HEALTH PSYCHOLOGY REVIEW
https://doi.org/10.1080/17437199.2024.2385525

Routledge
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS Check for updates

Preventing medication nonadherence: a framework for interventions to support early engagement with treatment

Sarah Chapman [a], Lisbeth Frostholm [b,c], Trudie Chalder [d], Christopher Graham [e], Annette de Thurah [c,f], Tess van Leeuwen [a,g], Mahbritt Mostrup Pedersen[h], Tina Carstensen [b,c] and Ohn Weinman [a]

[a]Centre for Adherence Research and Education, Institute of Pharmaceutical Science, King's College London, London, United Kingdom; [b]Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, Aarhus, Denmark; [c]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; [d]Institute of Psychiatry, Psychology & Neuroscience (IoPPN), Department of Psychological Medicine, School of Academic Psychiatry, King's College London, London, United Kingdom; [e]Department of Psychological Sciences and Health, University of Strathclyde, Strathclyde, United Kingdom; [f]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark; [g]Hogeschool Inholland, Inholland University of Applied Sciences, The Hague, Netherlands; [h]Department of Clinical Medicine – Research Clinic for Functional Disorders, Aarhus University Hospital, Aarhus, Denmark

ABSTRACT

Medication nonadherence is common and results in avoidable morbidity, mortality, and burdens on healthcare systems. This paper proposes a preventative approach to medication nonadherence. We consider existing evidence on the prevalence and determinants of nonadherence early in a patient's medication-taking journey, and map these to potential opportunities for intervention. Many patients stop taking a new medication soon after they are prescribed it, often not collecting the medication. Early patterns of nonadherence are linked to later nonadherence via processes such as habit formation and symptom experiences. Known predictors of nonadherence may be present before someone starts a new treatment, when patients experience disruption to their lives and identity due to illness. Healthcare professionals typically have contact with patients around this time. We argue that it may be possible to prevent medication nonadherence: at the population level; by optimising the prescription process; and through low- and high-intensity interventions for patients with identified early barriers. We give examples of specific interventions and tools that might be needed to operationalise this approach in practice and propose new directions for research to promote early engagement with medication to prevent nonadherence.

ARTICLE HISTORY
Received 14 December 2023
Accepted 23 July 2024

KEYWORDS
Medication adherence; prescribing; psychosocial factors; prevention; behavioural interventions

Medication nonadherence is common, costly, and a critical barrier to patients achieving the full benefits of effective medications. Rates of nonadherence vary with medication, patient characteristics, treatment setting, and condition (Gellad et al., 2017). However, about 30-50% of patients globally do not take their medication as prescribed (Sabaté, 2003). Where medications are appropriately prescribed, nonadherence leads to avoidable morbidity and mortality (Faught et al., 2008; Glass et al., 2015; Ho et al., 2006), additional healthcare utilisation (Fitzgerald et al., 2011), and economic costs

CONTACT Sarah Chapman sarah.chapman@kcl.ac.uk

(Cutler et al., 2018). Despite this, there are few effective interventions to reduce nonadherence that can be implemented into daily clinical practice within current healthcare systems and a lack of evidence about which interventions work for which patients (Nieuwlaat et al., 2014).

Medication adherence is a dynamic process, in which a patient is prescribed medication sometimes for decades with huge variation in how patients are followed-up over time. This means that different interventions tailored to different time points of the patients' healthcare journeys may be the most efficient way to reduce nonadherence. For medication adherence three separate phases have been described: initiation (taking the first dose of a treatment), implementation (taking the course of treatment as prescribed), and persistence (taking the treatment for the full duration). In this paper, we focus on the period immediately before and after starting a new treatment which can include all aspects of medication adherence (Vrijens et al., 2012).

We argue and present evidence below to the effect that the time when patients start a new treatment is a 'critical period' for nonadherence because: patients commonly fail to initiate new treatments; patients typically have contact with a healthcare provider when prescribed a new treatment; many causes of nonadherence are potentially identifiable and/or modifiable before treatment initiation; and because nonadherence at the point of initiating a treatment may predispose patients to longer-term nonadherence. We also know that patients are often cautious to disclose nonadherence and treatment doubts (Quirk et al., 2013). Starting treatment is therefore an opportunity to intervene and prevent nonadherence rather than reacting to later nonadherence. Building on existing literature on reducing initiation nonadherence, we will describe a potential stepped care approach for prevention of nonadherence at treatment onset and suggest new directions for research and practice.

Why focus on prevention?

(1) Starting a new treatment as a 'critical period' for risk of medication nonadherence

We argue that the point of treatment initiation is analogous to a 'critical period' for adherence. In classic developmental psychology, a 'critical period' is a stage when a person is biologically primed to acquire a new ability, has a heightened sensitivity to relevant stimuli, and can find it harder to learn later when the relevant stimuli are not present at this stage (Colombo, 1982). Nearly all competent patients should receive some support and information when medication is initiated. The WHO Guidelines of Good Prescribing (World Health Organisation, 2021; reviewed in Tichelaar et al., 2020), include providing information as part of step 5 in a 6-step prescribing process that is recommended for both medical and non-medical prescribers. In many European countries, New Medicines Services have been launched in the last 10–20 years with pharmacists providing support for groups of patients, often by addressing concerns and practical challenges with treatment (e.g., Merks et al., 2024). Nurses also may be involved in the initiation of new treatments particularly those requiring new skills to administer. For example, specialist paediatric endocrine nurses commonly provide training for children and parents in how to administer injectable growth hormone treatments (Savage et al., 2022).

Estimates of the number of people who do not initiate a treatment vary widely across healthcare contexts, medications, patient groups and initiation measurement and definition. What seems clear however is that much nonadherence occurs early in patients' medication-taking journey: an estimated 0.5-57.1% (McHorney et al., 2007) of patients prescribed medication for a long-term condition do not fulfil a new prescription (also known as 'primary nonadherence'). For example, one US study found over 3% of prescriptions are not collected from pharmacies (Shrank et al., 2010). Once medications are collected there is further nonadherence with many patients not initiating the treatment. For example, a meta-analysis estimated approximately a quarter of patients did not start a prescribed treatment (Cheen et al., 2019; Lemstra et al., 2018). Despite the number of treatments not initiated,

most research has focused on implementation of treatment with comparatively little focus on how many patients do not initiate a treatment or why this might be (Dima et al., 2015). Moreover, we know that many patients initiate treatment but then do not implement as prescribed and/or discontinue treatment within weeks of starting. One study of patients with schizophrenia discharged from hospital whose adherence was tracked using electronic monitoring devices found over half discontinued treatment within 6 weeks of discharge (Misdrahi et al., 2018). For many medications, rates of adherence decrease over time (Carmody et al., 2019), and the initial weeks may see a particularly fast decline in adherence for a systematic review see (Alhazami et al., 2020). For those that persist with treatment, early patterns of adherence are frequently stable for years of follow-up. Newman-Casey et al. (2015) tracked the adherence of 1,234 patients with glaucoma for four years and found over 90% of patients with initially good or poor adherence maintained this pattern for the whole follow up period. Thus, nonadherence due to non-initiation, poor implementation, and discontinuation may all occur soon after prescription of a new treatment, suggesting that timely intervention is necessary to prevent later nonadherence.

(2) Reasons for early nonadherence are modifiable.

As with all aspects of nonadherence, patients do not initiate treatment for a wide range of reasons (Jackson et al., 2014). Barriers to adherence can be conceptualised with the COM-B (Capability Opportunity Motivation-Behaviour) framework of behaviour change (Michie et al., 2011). Nonadherence is seen as occurring due to barriers in capability (does the person have the physical and psychological ability to take their medication?), opportunity (does the physical and social environment support them to take their medication?), and motivation (do they have the automatic and reflective motivation to take a treatment?).

Evidence of reasons for non-initiation of treatment suggests this approach could also apply to early nonadherence. For example, 'Motivational' factors linked to non-initiation of medication include the perception that an illness will have few consequences on the individual's life. In addition, the belief that disease can be controlled using lifestyle changes rather than medication can lead to non-adherence (Kalungwe et al., 2022; Marmarà et al., 2017). Doubts about whether treatment is needed or whether it is effective (Lee et al., 2018), and concerns about medication's negative effects also influence adherence (McHorney et al., 2007). Psychological 'Capability' such as the ability to remember information about a prescribed treatment has been associated with early treatment adherence for people with inflammatory bowel disease (Linn et al., 2013). Also, 'Opportunity' factors such as social support (Lemstra et al., 2018) and higher medication co-payments (Zeber et al., 2013) have been associated with non-initiation. Many of these factors are known to be modifiable, and can be addressed (Nieuwlaat et al., 2014).

We know that support given at the point of prescription can impact on subsequent adherence. For example, a lack of shared decision-making and information gathering by prescribers, may mean patients are prescribed medication that is inappropriate for their condition or preferences (Moudallel et al., 2021). Patients who do not have the opportunity to articulate that they disagree with a decision may be prescribed a treatment they have already decided not to take. One US study found patients who were dissatisfied with the care their physician expressed for them were approximately twice as likely to delay or not initiate medication (Wroth & Pathman, 2006). This suggests that interactions between the patient and their prescriber offer an opportunity to address barriers to adherence and prevent primary nonadherence. Barriers and facilitators to early adherence are both modifiable and present in the routine interactions many patients have with the healthcare professionals at the point of initiating a new treatment, suggesting that changes to the support at this point may be able to prevent nonadherence.

(3) Early adherence experiences are a foundation for later adherence habits, beliefs and symptom expectations.

The period immediately after treatment initiation may be when medication habits and beliefs develop, creating a foundation for future adherence behaviour. It has been hypothesised that, over time, adherence to medication may become more habitual i.e., more automatically triggered by environmental cues and so requiring less cognitive resource (Phillips et al., 2013; Phillips et al., 2016). Others have hypothesised that during initiation there is a need to form goals relating to medication-taking and for resources such as social support to be utilised to support achievement of the goal, whereas during implementation, goals may continue to influence adherence but become more implicit (Bosworth et al., 2018).

This early period may also be a time when patients are more attentive to the effects of their medication (e.g., effects on bodily sensations), meaning that medication representations are elaborated and refined. The Common-Sense or Self-Regulatory Model (Hagger & Orbell, 2022; Leventhal et al., 2016), characterises medication-taking as a 'coping strategy' used to reduce a threat to health. Thus, when a treatment is initiated a cascade of dynamic cognitive and emotional responses occur leading to future behaviours (e.g., stopping treatment, information-seeking). For example, a patient with polymyalgia may experience a 'health threat' e.g., severe muscle pain that triggers cognitions about illness ('I have polymyalgia which will get worse unless it is treated with prednisolone; Weinman et al., 1996) and negative emotions (e.g., fear, sadness). Within the model, the patient will then evaluate whether medication-taking has reduced the initial threat ('my pain has gone') or the cognitive or emotional sequelae (e.g., 'my polymyalgia is not getting worse', reducing anxiety). During the first weeks after starting a treatment, patients may 'experiment' with their new treatment (e.g., skip a dose to test whether it reduces the effects, Phillips et al., 2013), refining beliefs about medication-taking and influencing subsequent adherence.

At initiation, many medications may have the highest burden of adverse effects and the smallest benefits, particularly if the medication prevents future illness rather than current symptoms, or if time is needed accumulate therapeutic levels of a drug with a long half-life (Tozer & Rowland, 2006). A discrepancy between patients' hopes for a new medication and their experience may peak at the point when people start taking treatment. It has been shown that patients miss or stop taking new medication perceived as negatively affecting their health through side effects (McHorney et al., 2007), or as not reducing symptoms or enabling them to undertake activities they value (Emad et al., 2022). This is particularly pertinent for preventative treatments e.g., antihypertensives, where the patient may experience adverse effects but often no symptom reduction from the treatment (Wilhelm et al., 2018).

It is also likely there is a vicious cycle between pre-existing perceptions of treatment and treatment experiences, with beliefs affecting the interpretation of bodily changes occurring at the point of treatment initiation in ways that may reinforce negative perceptions. For example, evidence from rheumatoid arthritis patients (Nestoriuc et al., 2010) suggests that patients who are more concerned about potential adverse effects are more likely to report adverse effects upon starting a new medication. This suggests that 'placebo' and 'nocebo' like mechanisms such as expectation and conditioning may be important in understanding initial experiences of treatment. Using placebo experiments and analogue studies Heller et al. found that when healthy participants have more concerns about a placebo medication they may notice more bodily sensations, label these symptoms as side effects more frequently, and recall a larger number of symptoms as potential side effects (Heller et al., 2017, 2022), whereas students 'prescribed' a placebo reported more psychological and physical benefits where they had greater expectation of benefit (El Brihi et al., 2019). Thus, early intervention to prevent nonadherence may stop the formation of habits, beliefs and perceptions about treatment becoming entrenched and leading to later nonadherence.

In summary, the period around initiating medication is potentially a critical period for the development and maintenance of adherence. Many of the factors that influence adherence can be modified, and patients are often in contact with healthcare professionals and systems at this time, providing a potential opportunity to prevent nonadherence.

What opportunities and challenges are there for prevention of nonadherence?

(1) Could we use insights from pre-existing comorbidity, self-management behaviours, and nonadherence patterns to bolster nonadherence prevention?

The start of taking a new medication may happen alongside many health behaviours required to self-manage a long-term health condition. A patient diagnosed with diabetes may receive advice about diet, physical activity, blood sugar monitoring, mental health, smoking cessation, and foot care as part of the consultation at which medication is also considered. This adds complexity; patients and healthcare professionals can find it overwhelming and impractical to discuss multiple behaviours at once (Alageel et al., 2018). Post-prescription, a range of factors may disrupt initial adherence patterns. For example, receiving a new diagnosis, experiencing symptom exacerbations or reductions, or prescription of additional medications. Behaviours other than medication adherence may be prioritised or even undertaken to avoid the need for medication e.g., eating more healthily to avoid the need for antidiabetic medication (Forestier et al., 2020). Likewise, barriers and strategies for self-managing other conditions or medication may translate to a new medication or new diagnosis; past nonadherence is a strong predictor of future nonadherence (Franklin et al., 2018). Few interventions have utilised this information to prevent nonadherence.

Some adherence interventions exist to support adherence alongside treatment for another condition. Safren and colleagues developed interventions to simultaneously increase adherence to HIV medications and treat depression (Safren et al., 2014, 2021), reasoning that patients are more able to engage in discussions about self-care when depression has been addressed. Others have applied the same intervention strategy to address nonadherence to multiple medications e.g., (Kassavou et al., 2020). However, some interventions which have targeted multiple conditions and health behaviours have had small or nonsignificant effects (Cross et al., 2020; Griffin et al., 2014). In some cases, comorbid conditions may be cyclical or fluctuating meaning that initiation of a new treatment may co-occur with changes to prescribed treatments, symptoms, healthcare, and priorities associated with changes in comorbid conditions. These patterns may be complex; comorbidities may be associated with an increased likelihood of refusing some treatments (e.g., Amini et al., 2020), however, receiving healthcare support for one condition may facilitate adherence to another in other situations. For example, one US study found patients with schizophrenia had higher adherence to statins than matched patients without schizophrenia, with this effect becoming nonsignificant if emergency care visits were included in the model, leading the authors to suggest that perhaps patients with schizophrenia who had sought emergency care had incidentally received greater support with their statin adherence (Owen-Smith et al., 2016). We need better understanding of how comorbidities may affect early adherence and whether there is potential to better support early adherence in the context of other treatments and conditions, for example by using understanding and resources for one condition/medication to prepare patients to start other treatments.

(2) Could we use population or system-level interventions to address predictors of early non-adherence that are present even before prescription?

We know that nonadherence in the period after a new prescription is influenced by factors that are present and identifiable at the point of initiating a new treatment. For example, lack of social support (Brook et al., 2006; Lemstra et al., 2018), low trust in the healthcare provider (Bauer et al., 2014), and doubts about pharmaceuticals in general (Thorneloe et al., 2019) have been associated with poorer adherence in the period immediately after prescription of a new treatment.

Adherence is a learnt behaviour, and even though patients may learn to adhere to a new prescription they will be building on previous direct or vicarious experiences of medication (e.g., seeing another patient benefit from a medication) (Johnson et al., 2006). More broadly, their general

approach to relationships (e.g., attachment style) and past healthcare experiences (Chitkara et al., 2008) may influence engagement with healthcare (Bennett et al., 2011). Past experiences influence representations of illness, which in turn influence adherence (Leventhal et al., 2016). Perceptions of medication effects may also be influenced by neurobiological changes which increase/reduce sensitivity to somatic sensations (which might include adverse effects, symptoms of illness, and treatment benefits, Tracey, 2010). Some past experiences e.g., of trauma may also be associated with factors such as unstable housing and unemployment which impact on adherence (Glynn et al., 2021). Prevention of nonadherence may be possible by identifying and addressing these pre-existing factors, rather than focusing simply on medication focused risks and benefits. Although these factors may be challenging to address at an individual or interpersonal level (e.g., between the prescriber and patient), there may need to be recognition that broader support services and policies at a system or population level (e.g., relating to housing, employment and mental health support) have a role to play in preventing nonadherence to medication. This approach is widely recognised for other health behaviours (e.g., diet, physical activity, tobacco use) but for medication adherence it is less frequently considered.

(3) Could we use existing knowledge of how medication initiation can occur at a point when diagnosis can disrupt patients' meanings, identity, and values to develop psychologically informed support?

Interventions to prevent nonadherence will be part of a raft of healthcare interventions and healthcare challenges that the patient and their healthcare professionals are navigating. Prescription of a new medication often co-occurs with diagnosis and discussion of other concerns (Stuart et al., 2019). We know that the risk of nonadherence increases for patients with multiple comorbid conditions and complex medication regimens (Vik et al., 2006). Patients may be at a point of transition where they are experiencing disruption to their identity, roles, and hopes for the future. For example, a cancer diagnosis may disrupt someone's previous 'healthy' identity (Mathieson & Stam, 1995). Medication itself may exacerbate this with some patients feeling overwhelmed by new information and treatments (Wong et al., 2019). Diagnosis can trigger emotional responses including anxiety (Butler et al., 2019) or grief (Mgbako et al., 2020).

While for some, medications may represent instrumental coping mechanisms for reducing a health threat (Leventhal et al., 2016), for others medication could function as a tangible reminder that one is facing a health threat, and bring additional challenging thoughts and feelings that could become barriers to adherence (Graham et al., 2022). Where challenging emotions and thoughts accompany medication-taking behaviour, the extent to which an individual avoids uncomfortable medication-related experiences could then impact on adherence. Further, nonadherence could also result from a difficulty linking treatment consequences to one's overarching goals and values. For example, an individual may not see how medication protects valued activities or relationships outside of the condition being managed, or indeed may see that medication consequences interferes with these activities. There is preliminary evidence of an association between the extent of an individual's connection with over-arching values and adherence to treatments (Fernandes-James et al., 2019). Thus, to prevent nonadherence, we may need flexible provision of support, to consider the role of aversive emotions and treatment effects, and to explore how medication links to the patients' experiences, values, and goals. Graham et al. (2022) argued that exploring how medication taking may be a step towards or away from patients' overarching values may be a useful supplement to information about direct treatment benefits and risks. The links between values and adherence can also be seen in the way patients and healthcare professionals frame adherence in moral terms, such as who is deserving of scarce healthcare resources and whether nonadherence is the responsibility of patients or healthcare professionals (Murdoch et al., 2013). Interventions to enhance the link between adherence and patient values are under trial with women prescribed hormone therapies following breast cancer (Arch et al., 2022; Green et al., 2022).

See Figure 1 for a summary of factors involved in early treatment adherence.

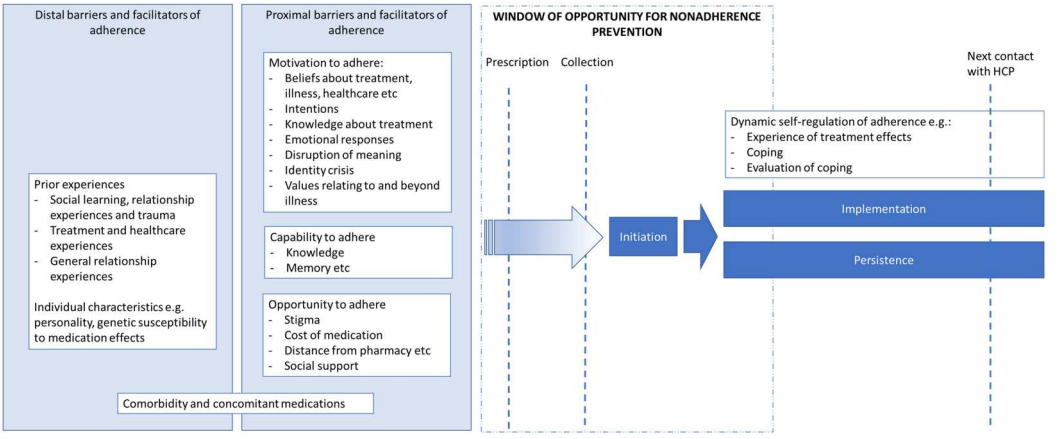

Figure 1. Summary of factors involved in early treatment adherence.

From an understanding of early nonadherence towards a framework to inform development of interventions to prevent nonadherence

There is broad agreement of a need for a wider range of more effective adherence interventions that can be implemented in practice. Numerous reviews of adherence intervention trials across different conditions, medications, and settings (Conn & Ruppar, 2017; Nieuwlaat et al., 2014; Verloo et al., 2017) have identified interventions that can reduce nonadherence. But, most have only small-moderate effects, including those targeted at patients initiating treatment. For example, a small trial of electronic monitoring and motivational interviewing for patients with rheumatoid arthritis initiating a disease modifying anti-rheumatic drug resulted in a 5% increase in adherence over the following year (Hebing et al., 2022). For adherence interventions there is a need not just for efficacy, but also for interventions to be cost-effective, scalable, and implementable (Hogervorst et al., 2022), given that many patients are adherent and that many medications only benefit some of the patients who take them. For example, for a medication with a number-needed-to-treat of 10 and a typical adherence rate of 50%, only one person in 20 would be expected to benefit from a highly effective adherence intervention. Tailoring to both patients and the healthcare system to focus intensive resources on high-risk patients is particularly important when considering interventions to prevent nonadherence.

A suggested framework for developing nonadherence prevention interventions

We would propose that there are four broad categories of intervention which may be useful for preventing nonadherence and which further research could investigate: Population level interventions delivered to patients and healthy individuals; Interventions at the point of prescription targeting all patients receiving a particular medication; Low intensity interventions for people at risk of nonadherence deliverable by the direct healthcare team; High intensity interventions for people at risk of nonadherence that require additional resource and team members. There is a need for development and testing of nonadherence prevention interventions across all categories, and as well as a need for screening tools to identify participants at need of high intensity interventions. See Table 1 for examples and Figure 2.

Preventing nonadherence at the population level

As highlighted above, many of the determinants of nonadherence precede prescription for a new medication. This includes both distal factors e.g., experiences with healthcare providers and

Table 1. Examples of different nonadherence prevention interventions in a stepped-care approach.

Intervention type	Example barrier(s) addressed	Potential intervention
Population level	Difficulty accessing medication due to costs	Government level policies to reduce costs for individual patients
Optimised prescribing consultation	Lack of knowledge of how to take medication (e.g., injectable, specific time points etc.)	Ensuring effective training in how to administer medication before treatment initiation
Low intensity	Difficulty managing multiple medications; uncertainty about benefit of new treatment	Mobile phone app allowing patient to set reminders and access additional information about treatment
High intensity	Identity and meaning crisis triggered by new diagnosis	Individual support session where patient can explore the meaning of the new treatment for them and link to values beyond illness

systems, and proximal factors such as perceived stigma for taking a particular medication. Potentially, interventions delivered outside of costly, time-pressured healthcare settings may be able to prevent or reduce nonadherence at a population level. For example, by seeking to reduce population-level stigma around medication use, increase trust in medication safety, prompt adherence in healthcare settings, increase health literacy via educational systems, or improve physical access to medications and medication advice. Unlike other health behaviours such as diet where a 'whole systems approach' is increasingly used (Bagnall et al., 2019), the importance of environmental level factors such as the 'obesogenic environment' are in common use (Townshend & Lake, 2017). There has been relatively little focus on environmental and systemic factors that increase nonadherence. With perhaps the exception of research on the effects of policies on paying for medication (e.g., Maciejewski et al., 2010), medication adherence is typically framed as a personal choice within the context of a conversation with a healthcare practitioner, with interventions targeting individuals (Nieuwlaat et al., 2014). Societal and cultural factors may offer new avenues for preventing nonadherence.

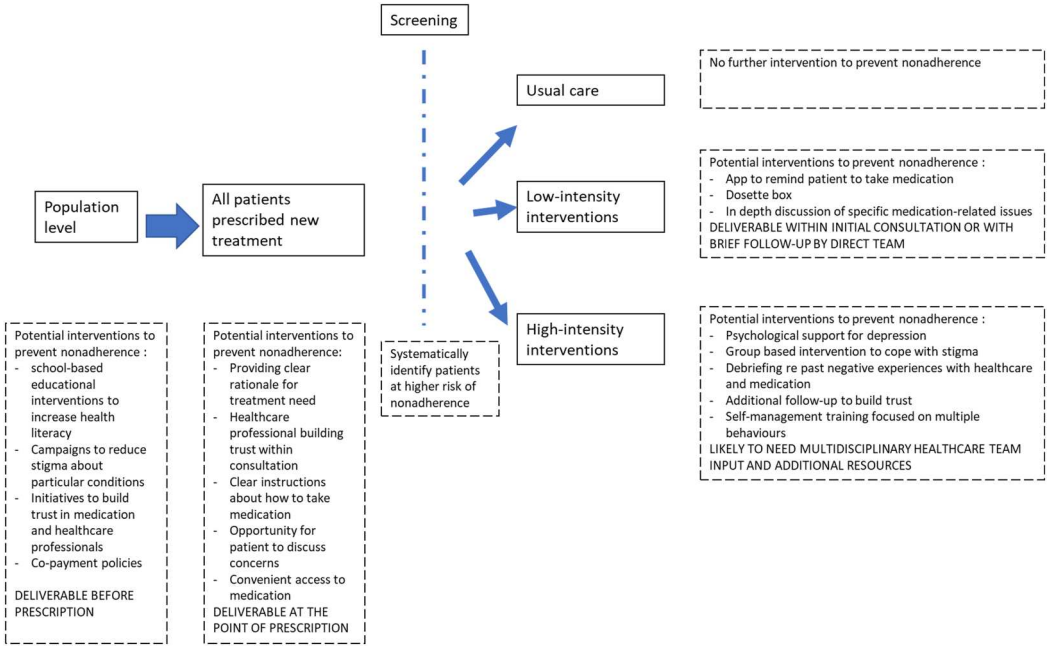

Figure 2. Diagram of potential stepped-care approach to preventing adherence.

Optimising the initial prescription consultation

A further relatively new avenue for addressing nonadherence may be reviewing the initial prescription process and identify changes that might optimise this so that this process does not increase risk of nonadherence. Rather, it could provide an 'additional' intervention to patients. For example, all patients in the EU and UK currently receive information about the potential adverse effects of a new medication, but not all patients receive information about how the medication works which might address doubts about whether a treatment is appropriate to address their condition. Likewise, consultation behaviours which encourage trust in healthcare providers such as expressing empathy, shared decision-making, demonstrating expertise and knowledge of the patient and medication should be promoted.

Low intensity interventions

Many of the determinants of early nonadherence described above may require more resources to address than are routinely available. For example, someone who doubts that they have received the correct diagnosis because of previous incorrect diagnoses and therefore is unsure about a treatment may require an additional brief consultation to discuss these doubts (e.g. Elliot et al., 2016). Or someone who does not know how to use a new inhaled medication may require an additional demonstration. Depending on the setting there may be a need for additional support to address these brief queries.

High intensity interventions

Given the complexity of factors involved in medication nonadherence many patients will need additional support that is unfeasible or unacceptable to deliver to all individuals. For example, group-based interventions to increase social support may place a high burden on patients and healthcare practitioners if delivered to everyone. Potentially, there might also be many challenges that are unlikely to be addressed using low-intensity approaches – for example, someone whose medication impacts their ability to undertake their work, someone experiencing significant distress about a new diagnosis, or someone who is receiving a new medication at the same time as being told to modify diet and other behaviours. Some barriers may also be linked to broader cultural factors (such as religious beliefs about treatment, or stigma) or tied to other conditions such as depression. Addressing barriers which are interwoven with many elements of patients' lives or other elements of their health is likely need more personalised or high-intensity support. We would argue that it is also not correct to lay all the responsibility for addressing adherence with individual prescribers and that adherence needs to be addressed systematically across multidisciplinary healthcare teams, healthcare systems and other services. These high intensity interventions may at times be most appropriately delivered by professionals with specialist expertise beyond medication/disease management, for example health or clinical psychologists, social care workers or family workers. As there are such a range of potential intervention techniques, it is unlikely to be realistic to expect any individual healthcare professional to have the requisite knowledge and skills to deliver all potential interventions.

Screening tools and personalisation

The consequence of a need for multiple interventions is that tools or approaches will be required to identify the appropriate type and level of intervention for a patient who is non-adherent. There are currently no evidence-based tools that screen for risk factors for early nonadherence, and no tools which map risk factors to potential interventions. Approaches such as the behaviour change wheel (Michie et al., 2011) or intervention mapping (Green et al., 2022) might be useful for

mapping links between potential barriers and facilitators and potential interventions, but these have not been applied to preventing nonadherence.

Recommendations for research and practice

There is little research or existing practice focused particularly on prevention of nonadherence. Drawing on the framework above, there is a need to improve knowledge of what factors predict early nonadherence to a new treatment, both through longitudinal research exploring predictors of primary nonadherence and through systematic reviews synthesising evidence about predictors of early nonadherence and identifying gaps in knowledge. 'Big data' studies, using databases of routinely collected healthcare data may be able to test some predictors, for example, associations between prior nonadherence to other medications or prior experience of adverse effects, and subsequent early nonadherence to treatment. For other elements discussed in this framework, qualitative work with patients who have early nonadherence to treatment may be useful to explore processes around identity or values. Notably, there are a dearth of intervention studies, and a need for systematic synthesis of those studies that have already been conducted. Further development of theories to explain the key factors that influence early adherence and processes of change for these factors may also help inform interventions. Although we believe that understanding how interventions can be implemented cost-effectively within existing healthcare contexts is essential, there is little evidence on healthcare system factors that might affect the delivery of interventions to prevent nonadherence. For example, we do not know how much time is required or skills needed to deliver different interventions, the views of healthcare professionals on the acceptability of different interventions, or the most effective ways of training healthcare teams to deliver interventions. Finally, there are no screening tools to stratify patients into different risks of nonadherence. Potentially, it may be possible to screen for some of the factors explored above, (e.g., beliefs, prior experiences, extent to which the patient links the consequences of medication with their values, emotional responses, and environmental factors) to identify patients needing additional support. Future work could identify the appropriateness and utility of such an approach.

Conclusion

Preventing nonadherence before it becomes established might be achievable and could arguably result in greater benefit for patients, healthcare professionals, and healthcare systems. Although there are many insights into how, why, and when it might be possible to prevent nonadherence from existing practice and research on nonadherence, there is a dearth of evidence explicitly addressing these topics. We need a better understanding of the determinants of early nonadherence; the development, testing, and implementation of effective tools to identify risk of nonadherence; and appropriate theory driven interventions to reduce risk. In this paper, we have presented a framework for considering nonadherence prevention that we hope will highlight key opportunities and questions in this field.

Acknowledgements

All authors contributed to the conceptualisation and editing of this manuscript, SC wrote the initial draft. JW, TvL and LF acquired funding for the meetings from which this manuscript arose.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research was funded by a Circle U European University Alliance Seed Funding grant co-funded by the Erasmus+ programme of the European Union.

ORCID

Sarah Chapman http://orcid.org/0000-0002-7612-1605
Lisbeth Frostholm http://orcid.org/0000-0002-9683-7416
Trudie Chalder http://orcid.org/0000-0003-0775-1045
Christopher Graham http://orcid.org/0000-0001-8456-9154
Annette de Thurah http://orcid.org/0000-0003-0103-4328
Tess van Leeuwen http://orcid.org/0009-0006-4707-1369
Tina Carstensen http://orcid.org/0000-0001-5086-4331
Ohn Weinman http://orcid.org/0000-0002-6786-0166

References

Alageel, S., Gulliford, M. C., McDermott, L., & Wright, A. J. (2018). Implementing multiple health behaviour change interventions for cardiovascular risk reduction in primary care: A qualitative study. *BMC Family Practice*, *19*(1), 171. https://doi.org/10.1186/s12875-018-0860-0

Alhazami, M., Pontinha, V. M., Patterson, J. A., & Holdford, D. A. (2020). Medication adherence trajectories: A systematic literature review. *Journal of Managed Care & Specialty Pharmacy*, *26*(9), 1138–1152. https://doi.org/10.18553/jmcp.2020.26.9.1138

Amini, A., Verma, V., Li, R., et al. (2020). Factors predicting patient refusal of head and neck cancer therapy. *Head & Neck*, *42*(1), 33–42. https://doi.org/10.1002/hed.25966

Arch, J. J., Crespi, C. M., Levin, M. E., Genung, S. R., Nealis, M., Mitchell, J. L., & Stanton, A. L. (2022). Randomized controlled pilot trial of a low-touch remotely-delivered values intervention to promote adherence to adjuvant endocrine therapy among breast cancer survivors. *Annals of Behavioral Medicine*, *56*(8), 856–871. https://doi.org/10.1093/abm/kaab118

Bagnall, A.-M., Radley, D., Jones, R., Gately, P., Nobles, J., Van Dijk, M., & Sahota, P. (2019). Whole systems approaches to obesity and other complex public health challenges: A systematic review. *BMC Public Health*, *19*(1), 8. https://doi.org/10.1186/s12889-018-6274-z

Bauer, A. M., Parker, M. M., Schillinger, D., Katon, W., Adler, N., Adams, A. S., & Karter, A. J. (2014). Associations between antidepressant adherence and shared decision-making, patient-provider trust, and communication among adults with diabetes: Diabetes study of Northern California (DISTANCE). *Journal of General Internal Medicine*, *29*(8), 1139–1147. https://doi.org/10.1007/s11606-014-2845-6

Bennett, J. K., Fuertes, J. N., Keitel, M., & Phillips, R. (2011). The role of patient attachment and working alliance on patient adherence, satisfaction, and health-related quality of life in lupus treatment. *Patient Education and Counseling*, *85*(1), 53–59. https://doi.org/10.1016/j.pec.2010.08.005

Bosworth, H. B., Blalock, D. V., Hoyle, R. H., Czajkowski, S. M., & Voils, C. I. (2018). The role of psychological science in efforts to improve cardiovascular medication adherence. *American Psychologist*, *73*(8), 968. https://doi.org/10.1037/amp0000316

Brook, O. H., van Hout, H. P., Stalman, W. A., & de Haan, M. (2006). Nontricyclic antidepressants: Predictors of nonadherence. *Journal of Clinical Psychopharmacology*, *26*(6), 643–647. https://doi.org/10.1097/01.jcp.0000246217.34024.53

Butler, E., Thomas, R., Carolan, A., Silber, E., & Chalder, T. (2019). It's the unknown – Understanding anxiety: From the perspective of people with multiple sclerosis. *Psychology & Health*, *34*(3), 368–383. https://doi.org/10.1080/08870446.2018.1541989

Carmody, J. K., Plevinsky, J., Peugh, J. L., Denson, L. A., Hyams, J. S., Lobato, D., & Hommel, K. A. (2019). Longitudinal nonadherence predicts treatment escalation in paediatric ulcerative colitis. *Alimentary Pharmacology & Therapeutics*, *50*(8), 911–918. https://doi.org/10.1111/apt.15445

Cheen, M. H. H., Tan, Y. Z., Oh, L. F., Wee, H. L., & Thumboo, J. (2019). Prevalence of and factors associated with primary medication non-adherence in chronic disease: A systematic review and meta-analysis. *International journal of clinical practice*, *73*(6), e13350. https://doi.org/10.1111/ijcp.13350

Chitkara, D. K., van Tilburg, M. A., Blois-Martin, N., & Whitehead, W. E. (2008). Early life risk factors that contribute to irritable bowel syndrome in adults: A systematic review. *The American Journal of Gastroenterology*, *103*(3), 765–774. https://doi.org/10.1111/j.1572-0241.2007.01722.x

Colombo, J. (1982). The critical period concept: Research, methodology, and theoretical issues. *Psychological Bulletin*, *91*(2), 260–275. https://doi.org/10.1037/0033-2909.91.2.260

Conn, V. S., & Ruppar, T. M. (2017). Medication adherence outcomes of 771 intervention trials: Systematic review and meta-analysis. *Preventive Medicine*, *99*, 269–276. https://doi.org/10.1016/j.ypmed.2017.03.008

Cross, A. J., Elliott, R. A., Petrie, K., Kuruvilla, L., & George, J. (2020). Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications. *Cochrane Database of Systematic Reviews*, *5*, CD012419. https://doi.org/10.1002/14651858.CD012419.pub2

Cutler, R. L., Fernandez-Llimos, F., Frommer, M., Benrimoj, C., & Garcia-Cardenas, V. (2018). Economic impact of medication non-adherence by disease groups: A systematic review. *BMJ Open*, *8*(1), e016982. https://doi.org/10.1136/bmjopen-2017-016982

Dima, A. L., Hernandez, G., Cunillera, O., Ferrer, M., & de Bruin, M. (2015). Asthma inhaler adherence determinants in adults: Systematic review of observational data. *European Respiratory Journal*, *45*(4), 994–1018. https://doi.org/10.1183/09031936.00172114

El Brihi, J., Horne, R., & Faasse, K. (2019). Prescribing placebos: An experimental examination of the role of dose, expectancies, and adherence in open-label placebo effects. *Annals of Behavioral Medicine*, *53*(1), 16–28. https://doi.org/10.1093/abm/kay011

Elliott, R. A., Boyd, M. J., Salema, N.-E., Davies, J., Barber, N., Mehta, R. L., & Gkountouras, G. (2016). Supporting adherence for people starting a new medication for a long-term condition through community pharmacies: A pragmatic randomised controlled trial of the New Medicine Service. *BMJ Quality & Safety*, *25*(10), 747–758. https://doi.org/10.1136/bmjqs-2015-004400

Emad, Y., Dalbeth, N., Weinman, J., Chalder, T., & Petrie, K. J. (2022). Why do patients with gout not take allopurinol? *The Journal of Rheumatology*, *49*(6), 622–626. https://doi.org/10.3899/jrheum.210950

Faught, E., Duh, M. S., Weiner, J. R., Guerin, A., & Cunnington, M. C. (2008). Nonadherence to antiepileptic drugs and increased mortality: Findings from the RANSOM study. *Neurology*, *71*(20), 1572–1578. https://doi.org/10.1212/01.wnl.0000319693.10338.b9

Fernandes-James, C., Graham, C. D., Batterham, A. M., & Harrison, S. L. (2019). Association of psychological flexibility with engagement in pulmonary rehabilitation following an acute exacerbation of chronic obstructive pulmonary disease. *Chronic Respiratory Disease*, *16*. https://doi.org/10.1177/1479973119880893

Fitzgerald, A. A., Powers, J. D., Ho, P. M., Maddox, T. M., Peterson, P. N., Allen, L. A., & Havranek, E. P. (2011). Impact of medication nonadherence on hospitalizations and mortality in heart failure. *Journal of Cardiac Failure*, *17*(8), 664–669. https://doi.org/10.1016/j.cardfail.2011.04.011

Forestier, C., Sarrazin, P., Sniehotta, F., Allenet, B., Heuzé, J. P., Gauchet, A., & Chalabaev, A. (2020). Do compensatory health beliefs predict behavioural intention in a multiple health behaviour change context? Evidence in individuals with cardiovascular diseases? *Psychology, Health & Medicine*, *25*(5), 593–600. https://doi.org/10.1080/13548506.2019.1653476

Franklin, J. M., Gopalakrishnan, C., Krumme, A. A., Singh, K., Rogers, J. R., Kimura, J., & Choudhry, N. K. (2018). The relative benefits of claims and electronic health record data for predicting medication adherence trajectory. *American Heart Journal*, *197*, 153–162. https://doi.org/10.1016/j.ahj.2017.09.019

Gellad, W. F., Thorpe, C. T., Steiner, J. F., & Voils, C. I. (2017). The myths of medication adherence. *Pharmacoepidemiology and Drug Safety*, *26*(12), 1437–1441. https://doi.org/10.1002/pds.4334

Glass, T. R., Sterne, J. A., Schneider, M.-P., De Geest, S., Nicca, D., Furrer, H., & Rickenbach, M. (2015). Self-reported non-adherence to antiretroviral therapy as a predictor of viral failure and mortality. *Aids (London, England)*, *29*(16), 2195–2200. https://doi.org/10.1097/QAD.0000000000000782

Glynn, T. R., Mendez, N. A., Jones, D. L., Dale, S. K., Carrico, A. W., Feaster, D. J., & Safren, S. A. (2021). Trauma exposure, PTSD, and suboptimal HIV medication adherence among marginalized individuals connected to public HIV care in Miami. *Journal of Behavioral Medicine*, *44*(2), 147–158. https://doi.org/10.1007/s10865-020-00191-w

Graham, C. D., McCracken, L. M., Harrison, A., Walburn, J., & Weinman, J. (2022). Outlining an acceptance and commitment therapy approach to treatment non-adherence. *British Journal of Health Psychology*, *27*(1), 1–12. https://doi.org/10.1111/bjhp.12579

Green, S. M., French, D. P., Graham, C. D., Hall, L. H., Rousseau, N., Foy, R., & Gardner, B. (2022). Supporting adjuvant endocrine therapy adherence in women with breast cancer: the development of a complex behavioural intervention using intervention mapping guided by the multiphase optimisation strategy. *BMC Health Services Research*, *22*(1), 1081. https://doi.org/10.1186/s12913-022-08243-4

Griffin, S. J., Simmons, R. K., Prevost, A. T., Williams, K. M., Hardeman, W., Sutton, S., Brage, S., Ekelund, U., Parker, R. A., Wareham, N. J., Kinmonth, A. L., & on behalf of the ADDITION-Plus study team. (2014). Multiple behaviour change intervention and outcomes in recently diagnosed type 2 diabetes: The ADDITION-Plus randomised controlled trial. *Diabetologia*, *57*(7), 1308–1319. https://doi.org/10.1007/s00125-014-3236-6

Hagger, M. S., & Orbell, S. (2022). The common-sense model of illness self-regulation: A conceptual review and proposed extended model. *Health Psychology Review*, *16*(3), 347–377. https://doi.org/10.1080/17437199.2021.1878050

Hebing, R. C., Aksu, I., Twisk, J. W., Bos, W., Van den Bemt, B., & Nurmohamed, M. T. (2022). Effectiveness of electronic drug monitoring feedback to increase adherence in patients with RA initiating a biological DMARD: A randomised clinical trial. *RMD Open*, *8*(1), e001712. https://doi.org/10.1136/rmdopen-2021-001712

Heller, M. K., Chapman, S. C., & Horne, R. (2017). No blank slates: Pre-existing schemas about pharmaceuticals predict memory for side effects. *Psychology & Health*, *32*(4), 402–421. https://doi.org/10.1080/08870446.2016.1273355

Heller, M. K., Chapman, S. C., & Horne, R. (2022). Beliefs about medicines predict side-effects of placebo modafinil. *Annals of Behavioral Medicine*, *56*(10), 989–1001. https://doi.org/10.1093/abm/kaab112

Ho, P. M., Rumsfeld, J. S., Masoudi, F. A., McClure, D. L., Plomondon, M. E., Steiner, J. F., & Magid, D. J. (2006). Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Archives of internal medicine*, *166*(17), 1836–1841. https://doi.org/10.1001/archinte.166.17.1836

Hogervorst, S., Vervloet, M., Adriaanse, M. C., Zamboni, K., Zullig, L. L., Schoonmade, L., & van Dijk, L. (2022). Scalability of effective adherence interventions for patients using cardiovascular disease medication: A realist synthesis-inspired systematic review. *British Journal of Clinical Pharmacology*, *89*(7), 1996–2019. https://doi.org/10.1111/bcp.15418

Jackson, C., Eliasson, ÂL, Barber, N., & Weinman, J. (2014). Applying COM-B to medication adherence: A suggested framework for research and interventions. *European Health Psychologist*, *16*(1), 7–17.

Johnson, M. O., Chesney, M. A., Goldstein, R. B., Remien, R. H., Catz, S., Gore-Felton, C., Charlebois, E., Morin, S. F., & Healthy Living Project Team. (2006). Positive provider interactions, adherence self-efficacy, and adherence to antiretroviral medications among HIV-infected adults: A mediation model. *AIDS Patient Care and STDs*, *20*(4), 258–268. https://doi.org/10.1089/apc.2006.20.258

Kalungwe, M., Mbalinda, S. N., Karonga, T., Simwanza, N. R., Mumba Mtambo, C. M., & Nyashanu, M. (2022). Exploring barriers to antiretroviral therapy adherence among pregnant women: A scoping literature review. *International Journal of Gynecology & Obstetrics*, *159*(2), 343–350. https://doi.org/10.1002/ijgo.14130

Kassavou, A., Mirzaei, V., Brimicombe, J., Edwards, S., Massou, E., Prevost, A. T., & Sutton, S. (2020). A highly tailored text and voice messaging intervention to improve medication adherence in patients with either or both hypertension and type 2 diabetes in a UK primary care setting: Feasibility randomized controlled trial of clinical effectiveness. *Journal of Medical Internet Research*, *22*(5), e16629. https://doi.org/10.2196/16629

Lee, S.-Q., Raamkumar, A. S., Li, J., Cao, Y., Witedwittayanusat, K., Chen, L., & Theng, Y.-L. (2018). Reasons for primary medication nonadherence: A systematic review and meta-analysis. *Journal of Managed Care & Specialty Pharmacy*, *24*(8), 778–794. https://doi.org/10.18553/jmcp.2018.24.8.778

Lemstra, M., Nwankwo, C., Bird, Y., & Moraros, J. (2018). Primary nonadherence to chronic disease medications: A meta-analysis. *Patient Preference and Adherence*, *12*, 721–731. https://doi.org/10.2147/PPA.S161151

Leventhal, H., Phillips, L. A., & Burns, E. (2016). The Common-Sense Model of Self-Regulation (CSM): A dynamic framework for understanding illness self-management. *Journal of Behavioral Medicine*, *39*(6), 935–946. https://doi.org/10.1007/s10865-016-9782-2

Linn, A. J., van Dijk, L., Smit, E. G., Jansen, J., & van Weert, J. C. M. (2013). May you never forget what is worth remembering: The relation between recall of medical information and medication adherence in patients with inflammatory bowel disease. *Journal of Crohn's and Colitis*, *7*(11), e543–e550. https://doi.org/10.1016/j.crohns.2013.04.001

Maciejewski, M. L., Farley, J. F., Parker, J., & Wansink, D. (2010). Copayment reductions generate greater medication adherence in targeted patients. *Health Affairs*, *29*(11), 2002–2008. https://doi.org/10.1377/hlthaff.2010.0571

Marmarà, D., Marmarà, V., & Hubbard, G. (2017). Health beliefs, illness perceptions and determinants of breast screening uptake in Malta: A cross-sectional survey. *BMC Public Health*, *17*(1), 416. https://doi.org/10.1186/s12889-017-4324-6

Mathieson, C. M., & Stam, H. J. (1995). Reneotiating identity: Cancer narratives. *Sociology of Health & Illness*, *17*(3), 283–306. https://doi.org/10.1111/1467-9566.ep10933316

McHorney, C. A., Schousboe, J. T., Cline, R. R., & Weiss, T. W. (2007). The impact of osteoporosis medication beliefs and side-effect experiences on non-adherence to oral bisphosphonates. *Current Medical Research and Opinion*, *23*(12), 3137–3152. https://doi.org/10.1185/030079907X242890

Merks, P., Chełstowska, B., Religioni, U., Neumann-Podczaska, A., Krasiński, Z., Kobayashi, A., Plagens-Rotman, K., Drelih, E., Fehir-Sola, K., Fijałkowski, Ł., Baj, I., Vaillancourt, R., Wieczorowska-Tobis, K., Mastalerz-Migas, A., Koziol, M., Pinkas, J., Szymański, F. M., & Hering, D. (2024). Enhancing patient adherence to newly-prescribed medicine for chronic diseases: A comprehensive review and cost-effective approach to implementing the New Medicine Service in community pharmacies in Poland. *Medical Science Monitor*, *30*, e942923. https://doi.org/10.12659/MSM.942923

Mgbako, O., Benoit, E., Iyengar, N. S., Kuhner, C., Brinker, D., & Duncan, D. T. (2020). Like a ticking time bomb": The persistence of trauma in the HIV diagnosis experience among black men who have sex with men in New York City. *BMC Public Health*, *20*(1), 1247. https://doi.org/10.1186/s12889-020-09342-9

Michie, S., Van Stralen, M. M., & West, R. (2011). The behaviour change wheel: A new method for characterising and designing behaviour change interventions. *Implementation Science*, *6*(1), 1–12. https://doi.org/10.1186/1748-5908-6-1

Misdrahi, D., Tessier, A., Husky, M., Lange, A.-C., Vrijens, B., Llorca, P.-M., & Baylé, F. J. (2018). Evaluation of adherence patterns in schizophrenia using electronic monitoring (MEMS®): A six-month post-discharge prospective study. *Schizophrenia Research*, *193*, 114–118. https://doi.org/10.1016/j.schres.2017.06.026

Moudallel, S., van den Bemt, B. J. F., Zwikker, H., de Veer, A., Rydant, S., Dijk, L. v., & Steurbaut, S. (2021). Association of conflicting information from healthcare providers and poor shared decision making with suboptimal adherence in direct oral anticoagulant treatment: A cross-sectional study in patients with atrial fibrillation. *Patient Education and Counseling*, *104*(1), 155–162. https://doi.org/10.1016/j.pec.2020.06.016

Murdoch, J., Salter, C., Cross, J., Smith, J., & Poland, F. (2013). Resisting medications: Moral discourses and performances in illness narratives. *Sociology of Health & Illness*, *35*(3), 449–464. https://doi.org/10.1111/j.1467-9566.2012.01499.x

Nestoriuc, Y., Orav, E. J., Liang, M. H., Horne, R., & Barsky, A. J. (2010). Prediction of nonspecific side effects in rheumatoid arthritis patients by beliefs about medicines. *Arthritis Care & Research*, *62*(6), 791–799. https://doi.org/10.1002/acr.20160

Newman-Casey, P. A., Blachley, T., Lee, P. P., Heisler, M., Farris, K. B., & Stein, J. D. (2015). Patterns of glaucoma medication adherence over four years of follow-up. *Ophthalmology*, *122*(10), 2010–2021.

Nieuwlaat, R., Wilczynski, N., Navarro, T., Hobson, N., Jeffery, R., Keepanasseril, A., & Jack, S. (2014). Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews*, *CD000011*, 11.

Owen-Smith, A., Stewart, C., Green, C., Ahmadani, B. K., Waitzfelder, B. E., Rossom, R., Copeland, L. A., & Simon, G. E. (2016). Adherence to common cardiovascular medications in patients with schizophrenia vs. patients without psychiatric illness. *General Hospital Psychiatry*, *38*, 9–14. https://doi.org/10.1016/j.genhosppsych.2015.07.010

Phillips, L. A., Cohen, J., Burns, E., Abrams, J., & Renninger, S. (2016). Self-management of chronic illness: The role of 'habit' versus reflective factors in exercise and medication adherence. *Journal of Behavioral Medicine*, *39*(6), 1076–1091. https://doi.org/10.1007/s10865-016-9732-z

Phillips, L. A., Leventhal, H., & Leventhal, E. A. (2013). Assessing theoretical predictors of long-term medication adherence: Patients' treatment-related beliefs, experiential feedback and habit development. *Psychology & Health*, *28*(10), 1135–1151. https://doi.org/10.1080/08870446.2013.793798

Quirk, A., Chaplin, R., Hamilton, S., Lelliott, P., & Seale, C. (2013). Communication about adherence to long-term antipsychotic prescribing: An observational study of psychiatric practice. *Social Psychiatry and Psychiatric Epidemiology*, *48*(4), 639–647. https://doi.org/10.1007/s00127-012-0581-y

Sabaté, E. (2003). *Adherence to long-term therapies: Evidence for action*. World Health Organization.

Safren, S. A., Gonzalez, J. S., Wexler, D. J., Psaros, C., Delahanty, L. M., Blashill, A. J., & Cagliero, E. (2014). A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in patients with uncontrolled type 2 diabetes. *Diabetes Care*, *37*(3), 625–633. https://doi.org/10.2337/dc13-0816

Safren, S. A., O'Cleirigh, C., Andersen, L. S., Magidson, J. F., Lee, J. S., Bainter, S. A., & Joska, J. A. (2021). Treating depression and improving adherence in HIV care with task-shared cognitive behavioural therapy in Khayelitsha, South Africa: A randomized controlled trial. *Journal of the International AIDS Society*, *24*(10), e25823. https://doi.org/10.1002/jia2.25823

Savage, M. O., Fernandez-Luque, L., Graham, S., van Dommelen, P., Araujo, M., de Arriba, A., & Koledova, E. (2022). Adherence to r-hGH therapy in pediatric growth hormone deficiency: Current perspectives on how patient-generated data will transform r-hGH treatment towards integrated care. *Patient Preference and Adherence*, *16*, 1663–1671. https://doi.org/10.2147/PPA.S271453

Shrank, W. H., Choudhry, N. K., Fischer, M. A., Avorn, J., Powell, M., Schneeweiss, S., & Brookhart, M. A. (2010). The epidemiology of prescriptions abandoned at the pharmacy. *Annals of Internal Medicine*, *153*(10), 633–640. https://doi.org/10.7326/0003-4819-153-10-201011160-00005

Stuart, B., Leydon, G., Woods, C., Gennery, E., Elsey, C., Summers, R., & Little, P. (2019). The elicitation and management of multiple health concerns in GP consultations. *Patient Education and Counseling*, *102*(4), 687–693. https://doi.org/10.1016/j.pec.2018.11.009

Thorneloe, R. J., Horne, R., Side, L., Wolf, M. S., & Smith, S. G. (2019). Beliefs About medication and uptake of preventive therapy in women at increased risk of breast cancer: Results from a multicenter prospective study. *Clinical Breast Cancer*, *19*(1), e116–e126. https://doi.org/10.1016/j.clbc.2018.10.008

Tichelaar, J., Richir, M. C., Garner, S., Hogerzeil, H., & de Vries, Th P. G. M. (2020). WHO guide to good prescribing is 25 years old: Quo vadis?. *European Journal of Clinical Pharmacology*, *76*(4), 507–513. https://doi.org/10.1007/s00228-019-02823-w

Townshend, T., & Lake, A. (2017). Obesogenic environments: Current evidence of the built and food environments. *Perspectives in Public Health*, *137*(1), 38–44. https://doi.org/10.1177/1757913916679860

Tozer, T. N., & Rowland, M. (2006). *Introduction to pharmacokinetics and pharmacodynamics: The quantitative basis of drug therapy*. Lippincott Williams & Wilkins.

Tracey, I. (2010). Getting the pain you expect: Mechanisms of placebo, nocebo and reappraisal effects in humans. *Nature Medicine*, *16*(11), 1277–1283. https://doi.org/10.1038/nm.2229

Verloo, H., Chiolero, A., Kiszio, B., Kampel, T., & Santschi, V. (2017). Nurse interventions to improve medication adherence among discharged older adults: A systematic review. *Age and Ageing*, *46*(5), 747–754. https://doi.org/10.1093/ageing/afx076

Vik, S. A., Hogan, D. B., Patten, S. B., Johnson, J. A., Romonko-Slack, L., & Maxwell, C. J. (2006). Medication nonadherence and subsequent risk of hospitalisation and mortality among older adults. *Drugs & Aging*, *23*(4), 345–356. https://doi.org/10.2165/00002512-200623040-00007

Vrijens, B., De Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppar, T., & Lewek, P. (2012). A new taxonomy for describing and defining adherence to medications. *British Journal of Clinical Pharmacology*, *73*(5), 691–705. https://doi.org/10.1111/j.1365-2125.2012.04167.x

Weinman, J., Petrie, K. J., Moss-Morris, R., & Horne, R. (1996). The illness perception questionnaire: A new method for assessing the cognitive representation of illness. *Psychology & Health*, *11*(3), 431–445. https://doi.org/10.1080/08870449608400270

Wilhelm, M., Rief, W., & Doering, B. K. (2018). It's all a matter of necessity and concern: A structural equation model of adherence to antihypertensive medication. *Patient Education and Counseling*, *101*(3), 497–503. https://doi.org/10.1016/j.pec.2017.09.007

Wong, S. S., George, T. J., Godfrey, M., Le, J., & Pereira, D. B. (2019). Using photography to explore psychological distress in patients with pancreatic cancer and their caregivers: A qualitative study. *Supportive Care in Cancer*, *27*(1), 321–328. https://doi.org/10.1007/s00520-018-4330-y

World Health Organisation. (2021). *WHO guide to good prescribing: A practical manual*.

Wroth, T. H., & Pathman, D. E. (2006). Primary medication adherence in a rural population: The role of the patient-physician relationship and satisfaction with care. *The Journal of the American Board of Family Medicine*, *19*(5), 478–486. https://doi.org/10.3122/jabfm.19.5.478

Zeber, J. E., Manias, E., Williams, A. F., Hutchins, D., Udezi, W. A., Roberts, C., Peterson, A. M., & ISPOR Medication Adherence Good Working Practices Group. (2013). A systematic literature review of psychosocial and behavioral factors associated with initial medication adherence: A report of the ISPOR medication adherence & persistence special interest group. *Value in Health*, *16*(5), 891–900. https://doi.org/10.1016/j.jval.2013.04.014