



WHAT CAN BE DONE TO IMPROVE MEDICINES ADHERENCE?

Jagjit Singh Samra., Patrick Ball and Hana Morrissey

School of Pharmacy, University of Wolverhampton, United Kingdom

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ABSTRACT

Background: Low rates of patients adhering to their medications is a major healthcare problem. This results in increased costs for healthcare providers.

Aim: This review aimed to understand the causes and consequences of medicines nonadherence and to suggest effective methods to improve adherence.

Method: The review focused on studies with primary outcome aimed at the impact of improving adherence on health outcomes and healthcare costs. Studies were appraised for their appropriateness as evidence using the Critical Appraisal Skills Programme tool. An initial scoping search was carried out on the following databases: **Cochrane** Library, PubMed, BMJ, and NICE. A total of 63 literary sources were used (systemic reviews, trials, reports, studies) and a further 6 sources were used to provide definitions. The data was interpreted to detect for bias.

Conclusion: This review highlights the need for further research to further understand the relationship between intentional and unintentional nonadherence among different patient groups, conditions and types of treatment. There is also need for research that are directly aiming to understand patient beliefs about and their medication adherence barriers; the financial cost of medicines nonadherence and developing models to improve integration between healthcare professions.

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INTRODUCTION

Medicines adherence is defined as the “extent to which a patient’s behaviour matches the treatment plan¹”. Lack of adherence is not just related to taking prescribed medications; the World Health Organization (WHO) states that adherence is the “extent to which a person’s behaviour - taking medication, following a diet, and/or executing lifestyle changes which corresponds with agreed recommendations from a health care provider.²”

In healthcare; adherence and compliance are almost used interchangeably, but there is a distinct difference between the two. Compliance assumes a patient’s passivity (German,1988), whilst adherence emphasises an agreement between the patient and healthcare provider³.

Nunes¹states nonadherence can have two overlapping categories; unintentional and intentional. Unintentional nonadherence occurs when factors outside of the control of a patient prevent adherence; the cost of medications, treatment complexity and low health literacy. Intentional nonadherence is when a patient actively decides not to follow recommendations. Assessing nonadherence starts with an understanding of patients’ perspectives of medicines and the reasons why they may not want to, or are unable, to use them.

It is estimated that 30% to 50% of medications are not taken as recommended⁴. This indicates that behaviour needs to change to see improvements. High rates of nonadherence are counterproductive when the National Health Service (NHS) aims to make efficiency savings of £22 billion by 2020/21⁵.

METHODOLOGY

A search of the literature included published guidelines, systematic reviews, studies, reports and economic evaluations. The following databases were searched, in the period between November 2017 and March 2018: Cochrane Library, PubMed, The BMJ, and NICE Evidence Search.

Inclusion Criteria: The study described an intervention aiming to improve medication adherence; adherence was measured within the study or adherence outcomes were reported.

Exclusion Criteria: (1) papers were written in a language other than English; (2) the research within the studies was still ongoing; (3) full published versions of the studies were not available.

A total of 63 sources were used (systematic reviews, trials, reports, studies) and a further 6 sources provided definitions. Table 1 shows the search terms used.

*Corresponding author: **Jagjit Singh Samra**

School of Pharmacy, University of Wolverhampton, United Kingdom.

Table 1 showing the search terms used to generate results on databases

Search terms used	Results from Cochrane Library	Results from PubMed	Results from The BMJ	Results from NICE Evidence Search
Unintentional + Adherence	1	217	154	327
Socioeconomic + Adherence	3	3822	481	1
Elderly + Adherence	3	39866	2800	2076
Ethnic minority + Adherence	3	556	249	839
Adolescent + Adherence	33	13898	1810	2518
Children + Adherence	75	14841	14739	4490
Health literacy + Adherence	4	832	86	640
Social support + Adherence	11	6337	15226	4267
Drug regimen + Adherence	39	7282	1234	2144
Disease + Adherence	116	32631	24816	8332
Recalling information + Adherence	3	188	2227	60
Prescription cost + Adherence	4	1712	1578	1886
Prescribing + Adherence	44	3581	6745	3779
Communication + Adherence	18	8509	14409	4740
Intentional + Adherence	3	263	5675	348
Beliefs + Adherence	5	10164	4875	1751
Health + Adherence	170	61950	20996	10921
Healthcare Costs + Adherence	34	6037	1025	3627
Causes + Adherence	67	45565	23233	5156
Behaviour + Adherence	62	43916	3218	4392
Interventions + Adherence	193	22649	4328	8485

RESULTS

Unintentional nonadherence

Socioeconomic status

It's difficult to accurately measure how low socioeconomic standing affects compliance with medications. Even the definition of socioeconomic deprivation is subject to debate. A large study in Sweden looked at this⁶. It was a cross-sectional population-based study of 31, 895 patients aged 21–84 years, who had any contact with a physician at a hospital or primary care centre. The study found that socioeconomic disadvantage was associated with low adherence to medication. This was independent of patients having chronic diseases, poor education, living alone, risky lifestyle and low approval for healthcare providers. Non-adherence was also higher in elderly patients, especially elderly women⁶.

Elderly Patients

Bae⁷ surveyed 201 subjects aged >65 taking antihypertensive medications. The subjects were allocated to three groups: (1) adherent, (2) unintentional nonadherence and (3) intentional nonadherence. The results showed just over 45% of the elderly subjects were adherent. However, 48.9% admitted to behaviours which fell into the unintentionally nonadherent group⁷. Another study investigated medicines adherence in chronic diseases and found elderly people struggle with adherence. This was attributed to lack of understanding of drug regimens and forgetfulness noting a higher prevalence of cognitive problems, multiple pathologies and increased rates of polypharmacy⁸.

Ethnic Minorities

A systematic review looking into adherence influencing factors found that belonging to an ethnic minority had a consistently negative effect⁹.

Differences in cultural beliefs, language barriers and lack of access to appropriate healthcare were suggested as possible reasons.

Adolescents and Children

A study of adherence rates in children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD) found nonadherence to medication to be at 19%. The study included 35 children (aged 6 to 12 years) and 57 adolescents (aged 13 to 18 years) assessed through a specialist clinic¹⁰. Chan *et al.*¹¹ looked into medicines adherence in school-aged children with asthma and reported that median adherence to asthma medications was at 30% (17–48%) for the 101 participants. The children had a mean age of 8.9 years. They found that being a female or having Asian ethnicity increased adherence by 12% and 19%, respectively. Children who were diagnosed at a younger age had adherence increased by nearly 3% for every year of age less at diagnosis. However, children in a smaller household were found to have decreased adherence to asthma medications. Adherence rates in younger people cannot solely be based on age; but varies with disease, comorbidities, drug regimens, financial situation, social support, side effects to medications and parent's beliefs¹².

Health Literacy

Health literacy is defined as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions¹³”. Many studies have been conducted to determine whether it is a primary cause of nonadherence. Geboers *et al.*¹⁴ reviewed 17 studies of the impact of health literacy as a predictor of medication adherence in adults. There was inconsistent evidence concerning causes of low health literacy and how it adversely affected adherence to medications. The review found vulnerable populations with low health literacy may benefit from adherence interventions such as improving education and making adherence instructions easier to understand¹⁵. For example, a patient may decide not to take a medication for reasons not connected with the patient not knowing how to take it through low health literacy. Also, the criteria used to determine health literacy vary significantly so comparison is difficult¹⁶.

Nevertheless, research suggests patients do require a basic level of health literacy. A meta-analysis of 220 articles found

that health literacy interventions increased adherence, especially among vulnerable patient groups¹⁷.

Social Support

A meta-analysis conducted by DiMatteo¹⁸ found adherence "1.74 times higher in patients from cohesive families and 1.53 times lower in patients from families in conflict." Being married and not living alone modestly increased adherence. Twenty-nine of the studies analysed focused on practical support. Adherence rates were 3.6 times higher in patients who received practical support. Patients who received no support had approximately double the risk of becoming non-adherent. Social support it appears has a positive effect on, but it is difficult to judge its effectiveness between different diseases.

Patient Drug Regimens

There is growing evidence that the more complex the drug regimen, the less likely a patient is to be adherent. A systematic review examining the association between dose regimen and medication compliance found that the prescribed number of doses per day was inversely related to adherence. Adherence rates were much higher for once daily-dosing compared to multiple daily dosing regimens¹⁹. Another systematic review of 38 randomised controlled trials looked at adherence with antihypertensive medications. Reducing the number of daily doses was effective in increasing adherence. Simplifying regimens increased adherence in 7 of the 9 studies, with a relative increase in adherence of 8% to 19.6%²⁰.

Diseases

WHO stated that in general "adherence rates are higher among patients with acute conditions compared to patients with chronic diseases²." A study observing adherence to statin therapy in elderly patients with and without acute coronary syndromes over a two year period, found adherence rates to be at 40.1% for patients with acute coronary syndrome and 36.1% for patients with chronic coronary artery disease²¹. Another study of 34,501 participants found adherence rates of patients receiving long-term HMGCoA reductase therapy to be at 60%, 43%, 26%, and 32% after 3, 6, 60, and 120 months, respectively²².

A cross-sectional study of 633 participants, which measured adherence among patients affected by chronic diseases (hypertension, diabetes, and chronic obstructive pulmonary disease) found that just over 39% of patients reported themselves adherent across a period of 4 weeks²³. However, a study looking into the factors influencing compliance with long-term antiepileptic drug regimens found adherence relatively high. Out of 696 epileptic patients, 95% were taking their antiepileptic drugs (AEDs). Of this 95%, over 70% of patients did not miss a dose, 15% of patients missed <1 dose a month and 9% missed a >1 dose in a month. Under 5% of patients missed a dose at least once a week²⁴. Most of the studies reviewed revealed that adherence rates are generally lower in patients suffering from chronic conditions²¹⁻²³. Many of the causes for low adherence in chronic conditions relate to the specific diseases e.g. side effects, cost, lacking knowledge of the treatment, regimen complexity, patient's beliefs, depression, poor communication from treatment provider and lack of access to appropriate healthcare².

Recalling Information

Linn, examined the relationship between recall of medical information and adherence in patients with inflammatory bowel disease (IBD)²⁵. The study (n=68) found that only 52.6% recalled the information they were given immediately after a consultation and 53.8% after three weeks. The consultations were recorded, and patients surveyed immediately after consultation and after three weeks. Jansen studied 260 patients with heterogeneous cancers, finding that younger and older patients correctly recalled 49.5% and 48.4% of the information they were provided, respectively²⁶. Poor recall is also correlated with reduced adherence rates in Chronic Obstructive Pulmonary Disease²⁷ and Human Immunodeficiency Virus infection²⁸.

Prescription Costs

For England, in 2013, over 90% of all prescription items were dispensed free of charge. The majority of these (64.2%) were age exemptions²⁹. A study exploring the non-dispensing of NHS prescriptions in community pharmacies (n=514) found cost-related reasons for not presenting prescriptions for dispensing included the availability of cheaper over-the-counter (OTC) products (78.6%) and incidents of customers unwilling or unable to pay the prescription charge (20.1%). Consequent upon this, 242 OTC products were sold, 97.0% of which contained the same active ingredient as the prescription item. There were 62 incidents where a prescribed item was not dispensed, or substituted, because of cost, and more than one-third would be considered to be clinically important³⁰. A report prepared by WHO noted the effect of prescription charges differs between groups of patients; it noted that the "implementation of full coverage of free prescriptions appeared to be associated with a greater increase in the use of medicines by those with a lower health status³¹".

Healthcare Professionals (communication and prescribing)

Effective communication can produce a positive effect³². In 1998, the American Academy of Orthopaedic Surgeons surveyed 807 patients and 700 orthopaedic surgeons. An interesting difference was found in how the surgeons perceived their communication with patients compared to how their patients perceived them. Three-quarters of the surgeons believed they communicated satisfactorily but most patients felt communication was not satisfactory. Only 21% of patients deemed the communication satisfactory³³. Another study looked at patient and provider factors in the lack of adherence in type 1 and type 2 diabetes. The 367 patients were assessed for level of adherence to treatment, depression, attachment and disease severity. Adherence to medications and glucose monitoring was significantly worse in patients who rated their patient-provider communication as poor³⁴.

A questionnaire-based study of the appropriateness of prescribing in general practice within England included 24 general practitioners and 186 patients who completed questionnaires before and after consultations³⁵. Phone interviews were then conducted one week after their consultations. The results from the questionnaires showed that 31% of prescriptions were either not wanted by the patients, were technically inappropriate or the prescriber thought they were not strictly indicated. The telephone interviews revealed 18% of patients were potentially non-adherent (had not started taking their medicine, had stopped early, had missed doses, or had altered the dosages). Results from a collaborative audit of

pharmacy-led medicine reconciliations in 56 NHS trusts across England, showed that when admitted most patients have a medicine omitted (73%) or a wrong dose recorded (14%). Patients on multiple long-term medications were most likely to have errors. These results came from 8621 medicines reconciliations covering 49,099 medications²³.

Intentional nonadherence

Intentional nonadherence is influenced by a patients' beliefs. It includes those who do not take their medicines at all (absolute noncompliance) and those who alter the dose or frequency of their medicines or only take the treatment as perceived necessary (Horne *et al.* 2005). A meta-analysis of 94 studies covering 24 long-term conditions involving 25,072 patients from multiple countries showed the decision to take a medicine is decided by individual perceptions of the need for the medicine (necessity beliefs) and concerns about potential adverse consequences of taking it. Patients believing their treatment necessary and those with fewer concerns about their treatment had higher adherence. The study concluded that accounting for necessity beliefs and concerns enhanced the quality of prescribing by helping clinicians to engage patients in treatment decisions and support optimal adherence³⁶. Pound *et al.*³⁷, conducted a meta-analysis of 37 qualitative studies and found similar results to Horne³⁶. Patients don't adhere to medications correctly because of concerns about the medicines themselves (adverse drug reactions, lay evaluation of medicines) and those on long-term treatments test their requirement through dose alteration or trial cessation. Patients appear reluctant to take medicines and prefer to take as few as possible.

A United Kingdom study (n=161) found 34% of patients were taking their medicine differently to that prescribed, through a conscious decision. The two most frequent reasons were; side effects and adjustment of the regimen in response to symptoms³⁸. Sjölander, Eriksson and Glader³⁹ conducted a cross-sectional questionnaire completed by 595 stroke patients to find out about patients' beliefs on stroke and drug treatment and their adherence to drug treatment. Of the patients 12.5% were classified as non-adherent. A significant number of non-adherent patients scored lower on positive beliefs about medicines and higher on negative beliefs.

Gagnon *et al.* surveyed 343 participants about whether beliefs about their medications had a greater impact on adherence compared to other barriers (cost, access, forgetting to get refills, transportation, hospitalisation)⁴⁰. Patients reporting more negative beliefs towards their medicines were 49% less likely to adhere, whilst barriers to adherence showed no significant.

Effect of adherence on health outcomes

Poor adherence is associated with a poor glycaemic control in type two diabetics^{41,42}, whilst higher adherence gives better glycaemic control⁴³⁻⁴⁵. Type 2 diabetics with poor adherence to diet and exercise show decreased glycaemic control⁴⁶. In patients who already have glucose intolerance, adherence to a low-fat diet improves body weight and glucose tolerance over 2-3 years⁴⁷.

Low adherence to antihypertensives has been associated with poor blood pressure control⁴⁸. Patients with high adherence were around five times more likely to have controlled blood pressure when compared to patients with low adherence⁴⁹. It

was also associated with significantly higher risk of stroke⁵⁰. A study by Alhalaiqa, *et al.* investigated adherence therapy (AT) compared with treatment as usual (TAU) in reducing blood pressure in noncompliant hypertensive patients⁵¹. There were 136 non-adherent participants; 68 patients received TAU and 68 AT. Systolic blood pressure was reduced in the AT group by 23.11 mmHg more than in the TAU group and similarly, diastolic blood pressure was by 15.18 mmHg more than in the TAU group at 11 weeks. Adherence was measured by pill counting and was improved by 37% in the AT group at 11 weeks.

A randomised controlled trial found adherence to selective serotonin reuptake inhibitors or tricyclic antidepressants had a positive impact on treatment; irrespective of the antidepressant used⁵². Sirey, Bruce and Kales examined the effectiveness of a psychosocial intervention to improve antidepressant adherence and depression outcomes⁵³. The group that had the psychosocial intervention (Treatment Initiation and Participation Program) was significantly more adherent to their antidepressant pharmacotherapy and had a significantly greater decrease in depressive symptoms compared to controls. Sokol, *et al.* studied the impact medication adherence had on hospitalisation risk in 137,277 patients (diabetes, hypertension, hypercholesterolemia or congestive heart failure) who were observed over the course of 23 months⁵⁴. Across all four conditions, patients that maintained high adherence to medications (between 80-100%) were significantly less likely to be hospitalised.

Adherence and Healthcare Costs

Finding data on the impact adherence has on healthcare costs is challenging. Trueman *et al.* attempted to explore the economic impact of poor adherence on NHS finances, examining long-term conditions (asthma; type 2 diabetes; high cholesterol/coronary heart disease; statins for primary prevention and secondary prevention; hypertension; and schizophrenia)⁵⁵. For each condition, they assessed whether non-compliance had a material impact on health. The results were provided in the form of quality-adjusted life years (QALYs- valued at £20, 000). They concluded if all patients were fully compliant with medications, savings would be £930 million per year, for the five conditions:

- “Asthma £130 million
- Type 2 Diabetes £100 million
- High cholesterol/ CHD £120 million
- Hypertension £390 million
- Schizophrenia £190 million”⁵⁵

The methods and assumptions used in this study are open to question but highlight the scale of the impact of nonadherence on healthcare finances.

Strategies to improve adherence

The scale of the problem

Haynes *et al.* stated current methods for improving adherence for chronic health problems are mostly complex and not very effective, resulting in suboptimal treatment⁵⁶.

A Cochrane review by Nieuwlaet *et al.*, looked into effective interventions to improve medication adherence⁵⁷. From >100 randomised controlled trials (RCTs), the review found only 5 RCTs reported improvement in both adherence and outcomes.

Between the 5 RCTs, no common intervention characteristics were apparent.

Potential solutions

To date, no known interventions lead to major improvements in adherence and clinical outcomes. However, some have found positive findings. Emerging strategies are signposting possible ways forward.

Understanding patient beliefs

Healthcare professionals must understand a patient's beliefs about their medications. Horne *et al.* reported a "patient's decision to take a medicine is often a balance between their perceptions of the personal need for the medicine (necessity beliefs) and concerns about potential adverse consequences of taking it."³⁶ These concerns are deeply rooted in a patient's psyche and relate to concerns about dependency and fears about negative effects of long-term medication use. Personal beliefs, previously negative experiences with medications, listening to the experiences of others and misinformation were all factors that were shown to influence these concerns. They concluded that such an understanding could help promote medications adherence and engage patients in treatment decisions.

A conceptual model called the Necessity-Concerns Framework (NCF) was created to help healthcare professionals with this issue. The NCF postulates that "adherence is influenced by implicit judgements of personal need for the treatment (necessity beliefs) and concerns about the potential adverse consequences of taking it"³⁶. The framework has been shown to be a useful tool in assessing what a patient thinks about their medications⁵⁸⁻⁶⁰.

Patient Behaviour

Understanding the causes of nonadherence and then having the appropriate behavioural tools to implement tailored adherence interventions could be one way forward. The Theoretical Domains Framework (TDF) was compiled from 33 theories and 128 key theoretical constructs related to behavioural change. They were synthesised into a single framework to allow easier assessment of behavioural problems and helps create effective interventions. The aim was to simplify and integrate the many behaviour change theories and make them accessible to, and usable by, other disciplines⁶¹. The Theoretical Domains Framework (TDF) is composed of "14 theoretical domains:

1. Knowledge
2. Skills
3. Social/Professional Role and Identity
4. Beliefs about Capabilities
5. Optimism
6. Beliefs about Consequences
7. Reinforcement
8. Intentions
9. Goals
10. Memory/Attention/Decision Processes
11. Environmental Context and Resources
12. Social Influences
13. Emotion
14. Behavioural Regulation"⁶¹.

The COM-B model (Capability, Opportunity, Motivation-Behaviour) requires a person to have the adequate capability,

opportunity, and motivation for a behaviour (such as adhering to medications) to take place. If there are deficits in any one of these areas, the behaviour is unlikely to occur⁶².

The TDF and COM-B models are closely linked; both allow determinants of behaviours (such as medicines-taking), to be explored in more depth than the binary model of intentional and unintentional non-adherence, allowing the actual cause for non-adherence to be determined⁶³. Advantages from using the models are that both were created using evidence-based behaviour change techniques^{61,62}. This allows for adherence barriers to be linked with evidence-based behaviour change techniques, which helps patients to overcome their adherence barrier(s)⁶³. Both models have been applied to medication adherence issues and were effective in identifying adherence barriers⁶⁴⁻⁶⁷.

Further research is required to elucidate whether using these models can improve adherence rates. It should focus on developing specific interventions that address individual adherence barriers, based on the domains of the models allowing individually tailored strategies to improve medicines adherence.

Pharmacist Interventions

A two-year RCT conducted in a hospital, to determine the effect of periodic adherence promoting telephone counselling by a pharmacist on mortality in patients receiving polypharmacy. Participants were deemed to be non-adherent to their medications but otherwise stable. Of the 442 randomised patients, 236 became adherent. When conducting telephone consultations, pharmacists measured adherence using a questionnaire and had access to medicines information. The intervention group had fewer non-adherent patients who remained non-adherent plus adherent patients that remained adherent. This intervention reduced the risk of mortality by 6% (from 17% to 11%)⁶⁸. A limitation of this study is that it's difficult to prove mortality effect with this intervention alone; other factors could have contributed to the death of the participants.

Elliott *et al.* studied the New Medicines Service (NMS) in England⁶⁹. The service increased adherence rates by around 10%, and increased the number of medication issues identified and resolved. In the short term, the service saved the NHS money on each patient included. Long term, the study suggested NMS would deliver improved patient outcomes at total reduced cost for the NHS.

DISCUSSION

This review focussed on the behaviour of individuals regarding adherence and how nonadherence arises in two categories; intentional and unintentional. Both categories demonstrate that within category, the level of adherence is still multifactorial. Consequently, nonadherence requires responses that are tailored to the individual cause. Patient nonadherence is due to many complex underlying issues, which can start off under the umbrella of unintentional nonadherence but manifest into a mixture of unintentional and intentional nonadherence. There is a need for further research into the relationship between intentional and unintentional nonadherence among different patient groups, conditions and types of treatment.

This review looked at the effects of low adherence on health outcomes and on healthcare costs. Poor adherence has negatively effects health outcomes across differing diseases.

More research is required and ideally, be brought together address adherence issues across various disease states to be highlighted and addressed.

Studies on the effect of low adherence on healthcare costs were reviewed. The published figures were approximations; no accurate figures were identified. However, the estimates still highlighted potentially huge financial burdens that nonadherence can have on healthcare costs. The NHS is currently required to make efficiency savings of £22 billion by 2020/21⁵. The estimates suggest potential savings could be considerable, but any implementation requires close monitoring to generate more accurate data.

Finally, strategies to improve adherence rates were considered. Clearly studies show adherence to be an extremely complex topic and a 'one size fits all solution' approach is inappropriate. Understanding beliefs is crucial; healthcare professionals must understand how the patient views their medications to design tailored interventions. Both the TDF and COM-B frameworks have proven effective in identifying the root cause(s) of nonadherence. Research must focus on developing interventions that address individual barriers, based on the domains of these models.

Limitations

Several studies used had a relatively small number of participants. Indeed, Britten *et al.*(2003) and Fine and Worling(2001) both acknowledged sample size as a limitation. Further and larger studies are required^{10,35}.

A number of studies in this review had been carried out across many different countries. This can be both an advantage and disadvantage. The limitations are that causes of low adherence will differ between countries due to differences in demographics, healthcare systems, healthcare budgets etc. Reviews which use studies from one country or countries that have similar demographics and healthcare systems may be able to provide more insightful reasons as to why medicines nonadherence occurs.

Any literature not written in English was not included in this review due to time and budget constraints. More information would have been available if literature from other languages had been translated and analysed. However, by looking at the English abstracts for foreign language papers no significant issues were found to have been overlooked.

CONCLUSION

This review examined the various causes of medicines nonadherence and looked at the consequences poor adherence has on health and healthcare costs. Several interventions which showed promising results in improving adherence were highlighted. To conclude, this review highlights the need for further research to be commissioned in the following areas:

- further understanding the relationship between intentional and unintentional nonadherence among different patient groups, conditions and types of treatment.
- bringing together literature to allow adherence issues across various disease states to be highlighted and addressed.
- further understanding patient beliefs about their medications.

- having more accurate data on the financial cost medicines nonadherence has on healthcare systems.
- further developing specific interventions that address individual adherence barriers by using behavioural change models (TDF and COM-B).
- further looking into methods to improve integration between healthcare professions.

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