has been placed on early involvement of users and stakeholders. The person-based approach leverages in-depth qualitative research to define guiding principles and key intervention features, essential across development stages, including planning, testing, and clinical evaluation. It aligns with in-depth approaches from information systems and human-computer interaction, emphasising understanding user knowledge, behaviour, motivations, and cultural contexts. Traditional user-testing focuses on utility and engagement, aiming to enhance technology usage. In contrast, the person-based approach, rooted in health psychology, targets behaviour

change techniques and their implementation to boost participant engagement, driving intended outcomes.

3.3 Optimised content—use of behavioural theories/frameworks

Behaviour change theories can be used to aid the development of interventions to address relevant barriers to adherence and identify solutions for improving adherence. There are many long-standing, influential theories, including the Theory of Planned Behaviour (Ajzen, 1991), Goal-Setting Theory (Locke and Latham, 2015), the Health Belief Model (Janz and Becker, 1984), and Bandura's (1986) Self-Efficacy Theory (Bandura, 1982). The Perceptions and Practicalities Approach (PaPA (Horne et al., 2019)) is a behaviour change theory developed specifically to understand non-adherence. The United Kingdom National Institute for Health and Care Excellence (NICE) guidelines for Supporting Adherence (Nunes, 2009) recommend the application of the PaPA, suggesting that any adherence support needs to consider the perceptual factors (e.g., beliefs about illness and treatment) that influence motivation to take a prescribed treatment, as well as the practical factors influencing ability to take the treatment (Horne et al., 2019). Evidence suggests that interventions which address both perceptual and practical factors influencing adherence are more likely to succeed. For example, a review of interventions to improve adherence to antiretroviral therapy found that interventions which addressed individuals' specific perceptual and practical barriers to adherence were more effective than those that just addressed practical barriers like forgetting (Zoe Moon et al., 2023).

Another approach is the Behaviour Change Wheel (Michie et al., 2011) developed by synthesising 19 different frameworks of behaviour change. The Behaviour Change Wheel provides a useful way of linking a model of behaviour to common functions of interventions to change that behaviour (e.g., education, persuasion, coercion, incentivisation), and in turn, linking these intervention functions to policy categories (e.g., service provision, guidelines) that facilitate behaviour change. In addition, the Behaviour Change Technique Ontology (BCTO) (Marques et al., 2023) promotes the use of Behaviour Change Techniques (BCTs), defined as the observable, replicable components of behaviour change interventions. The BCTO provides a standard terminology and comprehensive classification system for the content of behaviour change interventions that can be reliably used to describe interventions. The techniques included in the ontology have been synthesised from related constructs drawn from theories and frameworks across clinical and health psychology research and practice. Using the BCT ontology to design effective interventions is therefore not inconsistent with other theoretical approaches.

Kahwati and colleagues used the BCT Taxonomy to conduct a qualitative comparative analysis of a systematic review of 60 complex interventions to identify combinations of BCTs that were most effective for improving medication adherence in outpatients with chronic conditions. Improvement in adherence was reported in more than half of the studies (57%). Of these studies, there were seven different configurations of BCTs that increased adherence. However, the most common and efficacious combination of techniques was 'increasing knowledge' coupled with 'increasing self-efficacy' (Kahwati et al., 2016). A content analysis of the BCTs present in 166 available apps reported that 12 of a possible 96 BCTs were present across these apps, and that 96% of the apps included the BCTs of 'action-planning', and 'prompting/cues'. More than one-third of the apps that were reviewed featured the BCTs 'self-monitoring' and 'feedback on behaviour' (Morrissey et al., 2016).

3.4 Reach and inequalities in access

It has been suggested that digital technologies hold great potential for offsetting health inequalities, by increasing access and reaching those who may not traditionally receive support (Sharma and Patten, 2022; van de Vijver et al., 2023). However, there is also the potential for digital technologies to widen existing health inequalities, causing a "digital divide", should they not have equitable reach or effectiveness (Latulippe et al., 2017). For example, digital health literacy and internet access are reported to be lower in underprivileged populations such as immigrants and individuals with lower socioeconomic status or less formal education (Estrela et al., 2023). This is of concern as these are groups who are already facing health inequalities.

Research has highlighted differences in terms of who has access to relevant digital devices. A survey of 2009 women with breast cancer in the United Kingdom found that 20% did not have access to a Tablet or Smartphone, and that the women without access were more likely to be older, have less formal education and be from a more deprived area (Moon et al., 2022). In the US, whilst 97% of college graduates own a smartphone, this falls to 83% in people with no college education (Center, 2024). In the United Kingdom, 96% of the highest socioeconomic group are smartphone users compared to 84% of the lowest socioeconomic status group (Statista, 2024a). Across the world, a UN report cited in the least developed countries only 27% of the populations are Internet users (Nations, 2023).

However, access to the internet, smartphones or other devices is only one part of the picture. It is also important to consider whether there are any factors influencing willingness to engage with digital health interventions. For example, studies report that older adults, those who are less highly educated and people from minority ethnic groups are less likely to be users of mobile health apps or to seek health information online (Bol et al., 2018; Fareed et al., 2021). Receptivity towards mobile phone text messages as a healthcare intervention also reduces with increasing age, and lower education and income levels (Serrano et al., 2016). Specifically with regards to digital adherence interventions, a US study showed that people with diabetes with lower health literacy and who were not of white ethnicity were less likely to participate in the intervention (Nelson et al., 2016). However, engagement did not differ by age, gender, education, income or health literacy, suggesting fairly wide reach. In another study, people with HIV who had less formal education were less willing to adopt mobile phone technology to improve their adherence (Morano et al., 2019).

Taken together, these studies support the idea that digital health interventions may be less likely to be accessed or used by people from lower socioeconomic status backgrounds, which is of concern given the existing health inequalities in these groups. However, some

other studies have shown that patients in diverse or low-income communities show greater interest in mHealth apps than those from white or high-income communities (Humble et al., 2016; Ramirez et al., 2016).

Research has also highlighted potential differences in how effective digital behaviour change interventions are for different groups of people. Whilst this has not been explored in adherence specifically, a systematic review and meta-analysis of digital behaviour change interventions for physical activity found that the interventions were effective in those with high socioeconomic status but not in people of low socioeconomic status (Western et al., 2021). Therefore, attention may need to be paid to understanding whether the benefits of adherence interventions are equitable across all participants.

More research is warranted to fully understand whether adherence digital interventions will further the "digital divide" or help to close existing gaps. However, regardless, intervention developers need to be mindful of developing interventions in an inclusive and equitable manner. Several guidelines have been developed to assist with this (Latulippe et al., 2017; Miller et al., 2023), as well as the Carnegie United Kingdom Trust 12 recommendations for eliminating digital exclusion (Georgina Bowyer, 2020). Key elements of these guidelines include ensuring universal access to the tool, co-creating with a diverse and relevant stakeholder groups, accounting for varying levels of health literacy, and collecting quality data to monitor access and engagement.

3.5 Regulation and privacy

Rapid developments in digital technology has far outpaced regulatory bodies' capacity to address issues around quality, data regulation and privacy. A study by Backes et al. (2020) investigated whether healthcare providers could safely recommend mobile health apps to their patients to promote medication adherence (Backes et al., 2020). In their study they evaluated eligible apps and concluded that none of the apps had undergone a process for certification, little information was provided on security and data protection and that more clinical studies with chronic patients are necessary to measure long-term app impacts. The authors suggest that some of these shortcomings might be corrected through the introduction of General Data Protection Regulation (GDPR) in the European Economic Area (EEA) and more scrutiny through regulatory bodies in the EU/EEA and the United States. They further concluded that none of the applications should be recommended by healthcare providers.

Research by Grundy et al. (2019) found that the accuracy and quality of information provided within medical and health apps cannot easily be ascertained and these factors are likely to affect medication adherence and, more importantly, patient health outcomes (Grundy et al., 2019). They found that apps often involve communicating patient-specific data over the internet which raises the issue of patient privacy. They further reported that up to 80% of mobile health apps transmit user-related information to online services and 66% of apps sent unencrypted identifying information over the Internet. They conclude that the benefits of secure communication of information between health providers and patients cannot be ignored.

Magrabi et al. (2019) examined the challenges around regulation of apps to promote medication adherence and concluded that an evidence-based approach that is informed by the current landscape of health apps is required (Farah et al., 2019). They suggest that operational oversight and surveillance could be considered at a national and regional level using common frameworks so that it is possible to compare patterns over time and between settings, and to develop and prioritise preventive and corrective strategies. A professional foundation for regulation of such technologies would permit more widespread use of evidence-based apps to promote medication adherence. Finally, the role of citizen developers should also be considered within this digital health ecosystem.

3.6 Implementation and adoption

A final issue with digital adherence interventions is that they are often under-utilised and few are implemented at scale (Kardas et al., 2022). Trials of adherence interventions tend to fail to consider factors relevant to implementation into real-world settings (Kostalova et al., 2022), and reviews have concluded that the long-term sustainability and feasibility of digital adherence interventions remains to be determined (Chan et al., 2022; Griffee et al., 2022). Barriers to the successful implementation of eHealth interventions in general include cost, increased workloads, lack of healthcare professional motivation, issues with interoperability, and lack of suitable infrastructure, training and support (Kardas et al., 2022; Ahmed et al., 2019; Granja et al., 2018; Chimweta et al., 2025). Particularly in the developing world, issues with local telecommunication networks may act as a barrier to intervention implementation (O'Connor et al., 2022). Across all contexts, acquiring the funding for ongoing maintenance and hosting can be a barrier to implementation and utilisation (Ahmed et al., 2019). Implementation science can provide useful insights and should be considered from the start of any project to ensure that the digital adherence interventions developed have a chance of being implemented (Kostalova et al., 2022; Zullig et al., 2019). Issues around reimbursement are also a barrier to implementation, and more data on long-term clinical effects and cost-effectiveness may be needed to overcome this (Kardas et al., 2022; Borah et al., 2025).

4 Conclusion

Digital technologies have emerged as a promising tool for addressing the significant global issue of medication non-adherence. However, the evidence supporting the effectiveness of these digital interventions is mixed, with many studies showing inconsistent or short-term improvements in adherence. This variability is largely due to the diverse designs, content, and delivery methods used in digital tools, many of which lack a strong evidence base or user-centered design. While digital interventions have the potential to reduce healthcare costs and improve medication adherence, careful attention must be paid to ensure these technologies do not inadvertently widen existing health inequalities. Addressing the "digital divide" by ensuring equitable access, usability, and acceptability across diverse populations is essential to prevent exacerbating disparities in healthcare access and outcomes.

Future interventions aimed at improving medication adherence should emphasise personalised approaches that consider individual patient needs, beliefs, and preferences. Leveraging AI and machine learning algorithms can enhance engagement and effectiveness by tailoring content, reminders, and feedback. Incorporating interactive elements, such as communication with healthcare providers and peer support networks, can further boost adherence. Rigorous evaluation and the establishment of quality standards are essential, with a focus on long-term outcomes, patient engagement, and clinical benefits through well-designed clinical trials.

Author contributions

ZM: Conceptualization, Investigation, Writing – original draft, Writing – review and editing. JW: Conceptualization, Investigation, Writing – original draft, Writing – review and editing.

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