Concordance, adherence and compliance in medicine taking

Report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R & D (NCCSDO)

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Executive Summary

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This report is a product of a scoping exercise commissioned by the NHS National Coordinating Centre for Service Delivery and Organisation (NCCSDO) with the following aims:

1. Summarise current knowledge about the determinants of medication-taking.
2. Construct a conceptual map of the area of compliance, adherence and concordance.
3. Identify priorities for future research of relevance to the NHS, with particular emphasis on identifying what new knowledge is needed to be able to develop effective, realisable, efficient and equitable interventions to promote the appropriate use of medicines for the benefit of patients and the NHS.

The scoping exercise involved analysis of the literature, a listening exercise involving consultation with both a user group and with a group of academics, health care professionals and managers, plus feedback from an Expert Panel.

Main findings and take home messages

Nonadherence to appropriately prescribed medicines is a global health problem of major relevance to the National Health Service (NHS).

Nonadherence prevents patients from gaining access to the best treatment, and this may be particularly problematic in chronic medical conditions, including current NHS priorities such as mental health, cancer, diabetes and respiratory illness.We agree that: 'Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments'.[1] The NHS should take action but requires quality research to guide and evaluate this.

[1] Haynes, R., McDonald, H., Garg, A., & Montague, P. (2002). Interventions for helping patients to follow prescriptions for medications. *The Cochrane Database of Systematic Reviews,* 2, CD000011.

The challenges for research in medication adherence are similar to those for other health-related behaviours, such as smoking cessation, exercise and diet: how to influence and change behaviour.

Our review offers clear insights into not only why previous interventions have failed, but also how we can improve the content, development and testing of new approaches.

We recommend that the NCCSDO commissions a coherent programme of research to inform the development of effective, patient-centred interventions to facilitate informed choice and optimal adherence to appropriate prescriptions where adherence matters most.

The time is right to address this agenda as there is a strong coherence with the concept of a patient-led NHS and related policy developments, such as the expert patient programme and medicines usage review.

Why this scoping exercise is necessary

The prescription of a medicine is one of the most common interventions in healthcare. In England there were 686 million NHS prescriptions dispensed in 2004, costing £8 billion. The optimal use of appropriately prescribed medicines is vital to the self-management of most chronic illnesses including those designated as NHS priorities.

Reviews conducted across disease states and countries are consistent in estimating that between 30 and 50 per cent of prescribed medication is not taken as recommended.

This represents a failure to translate the technological benefits of new medicines into health gain for individuals. There are potential losses for patients, the NHS and pharmaceutical industries.

Nonadherence is often a hidden problem: undisclosed by patients and unrecognised by prescribers.

There is no evidence that the problem of nonadherence has been solved by recent advances in the design and presentation of medicines or by the evolution of healthcare services that have tended to become more 'patient-centred.'

There is a pressing need to develop effective strategies to make the delivery of healthcare more efficient and responsive to patients' needs by addressing the problem of nonadherence.

A conceptual map and research agenda

The size and scope of the literature on medication-taking can make it difficult for practitioners to find their way around. The complexity of the topic is illustrated by the fact

that there are at least three terms in common usage: compliance, adherence and concordance.

This document does not involve an exhaustive review of the primary literature – this has already been researched to good effect and is beyond the scope and timescale of the project. Rather it provides a conceptual map to guide policy-makers, clinicians and health services researchers through this complex field. The conceptual map has two elements:

An explanation of the concepts of compliance, adherence and concordance and recommendations for use of terminology.

A summary of current knowledge about the factors influencing medication-taking and how these might be influenced.

Terminology – compliance, adherence and concordance

Compliance is defined as: 'The extent to which the patient's behaviour matches the prescriber's recommendations.' However, its use is declining as it implies lack of patient involvement.

Adherence is defined as:'The extent to which the patient's behaviour matches agreed recommendations from the prescriber.' It has been adopted by many as an alternative to compliance, in an attempt to emphasise that the patient is free to decide whether to adhere to the doctor's recommendations and that failure to do so should not be a reason to blame the patient. Adherence develops the definition of compliance by emphasising the need for agreement.

Concordance is a relatively recent term, predominantly used in the United Kingdom (UK). Its definition has changed over time from one which focused on the consultation process, in which doctor and patient agree therapeutic decisions that incorporate their respective views, to a wider concept which stretches from prescribing communication to patient support in medicine taking. Concordance is sometimes used, incorrectly, as a synonym for adherence.

It can be seen that these terms are related but different. Two issues underpin this. First, whether patients should take their medicines or not depends on whether the prescribing was appropriate – we do not want to promote patients taking inappropriate medicines. Hence all terms refer back in varying degrees to the act of prescribing. Second, all these terms involve varying normative agendas – understandings of what is good and right about prescribing and medicine taking; we explore these concepts in Chapter 5.

Terminology recommendations

We recognised that these three terms are now used interchangeably and that this has generated some confusion. After discussion within the Project team and with our Expert Panel and Consultation Groups, we recommend 'adherence' as the term of choice to describe patients' medicine taking behaviour.

We recognise that adherence is not always a 'good thing' as a prescription may be inappropriate or not reflect the patients' changing needs. We assume that adherence is appropriate and beneficial if it follows a process that allows patients to influence the decision making if they wish, and an appropriate choice of medicine is made by the prescriber.

Determinants of medication-taking behaviour

We grouped the literature on adherence into four core themes: explaining patient behaviour: patient-provider interactions; societal policy and practice; and interventions. These are underpinned by complex notions of the various, and sometimes conflicting, things we consider to be 'good' about prescribing and medicine taking. We pause to explore these issues in between the policy and intervention themes. Medicine-taking needs to be understood as a variable behaviour, which occurs within, and is influenced by, external, environmental factors including interactions with healthcare providers and by the wider context of societal-policies and practice. Theme four spans these domains as interventions to facilitate optimum medicine-taking can be targeted at one or more of these domains. Below we present a résumé of current knowledge and key outstanding research questions for each them. The research agenda as it relates to SDO research priorities is presented at the end of this Executive Summary.

Theme 1: Explaining medication-taking behaviour

The research evidence shows that variation in adherence cannot be explained by a range of fixed factors, such as the type or severity of disease; sociodemographic variables or personality traits. Adherence is positively correlated with income when the patient is paying for treatment but not with general socio-economic status. Furthermore, providing clear information, although essential, is not enough to guarantee adherence. Nonadherence is often lower for more complex regimens, but significant nonadherence remains when the frequency of dosing is reduced. Depression, but not anxiety, is related to nonadherence to medication prescribed for conditions other than depression.

The main development in adherence-related research over the past decade has been an increasing recognition of the importance of patients 'common-sense' beliefs about their illness and treatment as determinants of adherence. This work shows that, although nonadherence may be puzzling or frustrating from the prescribers' perspective, viewed from the patient's perspective, it often represents a logical response to the illness and treatment in terms of their own perceptions, experiences and priorities, including concerns about side effects and other unwelcome effects of medicines. Patients therefore seek to balance perceived necessity and concerns and to minimise their use of prescribed medicines.

We endorse an approach to nonadherence that acknowledges patients' own beliefs and active decision-making but also recognises the constraints and practical barriers that reduce people's ability to take medicines as prescribed. Nonadherence is therefore best seen as variable behaviour with intentional and unintentional causes.

Unintentional nonadherence arises from capacity and resource limitations that prevent patients from implementing their decisions to follow treatment recommendations and involves individual constraints (eg, memory, dexterity, etc) and aspects of their environment (eg, problems of accessing prescriptions, cost of medicines, competing demands, etc). Intentional nonadherence arises from the beliefs, attitudes and expectations that influence patients' motivation to begin and persist with the treatment regimen.

Research to date gives a good indication of the factors influencing intentions and constraints but we know little about the extent of intentional versus unintentional nonadherence or their interrelationships. Internal factors such as motivation and capacity may be moderated by external factors, such as the quality of communication between the patient and healthcare provider, as discussed in Theme two (Chapter 3), and by the wider societal contexts, such as access to resources and societal policy and practice, as outlined in Theme three (Chapter 4).

Most research has been cross-sectional whereas adherence is a dynamic process that may change over time and needs to be followed-up. We now need longitudinal studies to investigate how patients' choices and adherence behaviours change over time and how they might be influenced by interventions. There is a particular need to examine intentional and unintentional influences in vulnerable groups, such as children, adolescents and the elderly, as well as vulnerable groups defined by social exclusion or other factors, such as ethnicity. We also need to include how patients judge their personal need for medication in different situations and stages of illness.

Theme 2: Patient-provider interactions and communication in healthcare

Our review of the empirical evidence identified surprisingly few studies that systematically evaluate the direct effects of the prescribing consultation on medication adherence behaviour. Further basic research is needed to clarify the effects of the consultation on medication adherence, the extent to which consultation skills training can improve adherence, and how different messages from different sources influence patients' medication-taking behaviour.

We know little about how physicians' beliefs influence the process and content of prescribing and this is a priority for further research. We also need to know more about how we can equip prescribers (and their patients) to deal with the cognitive and emotional challenges of working in partnership to achieve appropriate prescribing, and optimal adherence. This is a key challenge for NHS workforce development, especially as new prescribers (such as nurses and pharmacists) come 'on-line'. We need concomitant research on how prescribers can most efficiently support patient informed choice and optimal adherence both individually and as part of a multidisciplinary team.

Theme 3: Societal policies and practice

The impact of nonadherence at a societal level is probably substantial, but existing data in the UK are too poor to fully characterise this, possibly because, until recently, the management of adherence has not featured strongly in NHS policy. However, several core policy initiatives such as the Expert Patient programme, National Service Frameworks and Medicines Use Reviews (MURs) now place patient self-management and involvement in decisions at the forefront of healthcare delivery. These offer strong incentives and provide an excellent context for the development of interventions to help patients with long term illnesses to get the best from medicines. However, research is needed to inform their development and assess their impact on the medication needs and practices of patients and their carers.

Key policies that are predicted to affect medicines-taking behaviour are the prescription tax system, deregulation of prescription only medicines and expansion of prescribing rights. The accelerated rate of deregulation of medicines in the UK needs to be assessed: does use of medicines change and is this change in use appropriate or inappropriate? Does deregulation lead to financial barriers that reduce use in some groups? The recent introduction of supplementary and independent prescribing rights for non-medical prescribers has generally been welcomed by health professional groups. However, it is not clear whether patients will perceive this development as a welcome or confusing plurality of service provision, or whether or not it will improve medicines-taking behaviour.

Doing the right thing: the normative theme

Underpinning this whole report are two questions – what is good prescribing and what is good medicine taking? These questions, in contrast to questions of effectiveness, have had little in depth exploration in the literature, yet they must be addressed to inform policies and practices. We found these questions to be relevant across each of our four themes and devoted a separate chapter of the report (Chapter 5) to explore this normative agenda (questions of what is right and good). These questions are complex. For example, in Chapter 5 we identify a dozen values around these areas which can be legitimately held, yet there is little exploration of how patients and prescribers should deal with situations in which the values conflict. There is a need for more work in this area to support patients and prescribers in their practice.

Questions about 'good' and 'right' are normative questions; they need to be addressed partly by philosophical argument and partly by empirical research. In particular, work is needed on joint decision making. What is the ideal nature of communication? What sort(s) of reasoning should be used so that the decision is truly 'joint'? Which forms of joint decision making are possible and what are their strengths and weaknesses? Linked to this is the important research question of the effect of different forms of accountability on patient and prescriber. Currently decision making may be joint but accountability is with the prescriber; this limits the potential for patients to influence a decision. Research is needed into the practical and psychological implications of increasing patient accountability in line with their responsibility for the prescribing decision.

Theme 4: Interventions to facilitate adherence

The literature on adherence interventions has been the subject of three major systematic reviews over the past five years, culminating in a Cochrane systematic review in 2002. As part of our scoping exercise we extended the scope of the Cochrane review by including studies that met the stringent quality criteria, but were not eligible for inclusion in the Cochrane review because they had measured adherence but not clinical outcome. We do not dispute the Cochrane reviewers' rationale that improving adherence is only valuable if it brings clinical benefits to the patient. However, we wanted to examine whether including studies that had measured adherence (but not clinical outcome) might provide valuable information about how to change

adherence behaviours.[2] Our analysis of the findings of previous systematic reviews, including our extension of the Haynes review, can be summarised as:

1. Interventions to promote adherence are broadly efficacious. However, the effects were generally modest We know that adherence can be increased, but there is considerable room for improvement.
2. Few interventions have been systematically developed, using appropriate theoretical models, nor have they been modelled and piloted with assessment of process variables as well as outcomes (as recommended in the MRC framework for complex interventions to effect behaviour change). Consequently, it is difficult to tell why some interventions work and others do not.
3. Comprehensive interventions that combined approaches were typically more effective than interventions focusing on single causes of nonadherence. However, few interventions could be described as 'patient-centred' as they did not individualise the approach to match patients' needs and preferences.

Research priorities

Because medicines carry the potential for harm as well as benefit we have identified a *normative* agenda to address questions of what is good-prescribing and good medicine-taking and an *empirical* research agenda to address how adherence might be improved. In an ideal world the normative agenda would come first and inform the empirical agenda, however, realistically both need to be pursued in parallel.

There is an imperative to move ahead with the empirical agenda in conditions where there is strong supporting evidence for the benefits of medication and importance of adherence. This is particularly relevant for the NHS SDO programme as the prescription of a medicine is one of the most common and, therefore, costly medical interventions. Optimising use of prescription medicines is a key priority for the delivery and organisation of healthcare.

[2] There have been no large scale systematic reviews of the intervention literature since 2003. It is possible that more effective interventions may have emerged since then. However, neither the Project Team nor our Consultation Groups and Expert Panel were aware of a significant body of studies to contradict our analysis of the interventions literature, based on published systematic reviews.

The empirical research agenda

The main research priority is the development of effective, efficient, realisable and equitable interventions to facilitate adherence to appropriate prescriptions[3] where adherence matters most. These can be defined as:

1 Conditions where there is strong evidence supporting the benefits of medication, above other treatment options and over doing nothing.

2 Treatments where there is strong evidence that high levels of adherence are essential to ensure efficacy or prevent problems such as the emergence of treatment-resistance.

Although more work is needed to develop a framework for adherence priorities, we can immediately identify examples that seem to fit the criteria. These might include: highly active anti-retroviral therapy for HIV, pharmacological treatment of diabetes, immunosuppressant medication following transplantation, preventer medication in asthma, medicines for severe mental illness, preventative medicine for cardiovascular disease, anti-tuberculosis treatment and anti-cancer agents.

In this scoping exercise we grouped the literature on adherence into core themes: explaining patient behaviour, patient-provider interactions and societal policy and practice, all of which are relevant to our forth theme, the development of interventions. Our review of the literature identified existing knowledge and outstanding research questions within each of the themes that can inform the development of innovative interventions to facilitate optimal adherence to appropriate medicines.

Our analysis of the literature on the causes of nonadherence and our assessment of the reasons for the limited success of interventions provide clear pointers to improving content, development and testing of interventions. The main lessons are:

Content Interventions should be tailored to meet the needs of patients taking account of the particular perceptual (eg, beliefs and preferences) and practical (eg, capacity and resources) factors influencing intentional and unintentional nonadherence for that individual.

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[3] How we define an 'appropriate' prescription may vary according to individual circumstances, and this needs to be addressed within a normative research agenda. However, the essence of appropriate prescribing is the application of the scientific evidence base to the unique needs and preferences of the individual, taking account of their desires and capacity for involvement in the decision.

Development and testing Interventions should be developed using an appropriate theoretical framework with a phased approach to testing that includes assessment of the process (ie, the things that are targeted for change), as well as outcomes. The MRC framework for complex interventions to effect behaviour change may be useful in this respect.[4]

The fundamental questions that need to be addressed in order to develop such interventions are:

1. What are the most effective methods for addressing the cognitive (eg, beliefs; attitudes), emotional and capacity (eg, memory limitations; changes in routines/habits, etc) factors, which result in reduced adherence to appropriate medication?
2. How can we enable prescribers and other members of the NHS workforce to support patients by facilitating informed choice and optimal adherence to appropriate prescriptions?
3. How can we incorporate an awareness of patient needs in relation to medicines and adherence support into the organisation and delivery of everyday healthcare to meet the requirements of NSFs, a patient-led NHS and the drive for greater efficiency in healthcare delivery?

This research agenda is highly relevant to the NHS SDO research priorities of patient choice, access and continuity of care, workforce, e-health, methodological research and governance.[5] We have mapped the key research questions relating to facilitating informed choice and optimal adherence to appropriate prescription onto the NHS SDO priorities in Chapter 7 and at the end of this Executive Summary.

The normative research agenda

Work is needed on what types of prescribing can be considered 'good,' and what should be considered good medicine taking. These questions need to be answered in ways that are deliverable by patients and prescribers, and underpin the successful implementation of policy in areas such as the Expert Patient and NSFs. The normative questions are linked to empirical questions in Chapter 5 to ensure that realistic, acceptable, achievable answers will result. While the SDO may wish to fund some of this work they may also wish to draw the attention of humanities and social science Research Councils or other funding agencies to the need for fine grained philosophical work in this area.

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[4]Campbell, M., Fitzpatrick, R., Haines, A., Kinmonth, A. L., Sandercock, P., Spiegelhalter, D., et al. (2000). Framework for design and evaluation of complex interventions to improve health. *BMJ, 321* 694-696.

[5] http://www.sdo.lshtm.ac.uk/commissioninggroups.htm

Conclusions and Recommendation

1 The evidence from this and previous reviews is that nonadherence to appropriately prescribed medicines is a global health problem of major relevance to the NHS.

2 Current levels of nonadherence imply a failure to address patients' needs and preferences and represent a fundamental inefficiency in the delivery and organisation of the NHS. Nonadherence prevents patients from gaining access to the best treatment, and this may be particularly problematic in chronic medical conditions, including current NHS priorities.

3 We agree with the authors of a recent Cochrane systematic review that: 'Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments.'[6] The NHS should take action but we require quality research to guide and evaluate this and the development of novel patient-centred interventions to facilitate informed choice and optimal adherence to appropriate prescriptions which is the overarching priority.

4 The challenges for a research agenda in medication adherence are similar to those for other health-related behaviours such as smoking cessation, exercise and diet: how to influence and change behaviour.

5 Although previous interventions to facilitate adherence have met with only limited success, it would be a mistake to interpret this as an indication that intervention is likely to be futile. On the contrary, our review offers clear insights into, not only *why* previous interventions have failed, but also *how* we can improve the content, development and testing of new approaches. This includes work on the ideal types of patient-prescriber relationship and roles of the patient and prescriber during medicine taking.

6 This report sets out the key research questions that need to be addressed to enable us to do this and these map onto the NHS SDO research priorities.

7 We recommend that the NCCSDO commissions a coherent programme of research to inform the development of effective, patient-centred interventions to facilitate informed choice and optimal adherence to appropriate prescriptions where adherence matters most. This programme is essential to guide the delivery of recommendations for medicines use within NHS NSFs

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[6] Haynes, R, McDonald, H, Garg, A, and Montague, P. 2002. `Interventions for helping patients to follow prescriptions for medications', *The Cochrane Database of Systematic Reviews,* 2, CD000011.

and address a fundamental inefficiency in healthcare delivery. The potential benefits are likely to include: better care tailored to patient needs, higher rates of adherence to appropriate medication, fewer unwanted and unused prescriptions, more effective management of chronic illness, increased patient safety and satisfaction and fewer emergency admissions. The time is right to address this agenda as there is a strong coherence with the concept of a patient-led NHS and related policy developments, such as the expert patient programme and medicines usage review.

Mapping research questions onto the SDO research priorities

Key research questions mapped onto SDO research priority areas

Patient choice [7]

1 In what ways can and should patients' initial choices and preferences be modified?

2 In what ways and under what circumstances should patient choice form the basis for decision making in prescribing and medicine-taking?

3 What are most effective ways of representing evidence for the likely benefits and risks of medication?

4 How can we tailor medicines information to match the requirements of individual patients and their carers?

5 Where patients' decisions are based on misplaced beliefs or misconceptions about the illness and treatment, how and when should this be addressed?

6 How can we help people make 'informed choices' about adherence to prescribed medication?

7 How should we communicate and deal with uncertainty within prescribing-relating consultations?

8 How can professional and lay accountability be best aligned to support patient choice?

9 How do patient preferences for involvement in medication-related decisions vary and how should prescribers responds to this?

10 How do patients' perceptions, preferences, choices and medication-taking behaviour change over time in

[7] CARERS – Many of the questions that are relevant to patient choice and support will also apply to patients' carers and there is scope for synergy and continuity with the SDO Programme on carers.

conditions where adherence to medication matters most?

Access and continuity of care

11 How can we help patients to overcome the capacity and resource limitations preventing access to effective healthcare?

12 How can we address and identify misconceptions about illness and treatment that prevent access to appropriate medication

Workforce

13 How can we equip prescribers (and their patients) to deal with the cognitive and emotional challenges of working in partnership to achieve informed choice and optimal adherence to appropriately prescribed medicines, where adherence matters most?

14 How can adherence review and adherence support be incorporated into medication-usage review in a way that promotes informed choice and supports adherence to agreed, appropriate prescriptions?

15 What are patients' perceptions and behavioural reactions to new prescribers (eg, nurses and pharmacists)?

16 What are the barriers to effective and efficient multi disciplinary approaches to appropriate prescribing and adherence support? How can these be overcome?

17 How can we enable new and existing prescribers to identify patients who are priority for medication-review and adherence support?

18 How can we support prescribers to meet the challenges of quality frameworks relating to medication-usage as a component of self-management?

19 In what ways is it possible to supplement the activities of the NHS workforce in facilitating optimal mediation usage through other, complimentary approaches (eg, the use of 'expert patients', family support, etc).

e-Health

20 How can technological developments (eg, computers, mobile telephones, etc) be utilised to provide ongoing support for informed choice and adherence to agreed prescriptions?

21 How can we develop and apply effective 'technologies' to facilitate behaviour-change to achieve optimal adherence to appropriate and agreed prescriptions? Here technologies may be 'talk treatments,' such as cognitive behaviour approaches.

Methodologies

22 How can we facilitate the honest disclosure of medication-taking behaviours within prescribing-related consultations and medication use reviews? How can we equip health practitioners to respond appropriately and effectively?

23 What are the alternatives to full-scale Randomised Controlled Trials (RCTs) that can be used to conduct preliminary evaluations of the components of interventions to support informed choice and adherence? (corresponding to MRC Phases 1 and 2)

24 How can existing validated methods for assessing adherence-related perceptions and adherence behaviours be adapted for routine use in the NHS?

25 How can we enable new and existing prescribers to identify patients at risk of nonadherence or who are a priority for medication-review and adherence support and how can we provide it – new methods, new practitioners (eg, health trainers)?

26 How should we operationalise 'informed choice' in relation to medications taking?

Governance

27 How do differences in the arrangements existing in England, Wales and Scotland, such as the role of prescription charges, affect prescription filling for essential and non-essential medicines, subsequent patient health, present and future health service and societal cost?

Adherence in vulnerable groups

Consideration of vulnerable groups cuts across the explanatory themes and is relevant for most research questions, regardless of whether research is targeted at explaining individual behaviour, investigating communication in healthcare, societal policy and practice or evaluating interventions. Work in this area requires systematic reviews of the available literature followed by empirical studies. Specific questions are:

1 What are the effects of social disadvantage and ethnicity on accessing prescriptions and adherence to prescribed medication?

2 How do the perceptions and life circumstances of different age groups (children, young adults, elderly people) influence adherence and what are the implications for interventions?

3 What are the particular barriers to medicines use for people with multiple pathologies (and their informal carers) and what interventions are required?

The Report

Section 1 Introduction

Rob Horne

Why we need this scoping exercise

In the UK and other affluent countries, most healthcare resources are devoted to the management of long-term conditions, such as cardiovascular disease, diabetes, cancer and mental health. Here, good outcomes depend as much on self-management by the patient as on good medical care and, for most of these conditions, self-management hinges on the appropriate use of medicines.

However, many patients do not achieve this. The incidence of reported medication nonadherence varies greatly from 4 to 92 per cent across studies (Haynes, 1976; Meichenbaum and Turk, 1987). The reasons for such a wide variation in the reported incidence are complex and relate to discrepancies in the definition and measurement of adherence across studies. However, most reviews agree that between one third and a half of medicines prescribed for long-term medical conditions are not taken as directed (World Health Organisation, 2003).

If we assume that the prescription was appropriate for the individual patient, then this level of noncompliance with prescription recommendations is a concern for those providing, receiving or funding healthcare because it not only entails a waste of resources but also a possible missed opportunity for therapeutic benefit.

For the patient it may mean a lost opportunity for health gain or more rapid disease progression and risks of further more intensive medical intervention. Although there may be short term financial gains for the NHS if patients use fewer medicines, the wider, longer term losses of sub-optimal use of appropriate medicines are likely to be more far more significant if the patient ceases to benefit and subsequently requires more intensive treatment. The pharmaceutical industry loses revenue as low persistence results in fewer prescriptions redeemed over time.

The issue came to prominence with the classic reviews of Sackett and Haynes in 1976 and 1979 (Haynes et al, 1976; Sackett and Haynes, 1976; Haynes, Taylor, and Sackett, 1979; Sackett and Snow, 1979). Since then, thousands of published studies have investigated the determinants of medication-taking behaviour and evaluated interventions to influence it. Several comprehensive reviews of the subject have been published (Meichenbaum and Turk, 1987; Royal

Pharmaceutical Society of Great Britain, 1997; Myers and Midence, 1998; Carter, Taylor and Levenson, 2003) culminating in a World Health Organisation report in 2003 (World Health Organisation, 2003).

The WHO and previous reports offer a comprehensive summary of knowledge about the causes and consequences of nonadherence and implications for healthcare policy and practice. However, several questions remain outstanding:

1. The WHO report obviously examined the question from a global perspective and there is a need for an evaluation of the topic from the perspective of the UK NHS.
2. In common with most other reviews, the WHO review examined the issues in streams determined by disease categories (eg, adherence in hypertension, asthma, HIV etc). This is helpful in identifying key issues relating to disease priorities. However, we also need to identify where there are commonalities across diseases to construct a conceptual map of the problem and to identify causes and potential solutions that can be applied across disease states. We also need to identify where insights from research in one disease group might inform approaches in other disease conditions.
3. Several systematic reviews of interventions to facilitate adherence have been published since the WHO report and there is a need to synthesise the findings from these.
4. There is a need to clarify terminology. At least three terms are commonly used in relation to patients' medication-taking behaviour: compliance, adherence and concordance, with apparently little consensus of meaning and appropriate usage.

Aims of the scoping exercise

This report is a product of a scoping exercise commissioned by the NHS National Coordinating Centre for Service Delivery and Organisation (NCCSDO) with the following aims:

1. Summarise current knowledge about the determinants of medication-taking.
2. Construct a conceptual map of the area of compliance, adherence and concordance.
3. Identify priorities for future research of relevance to the NHS, with particular emphasis on identifying what new knowledge is needed to be able to develop effective, realisable, efficient and equitable interventions to promote the appropriate use of medicines for the benefit of patients and the NHS.

Method

One of the main objectives of the project was to provide a conceptual map to guide policy makers and researchers through this complex field, enabling them to obtain a clear overview of current knowledge and outstanding questions and to identify priorities for research.

Conceptual Map

The conceptual map is designed to guide the reader through the extensive literature on compliance, adherence and concordance. This is a complex topic, as indicated by the fact that we have three terms to describe the behaviour (taking or not taking medication). It attempts to clarify concepts, summarise our current knowledge and identify what we need to know to help get the best from medicines. The map comprises the following elements:

- An explanation of the concepts of compliance, adherence and concordance and recommendations for use of terminology.
- A summary of current knowledge about the factors influencing medication-taking, considered under four themes:
  - Theme 1 Patient perceptions and behaviour
  - Theme 2 Patient-provider interactions and healthcare communication
  - Theme 3 Societal policy and practice
  - Theme 4 Interventions

These themes were selected to represent the major perspectives underpinning research but also to provide a conceptual model of the main issues that need to be considered. The patient is at the centre and medication-taking needs to be understood as a behaviour. However, the model also stresses the importance of other factors, external to the patient, such as interactions with healthcare providers and other information sources which occur within a wider context of societal-policies and practice. Theme four spans these domains as interventions to facilitate optimum medication-taking can be targeted at one or more of these domains (see Figure 1).

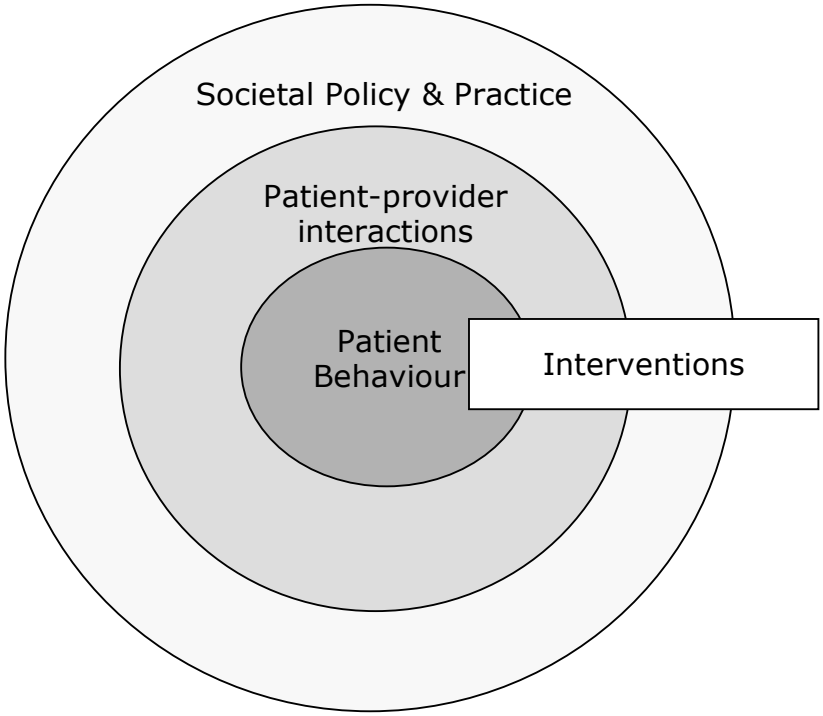

Figure 1. A conceptual map of the scoping exercise

Gathering and evaluating the evidence

The scoping exercise involved analysis of the literature, a listening exercise involving consultation with both a user group and with a group of academics, health care professionals and managers, plus feedback from an Expert Panel.

The scoping exercise did not involve an exhaustive review of the primary literature – this has already been researched to good effect and is beyond the scope and timescale of the project. We drew on good quality narrative and systematic reviews where available,. These were supplemented with literature searches to identify whether significant new knowledge had emerged since the completion of reviews. Our strategy included searches of electronic databases (MEDLINE, EMBASE, PsycINFO, Web of Science, Cochrane Review Database) and of the 'grey literature' obtained from other sources such as the websites of the Department of Health, Medical Research Council and Medicines Partnership. The task drew on the expertise of three groups:

1 A multidisciplinary Project Team.

2 A Consultation Group of stakeholders (service users, service providers and researchers).

3 An Expert Panel of nine opinion leaders within the field whose expertise complimented and extended that of the Project Team.

1) Project Team

The Project Team was a multidisciplinary group comprising five academics with extensive personal involvement in research into medication prescribing and administration and spanning the disciplines of pharmacy, health psychology, medical sociology and health economics. The Project Team evaluated the literature, derived the conceptual map and wrote the scoping report.

2) Stakeholder involvement: the Consultation Groups

The Project Team consulted widely with stakeholders in the development of the conceptual map and research priorities. We enlisted the help of a Service User Consultation Group and an Academic NHS Consultation Group.

Service User Consultation Group Early in the scoping exercise, the project team consulted with Medicines Partnership (http://www.medicines-partnership.org/), an initiative supported by the Department of Health aimed at enabling patients to get the most out of medicines by involving them as partners in decisions about treatment and supporting them in medicine taking regarding suitable patient representatives. We also consulted INVOLVE (a national advisory group, funded by the Department of Health, which aims to promote and support active public involvement in NHS, public health and social care research). Advice from INVOLVE and Medicines Partnership was pivotal to our decisions about how to elicit and incorporate user perspectives.

Academic-NHS Consultation Group This group comprised key opinion leaders on the topic of medicines prescribing and usage (see list of contributors above), who were able to attend a one-day seminar in central London. The seminar comprised a presentation from the Project Team of the scoping exercise methods and preliminary findings, followed by an open discussion in which we invited the Consultation Group to critique our methods and findings and to alert us to alternative approaches or work (published or ongoing) that we had failed to take account of.

The consultation process The stages of consultation with the various groups are shown in the project flow diagram in Figure 2. A service-user directed version of the scoping exercise protocol was posted on the Medicines Partnership website (see Appendix 1) and feedback was invited. In addition, an invitation to attend a patient representative consultation group meeting was advertised on the INVOLVE website (http://www.invo.org.uk/). Nine people responded and the panel convened on the 22nd February, 2005 (see Appendix 2 for a list of participants and a summary of issues discussed).

A second meeting was held on 14th March, 2005, and involved representatives from academia, health care professions and NHS policy and management, recruited following recommendations from both the Project Team and Expert Panel members. Both meetings generated broad and interesting discussions (see Appendix 2). This process informed the conceptual map and research priorities drafted by the Project Team and sent to the Expert Panel for comment.

An additional source of information on user perspectives on concordance, compliance and adherence that we found helpful was the review commissioned by Medicines Partnership (Carter, Taylor and Levenson, 2003). This was a narrative review of the literature on medication-taking, grouped under disease conditions. The review of medication-taking under each condition was supplemented by telephone interviews with users to seek their views. This contains a good deal of material on user perspectives and we direct the reader to it.

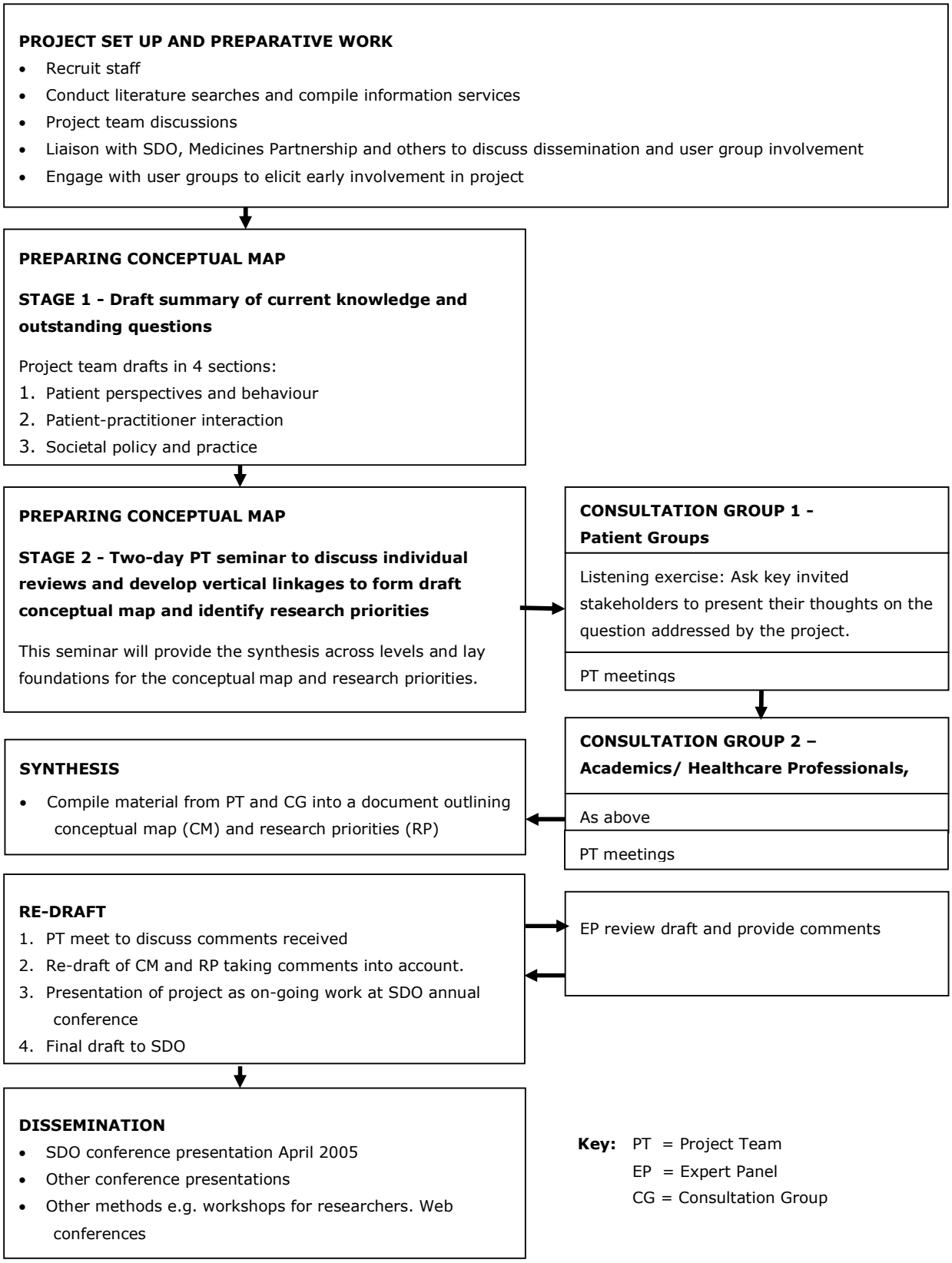

Figure 2. Flow chart of the project

3) Expert Panel

The Expert Panel consisted of nine opinion-leaders representing a range of expertise augmenting the Project Team: health informatics, health policy, medical ethics, evidence based medicine, medical education, specialist medicine, mental health, nursing, industry and NHS management. Following inclusion of the perspectives provided by the Consultation Group, the Expert Panel provided written feedback on the draft conceptual map and research priorities to the Project Team.

Following input from the Expert Panel, the Project Team reconvened to establish the nature and extent of the revisions to the conceptual map and research priorities, and subsequently presented an overview of these to the SDO annual conference. The final draft was drawn together with full input from the whole Project Team. The Project Team continue to pursue opportunities to disseminate elements of the scoping exercise via peer-reviewed journals, academic conferences, and in collaboration with Medicines Partnership.

Summary of deliverables

1 A summary of current knowledge about the process of medication-taking that identifies outstanding questions at three levels: patient, patient-provider interactions and societal policies and practice.

2 A conceptual map for understanding concordance, adherence and compliance. This map will focus on the identification of effective and realisable interventions to promote the optimum use of medicines, particularly in chronic illness, as here there is the greatest potential to enhance the quantity and quality of life.

3 A research agenda that focuses on the key areas of theory and evidence that are essential to inform future policies and practice around optimising medicines taking. This will include recommendations for the primary research, secondary research and methodology that is necessary to clarify our understanding of the process of medication-taking, as well as developing and evaluating interventions to facilitate the appropriate use of medication.

Use of the term 'patient'

Several of the service-users who we consulted over the course of this report had reservations about the term 'patient' and preferred the term 'service user,' especially when referring to particular illness categories (eg, asthma, bipolar disorder). Preference for the term 'service-user' was stronger among, but not limited to, representatives of those experiencing mental health problems.

Objection to the term 'patient' stems from its use in contexts that imply a disproportionate power imbalance between patients and doctors, where patients are expected to 'follow doctors' orders' and where involvement in decisions is discouraged. It was agreed that the term 'patient' can have positive connotations (eg, when used in connection with the Expert Patient Programme) and that the term is widely used in the literature and clinical practice without negative connotations.

After careful consideration, we decided to retain the term 'patient' within the report to be consistent with the literature and with common usage

within the Department of Health and in clinical practice within the NHS. However, we would like to stress that our use of the term is not intended to imply an expectation of a 'passive patient'. On the contrary, our approach is consistent with the notion of the respected patient, encouraged and supported by the NHS to achieve their desired level of involvement in decisions about their care and in the self-management of their condition.

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Section 2 Concepts and Terminology

Rob Horne

The subject of medication-taking has generated extensive literature and considerable controversy. The complexity of the topic is illustrated by the fact that at least three terms are commonly used in relation to medication-taking, with little apparent consensus. Other controversies include the best way to measure patients' medication-taking behaviour and the importance of compliance to medical outcomes. This chapter will attempt to explain some of the major controversies and, where possible, clarify the issues, beginning with terminology.

Compliance, adherence and concordance

Compliance Until relatively recently the most common term for following treatment instructions was 'compliance'. Compliance may be simply defined as:

'*The extent to which the patient's behaviour matches the* prescriber's *recommendations*' (Haynes, Taylor and Sackett, 1979).

Although the term compliance is commonly used in the medical and pharmaceutical literature, it has been criticised because it has negative connotations in terms of the clinician-patient relationship (Stimson, 1974). It seems to denote a relationship in which the role of the clinician is to decide on the appropriate treatment and issue the relevant instructions, whereas the role of the patient is to passively follow 'the doctor's orders'. Within this connotation, noncompliance may be interpreted as patient incompetence in being unable to follow the instructions, or worse, as deviant behaviour.

Adherence The term adherence (Barofsky, 1978) has been adopted by many, particularly within the psychological and sociological literatures, as an alternative to compliance, in an attempt to emphasise that the patient is free to decide whether to follow the prescriber's recommendations and that failure to do so should not be a reason to blame the patient. Adherence develops the definition of compliance by emphasising the need for agreement and may be defined as:

'The extent to which the patient's behaviour matches agreed recommendations from the prescriber'

Concordance The term concordance is increasingly used in relation to medication-taking. It is a complex concept originally defined as:

"a new approach to the prescribing and taking of medicines. It is an agreement reached after negotiation between a patient and a health care professional that respects the beliefs and wishes of the patient in determining whether, when and how medicines are to be taken. Although reciprocal, this is an alliance in which the health care professionals recognise the primacy of the patient's decisions about taking the recommended medications" (Medicines Partnership, 2001).

Concordance is a relatively recent term, predominantly used in the UK. Its definition has changed over time from one which focused on the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, to a wider concept which stretches from prescribing communication to patient support in medicine taking. Concordance is sometimes used, incorrectly, as a synonym for adherence.

The concept of concordance grew from a review of the literature on treatment compliance and discussions within a committee of health care researchers, clinicians and managers, established by the Royal Pharmaceutical Society of Great Britain (RPSG) and funded by Merck Sharpe and Dohme Ltd (MSD) (Royal Pharmaceutical Society of Great Britain, 1997).

The term concordance attempts to re-conceptualise the problem of compliance. It acknowledges that, for many patients, noncompliance is a rational response to their personal perceptions of the illness and treatment. Reviews of the literature had shown that noncompliance was often the outcome of a prescribing process that failed to take account of the patient's beliefs, expectations and preferences (Horne, 1993; McGavock, 1996), which could be an indicator of poor communication within the consultation. Moreover, the fault line within the consultation was the failure to recognise that patients and clinicians bring two sets of (potentially opposing) beliefs about the nature of the illness and treatment.

Consultations that ignored the patient's perspective would be more likely to lead to treatment decisions that were not 'agreed' by the patient resulting in an increased risk of noncompliance. Such consultations could be considered to be nonconcordant. Conversely, in concordant consultations, the patient's beliefs were elicited and considered to be of paramount importance (Marinker, 1997).

One label for two agendas

The fundamental problem with terminology (as discussed in more detail in Chapter 5) stems from the fact that we are trying to reconcile two agendas within one label:

1. The *scientific/clinical* agenda to describe and categorise patient behaviour - what patients actually do with prescribed medication and how it relates to what they were advised to do by the prescriber.
2. The *normative* agenda to describe what is 'right' and 'good' in relation to medication-taking.

The term 'compliance' works well in relation to the first agenda. It offers a concise definition of medication-taking behaviour that can be easily operationalised. However, it does not address the normative agenda and most of the objections to the term seem to stem from this fact. By not attempting to define a normative agenda (what is good and should happen), it seems to imply that compliance is good and noncompliance is bad.

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Concordance, adherence and compliance in medicine taking

Adherence seeks to avoid the normative problems of compliance by recognising that the patient is free to decide whether to adhere to the doctor's recommendations and that failure to do so should not be a reason to blame the patient. Adherence develops the definition of compliance by emphasising the need for agreement.

Concordance attempts to address the normative agenda. It appears to relate to both the process of prescribing consultations (eg, considering patients' views and negotiating treatment options) and their outcome (eg, shared agreement). The concordance initiative has made a valuable contribution to the debate about medication prescribing, highlighting the fact that good prescribing should entail a process of negotiation between patient and practitioner, in which the patient's views are taken into account. Few would disagree with its central tenet that prescribing should take account of patients' beliefs and expectations and involve patients as partners (with clinicians) in their own health care. However, there are a number of outstanding issues about medication-taking that are not adequately embodied within the concept of concordance. These are discussed in Chapter 5 and include:

1. Concordance is limited in its scope. It deals with normative aspects of prescribing-related consultations but does not address medication-taking. We still require terms that address the scientific/clinical agenda of describing patients' medication-taking behaviour and normative aspects of medication-taking behaviour.
2. Concordance is often used in a way that seems to imply that attaining 'concordance' will improve adherence. This may well be the case, but this is an assumption that needs to be tested.
3. Concordance does not fully address the potential tension between evidence-based medicine and patient-choice. What happens when the patient's preferences conflict with the prevailing evidence? What if a patient rejects a potentially life-saving treatment (such as immunosuppressant therapy following renal transplantation) due to erroneous interpretations of the likely risks and benefits or because of beliefs based on information that is factually incorrect? A similar set of questions apply in circumstances where the patient's preferences could result in harm to themselves or others (Horne and Weinman, 2004).
4. Concordance does not address the balance between individual rights (eg, patient autonomy) and responsibilities. There are often three parties involved in prescribing decisions: the patient, the prescriber and the payer.

Concordance has not been fully operationalised. We do not know how to recognise when it is present or absent and, without this, it is difficult to evaluate the concept through research or apply it in clinical practice (Dieppe and Horne, 2002).

These and other relevant issues are explained and discussed in more detail in Chapter 5.

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Terminology recommendations

Caution over the use of the term concordance

One unfortunate outcome of the concordance initiative is that the term concordance is now often used as a synonym for compliance or adherence (eg, '*The intervention was designed to improve patient concordance'*). This is not just a problem of semantics.

The terms 'adherence' and 'compliance' reflect different perspectives of the same phenomenon: the degree to which patients' behaviour matches the prescriber's advice. These terms describe the behaviour of one individual: the patient. Concordance is a much more complex and less clearly defined term relating to the process (eg, partnership) and outcomes (agreement or shared decision-making) of prescribing.

A clear prerequisite for a research agenda is to be clear about terminology. It is nonsensical to use the term concordance when we want to describe the behaviour of an individual (rather than their interaction with the prescriber).

More work is needed to clarify what we mean by 'good' prescribing and 'good' medicine-taking and how these concepts relate to the ethics of prescribing, communication about medicines and medicines taking. However, in the interim, we believe that there is an imperative to research better ways of helping patients to get the most from their medicines. We cannot ignore the fact that medicines need to be used in a particular way if they are to be effective and safe.

At the core of the research agenda for improved use of medicines is the need for a better understanding of how and why people make their decisions to use medicines. To achieve this, we need to assess what people actually do with medicines and the degree to which this matches the recommendations.

Adherence as the term to describe patients' behaviour

We recognised that these three terms are now used interchangeably and that this has generated some confusion. After discussion within the Project team and with our Expert Panel and Consultation Groups we recommend: *Adherence as the term of choice to describe patients' medicine taking behaviour.*

The concept of good and bad adherence clearly has no place, but referring to high or low adherence is perfectly acceptable. We use adherence to emphasise that it is the patient's right to choose whether or not to follow the doctor's recommendations and that failure to do so should not be a reason for blame.

In adopting adherence as our term of choice, we are not rejecting the principles of respect for patient beliefs and autonomy inherent within concordance. Neither are we advocating an agenda which tries to 'force' patients to take prescribed medication against their better judgements or with no consideration of their views and preferences.

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We recognise that adherence is not always a 'good' thing as a We assume that adherence is appropriate and beneficial if it follows a process that allows patients to influence the decision making if they wish, and an appropriate choice of medicine is made by the prescriber.

Informed choice and supported adherence

Our research agenda needs to go beyond the prescribing process (dealt with in the concept of concordance) to address the question of how medicines are actually taken by patients and the degree to which this matches the prescribers' recommendation (the concepts of compliance and adherence).

Finding appropriate terminology is essential because we need to answer the question: '*What are we trying to achieve when we intervene to influence the way in which patients use medication?*' We believe that neither concordance nor adherence provide, in themselves, an adequate answer to this question. Achieving a shared agreement or 'concordance' is limited if the patient is then not supported to implement their intentions to take the medication as recommended. Similarly, stipulating unconditional and unquestioning adherence to prescribers' instructions as our goal is, in most cases, not justified if the patient has not made an informed choice about taking the medication.

As an interim solution to this problem the concept of 'informed adherence' has been suggested as the behavioural implementation of a 'good' and appropriate prescription (Horne and Weinman, 2004). This term attempts to link the concepts of adherence with the notion of informed consent (see Figure 1 below). This follows Fink's notion of the 'consensual' regimen:

"A negotiated mutual contract in which both provider and client can be said to have given 'informed consent', which is practical in terms of the current set of health problems and resources, 'no-fault' attitudes towards noncompliant behaviour, and mutual responsibility for outcome" (Fink, 1976).

In most cases the patient is free to decide whether to take the treatment or not. However, the healthcare practitioner has a responsibility to help ensure that the choice is an informed one (see Box1). Informed patient choice, rather than 'compliance' is the desired outcome of the discussion. If the patient decides to accept the prescription, then the aim is to facilitate appropriate adherence to the agreed recommendations for how it should be taken to maximise its efficacy and safety for the individual and optimise benefits and reduce risk to greater good.

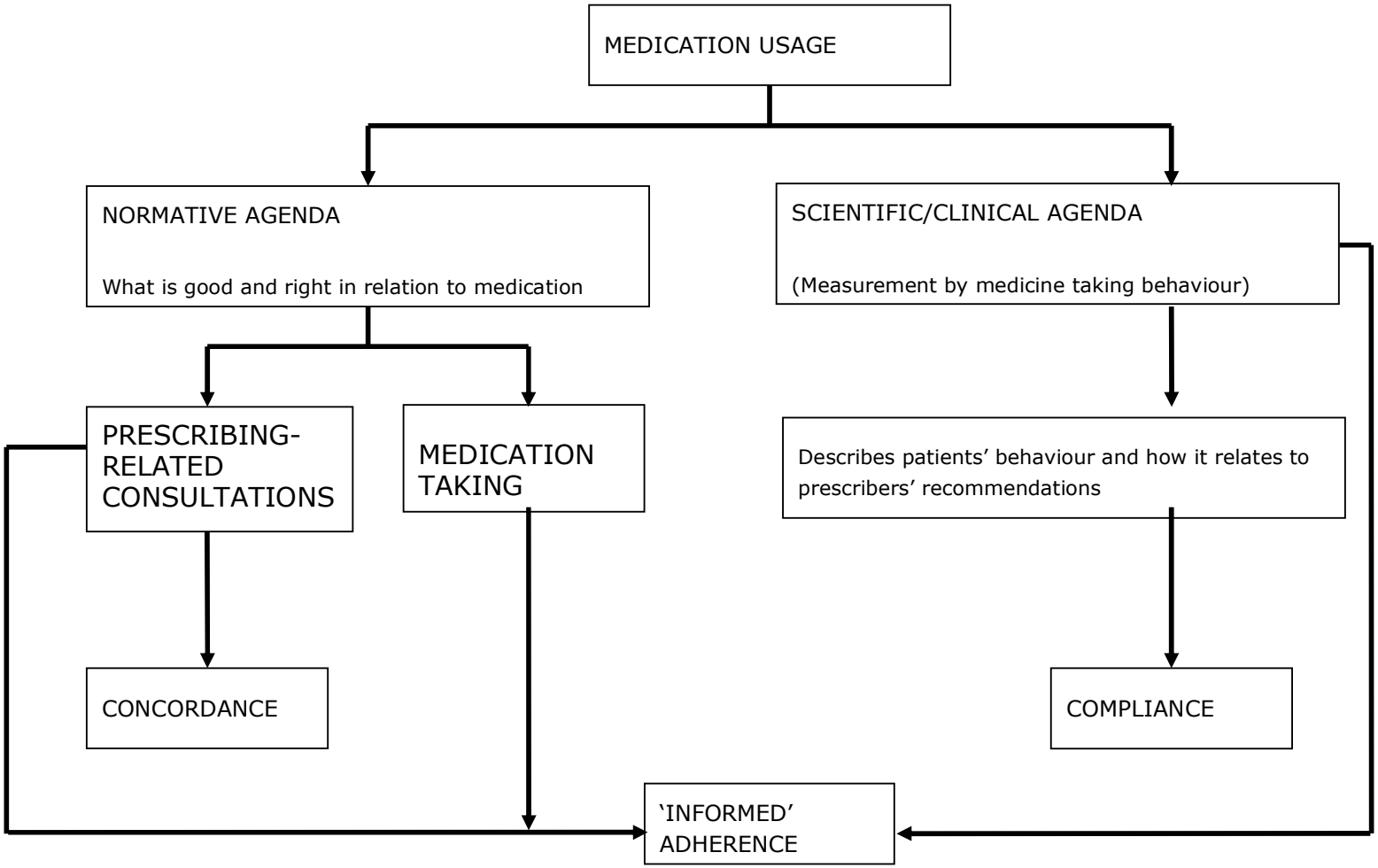

Figure 3. Terminology for medication-taking behaviour

Efforts to promote informed choice and support adherence need to be ongoing and responsive to the patient's experiences with the medication. This should go hand in hand with an evaluation of whether the prescription is still 'appropriate'.

We are not suggesting that the notions of informed choice and supported adherence (we have previously abbreviated this as 'informed adherence') address all of the problems with terminology. As later described in Chapter 5, further work is needed to clarify what we mean by 'good medication-taking' and to fully evaluate the concept of 'informed adherence'. However, in the interim, we identify *informed choice* and *supported adherence* as important target variables for interventions to facilitate optimum use of appropriately prescribed medicines.

Box 1: Informed choice and supported adherence ('Informed adherence')

Facilitating informed choice involves more than the provision of information. Michie and colleagues have outlined a model for informed choice in healthcare and this is a good starting point for discussion about informed choice in relation to adherence to medicines (Michie, Dormandy and Marteau, 2003). They propose that the key components of informed choice are knowledge and beliefs. The patient can be considered to have made an informed choice if they can demonstrate knowledge of relevant information about the screening test or the treatment and then act according to their beliefs.

We suggest that in applying this framework to choice about using treatments that are supported by a strong evidence base, the clinician has a duty that goes beyond providing information. Informing should be an active process, which involves more than simply presenting the evidence. It also entails eliciting the patient's beliefs and identifying whether pre-existing beliefs might act as a barrier to an accurate interpretation of the evidence. If the interpretation of information is influenced by misconceptions about the illness and treatment, then can the choice be truly informed?

We propose the concepts of informed choice and supported adherence as targets for consultations in which evidenced-based medicine is used to guide initial recommendations for treatment. These are then presented to patients in a way that takes account of their beliefs and preferences and attempts to help patients resolve any incompatibilities between their personal beliefs and the prevailing evidence.

We believe that this approach is not incompatible with the central tenets of concordance in that it places patients' beliefs and preferences at centre stage within the consultation. A fundamental question that can be addressed is the degree to which patients' and clinicians' beliefs and preferences match the available evidence. We are still left, of course, with the problem of uncertainty in medicine. In many cases, the available evidence will be inconclusive. Here the goal of the informed choice is to facilitate an interpretation of the available evidence that is unencumbered by misconceptions.

From Horne, R and Weinman, J. 2004. The theoretical basis of concordance and issues for research. In: Bond, C (ed) *Concordance, A Partnership in Medicine Taking*. London: The Pharmaceutical Press

When does nonadherence matter?

When should clinicians and patients worry about nonadherence? This is simple if adherence may be conceptualised as an `all or nothing' response in which the patient either follows the prescriber's instruction to the letter (adherence) or deviates from it in some way (nonadherence). But such a strict definition is of little use in practice. For most medicines, the need for total adherence is questionable. Medication dosage regimens are usually derived from dose-response data obtained from clinical trials. Variations in response to standard doses of medication observed between and within individuals mean that standard recommended dosages for most medicines are approximate. They represent the dose which is most likely to achieve maximal therapeutic benefit with minimal harm for most patients most of the time. Thus,

small deviations in adherence may add little to the variation in response inherent within the use of standardised dosages. The fact that less than 100 per cent adherence may be sufficient to bring about the desired therapeutic response suggests that a more pragmatic definition might be:

`The point below which the desired preventative or desired therapeutic result is unlikely to be achieved'

This definition raises the question: `When does nonadherence become clinically significant?' Many researchers and clinicians are understandably attracted to the idea of being able to categorise a patient as adherent or nonadherent. The problem is where to draw the line separating adequate adherence from inadequate adherence. In doing this one needs to consider not just the overall percentage of adherence but also the pattern of medication usage. Patients who have similar adherence rates may adopt very different patterns of usage as is illustrated in Figure 2 which shows Gordis's example of how 50 per cent adherence could be manifested as several very different patterns of behaviour.

Patient 1	-	-	-	-	-	+	+	+	+	+
Patient 2	+	+	+	+	+	-	-	-	-	-
Patient 3	+	-	+	-	+	-	+	-	+	-
Patient 4	+	+	-	-	-	+	+	-	+	-

Figure 4. Hypothetical results of sequential tests in four "50% compliers" (Gordis, 1979)

Faced with this problem, most researchers have taken a pragmatic approach contending that if the prescription is appropriate then the more patients' behaviour approaches the prescriber's instructions the more likely they are to benefit from the treatment. Evidence suggests that this approach is not unreasonable. For example, in a study of hypertensive patients, 80 per cent adherence to the regimen was sufficient to normalise blood pressure whereas 50 per cent adherence was insufficient to control blood pressure (Luscher, Vetter, Siegenthaler, and Vetter, 1985). A separate study of recovery rates following myocardial infarction revealed that patients who took >75 per cent of prescribed medication were approximately three times as likely to have survived after one year than those who took <75 per cent (Horwitz et al, 1990). However, some treatments are more 'forgiving' than others. For example, highly active antiretroviral treatment for HIV requires very high adherence rates (of over 95 per cent) to maintain efficacy and prevent the development of resistance (Paterson, Swindells, and Mohr, 2000). Attaining high adherence rates may be more of a priority in some situations than others.

A meta-analysis of the effects of adherence on treatment outcomes in 63 studies conducted across disease conditions found an outcome difference of 26 per cent between high and low adherence (DiMatteo, Giordani, Lepper, & Croghan, 2002). However, difference in the types of conditions and treatments and the way in which adherence was measured in separate studies prevents a definitive interpretation of the findings.

The extent of adherence necessary to achieve the desired effect varies between medications and between and within individuals. Further work is needed to develop a framework for identifying the priorities for high adherence and for establishing optimal adherence patterns for individual patients and treatments.

Can nonadherence be good for patients?

Nonadherence may not always be bad for the patient. It may be protective if the prescription is inappropriate and potentially toxic or have a neutral effect if the prescription is sub-optimal. In their classic review of the topic, Sackett and colleagues (1985) acknowledged that the prescription of a medicine is a 'therapeutic experiment,' the outcome of which is influenced by actions of the practitioner, in selecting an appropriate diagnosis and treatment, as well as the patient in adhering to the regimen.

In assessing the effects of the 'therapeutic experiment,' reviews of adherence and the appropriateness of the prescription should go hand in hand. Recognising the fallibility of the practitioner as prescriber emphasises the point that high adherence does not necessarily result in benefit to the patient. It highlights the fact that patients and practitioner carry mutual responsibility for the outcome of the therapeutic experiment. Health care practitioners (HCPs) have a responsibility to work with patients to identify treatments that are potentially appropriate, to help patients to make an informed choice about whether and how to use the medicine and then to support informed adherence to the regimen.

Identifying and measuring nonadherence

Types of nonadherence to medication

Three broad categories of medication nonadherence have been described in the literature:

Original prescription not filled Studies have shown that between five and 20 per cent of primary care patients fail to present the prescription for dispensing in the first place; this has been termed primary noncompliance (Beardon, McGilchrist, McKendrick and MacDonald, 1993; Begg, 1984; Rashid, 1982).

Refills not obtained This problem was illustrated in a study in which only 10 per cent of a sample of over 7000 patients with chronic heart failure filled enough prescriptions to ensure a regular daily supply of medication (Monane, Bohn, Gurwitz, Glynn and Avorn, 1994).

Suboptimal dosing Most of the published studies in the adherence area have focused on what the patient does with the medication once it has been dispensed. In this context, adherence may be categorical or incremental. In categorical definitions patients are judged to be adherent

or nonadherent based on the amount of medication taken in relation to a defined 'cut-off' point. Incremental definitions conceptualise adherence as a continuum.

Adherence assessment tools

In common with other assessment of behaviour, the measurement of patients' adherence to medication is fraught with difficulties (Gordis, 1979). One of the problems of measuring behaviours, such as adherence to treatment, is that the act of measurement can itself influence the behaviour. The measurement of adherence is vulnerable to reactivity and self-presentational bias on the part of the patient. Reactivity is the tendency of attention from others to influence behaviour. If patients are aware that their adherence is being monitored, this might stimulate adherence simply by drawing attention to the behaviour. This is because of self-presentational bias. Patients may perceive that adherence to treatment is one of the duties expected of the `good patient' and may be reluctant to admit to nonadherence because they fear that this will offend or disappoint their doctor or risk their disapproval. Consequently, in an attempt to present themselves as more adherent, patients may create a falsely elevated adherence score by taking more medication immediately prior to testing or by under-reporting nonadherence.

Adherence measures can be divided into two categories according to whether the assessment is direct or indirect. Direct measurement entails observing the ingestion of the drug or by detecting its presence in body fluids. Indirect measures assume ingestion based on proxy-evidence, such as the patient's report or number of dosages removed from a container. The strengths and weaknesses of direct and indirect methods are reviewed elsewhere (Horne, 2000) but the following section outlines the key issues relating to two of the most commonly used methods: electronic monitoring and patient self-report.

Electronic monitoring

This method is currently thought to be the 'gold standard' and has the potential to provide a detailed profile of usage over time. However, it is not without problems. The opening of the container does not guarantee ingestion of the medication: the dose might simply be discarded. Ethically, patients have to be told in advance that their adherence behaviour is being monitored with the risk that this might lead to temporary improvements in adherence as patients modify their behaviour to match the expectations of the observer. Moreover, electronic monitors cannot be fitted to many of the dosage forms and packaging used in routine care. Electronic monitoring is also expensive and does not provide information about the type of nonadherence (intentional or unintentional). These limitations mean that this technique may be less suitable for use in naturalistic studies and clinical practice than for use in clinical trials.

Patient self-report

Eliciting patients' self-reported adherence may be an inexpensive alternative to electronic monitoring for use in naturalistic studies and clinical practice (Garber, Nau, Erickson, Aikens and Lawrence, 2004). A recent review (Dunbar and Waszak, 1990) has confirmed that such measures generally concord with 'objective' measures, although some variation in agreement was found. The utility of adherence

questionnaires is, however, limited by several problems. Patients may exaggerate their adherence if they believe that reports of nonadherence will disappoint their clinician (Gordis, Markowitz and Lilienfeld, 1969; Haynes et al, 1980). This means that the accuracy of self-report varies according to the type of adherence. Reports of low adherence are more accurate than reports of high adherence (Haynes et al, 1980; Morisky, Green and Levine, 1986). The wording of questionnaire items may exacerbate this problem. For example, one item in a questionnaire developed by Morisky et al (1986) describes nonadherence as 'careless' behaviour, a description that might be misinterpreted as judgmental and cause the patient reluctance to truthfully report nonadherent behaviour. A further problem occurs if questionnaire items combine reports of nonadherence with reasons for nonadherence. For example, an item such as: 'I take less medication if I am feeling better' is difficult for patients to interpret. How should patients respond if they take less medication, but not because they feel better? Published self-report measures need to be refined but this is currently on-going with new techniques and methods showing early promise (Horne, 2004).

Conclusions regarding measurement of adherence

There is currently no 'gold standard' measure of adherence which can be used within the resource restraints of studies outside the controlled conditions of clinical trials. Interpreting studies comparing the performance of various adherence measures is therefore difficult. Each of the available methods have certain flaws which limit the accuracy, reliability or practical application of the technique. With the possible exception of electronic measurement devices, such as the MEMS, most of the available techniques function as indicators of adherence rather than exact, quantitative measures of behaviour. Thus the choice of adherence measures represents a compromise in which accuracy and comprehensiveness of the measure is balanced against reactivity, and the practical, ethical and cost limitations. Valid and reliable self-report scales appear to offer advantages for assessing adherence in 'naturalistic' studies (eg, following up a group of chronically ill patients who are treated in the community) and may have the potential for more widespread application in clinical practice.

A simple, valid and reliable method for detecting the prevalence and type of nonadherence would be useful to researchers conducting naturalistic studies of adherence and to health care professionals (Marinker, 1997; Marinker and Shaw, 2003). However, further evidence is required before we can recommend the use of self-report measures as the sole outcome measure in adherence intervention studies. In situations where study subjects receive an intervention designed to enhance adherence, self-presentational bias might be expected to be enhanced in the treatment group relative to the control. For this reason, there is increasing interest in techniques for combining information from self-report with other adherence indicators such as prescription collection records to produce amalgamated assessments (Horne, 2004).

The need for honest disclosure of nonadherence

One of the main problems with adherence assessment in clinical practice is that most nonadherence remains undisclosed. Patients rarely volunteer reports of nonadherence and professionals rarely ask. If they do, then many patients are reluctant to give truthful reports of

nonadherence because they fear that this will offend the prescriber. One of the urgent requirements, therefore, is to develop methods and techniques for facilitating honest disclosure of medication-taking behaviour, and open, non-judgemental discussions about adherence within medication-related consultations.

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Section 3 Explaining patients' behaviour

Myfanwy Morgan & Rob Horne

Introduction

This chapter summarises current knowledge about the causes of nonadherence. It draws on a range of narrative reviews and reports beginning with the seminal work of Haynes and Sackett (Haynes et al, 1976; Haynes, Taylor, and Sackett, 1979; Sackett and Haynes, 1976; Sackett and Snow, 1979) through to a recent report by the World Health Organisation (2003). The literature comprises hundreds of studies that have attempted to explain patients' medication-taking behaviour and spans several disciplines, including medicine, pharmacy, nursing, epidemiology, anthropology, sociology and psychology.

Communalities across disciplines We initially attempted to map this literature according to its disciplinary origin and framework. However, detailed disciplinary mapping was not successful in view of the considerable overlap and interaction between approaches. For example, it is difficult to maintain a distinction between sociological and anthropological studies in this area as they share common frameworks and both employ qualitative methods. Common ideas and findings have also been found between psychological and sociological approaches to medicines use, making it difficult to draw rigid boundaries. We have therefore identified a broad distinction between (a) studies adopting an epidemiological/clinical approach and focusing on the causes of patient 'default' from prescribed treatment regimes; and (b) studies that examine patients' perceptions and intentions regarding their medicines use.

Communalities across diseases Much of the research in the adherence field has studied particular medical conditions. However, this has demonstrated important commonalities, with key dimensions of patients' beliefs and behaviours characterising all medical conditions and treatments. Also, although it is assumed that adherence problems are less likely in more serious conditions, a recent review of the evidence showed that nonadherence is not significantly related to the type or severity of disease with rates of between 25 and 30 per cent noted across 17 disease conditions (DiMatteo, 2004). Low rates of adherence to medication are prevalent in most serious illnesses, including heart disease (Horwitz et al, 1990; Monane, Bohn, Gurwitz, Glynn and Avorn, 1994), asthma (Yeung, O'Connor, Parry and Cochrane, 1994), diabetes (Glasgow, McCaul and Scafer, 1986), cancer (Lilleyman and Lennard, 1996), kidney disease (Cleary, Matzke, Alexander and Joy, 1995) and following organ transplantation (Hilbrands, Hoitsma and Koene, 1995). We have therefore emphasised the commonalities rather than focus on particular conditions, but have also noted the significance of some specific aspects of conditions and treatments in relation to medicines use (eg, HIV, epilepsy and mental illness).

Research themes Studies have used a wide range of approaches spanning several disciplines including medicine, pharmacy, nursing, epidemiology, anthropology, sociology and psychology.

It is possible to separate three broad approaches:

1. Epidemiological/clinical approaches describe the incidence of nonadherence and explain the causes of nonadherence by identifying the factors distinguishing adherent from nonadherent patients. Much of the early research used this approach, investigating whether nonadherence could be explained by sociodemographic (such as age, gender, educational status and social class) and clinical (e.g. disease or treatment) factors.
2. Information and patient knowledge approaches focus on lack of knowledge and poor comprehension of treatment instructions as important causes of nonadherence.
3. Psychosocial approaches conceptualise adherence as a behaviour that varies within as well as between individuals, and which can be best understood in terms of patients' motivation and capacity to follow the treatment recommendations. This approach emphasises the patient as an active agent whose medication-taking behaviour is determined by their beliefs, preferences and resources. A key element of this approach was an attempt to understand the 'patients' world' and their perspectives on the illness and treatment. Early studies used qualitative methods in small sample interview-based studies to examine patients' beliefs and behaviour and their perspectives of illness and treatment. Later studies have built on this work using quantitative approaches to assess patients' beliefs about illness and treatment and how beliefs relate to adherence behaviour.

The present chapter attempts to provide a conceptual map through this literature, summarising the main findings of research across different disciplines and approaches. Its aim is to identify the key determinants of medication-taking behaviour and summarise our understanding of patients' perspectives of adherence.

Overview of explanatory factors

Regimen complexity

The complexity and demands of the treatment regimen are potential causes of nonadherence. A systematic review found that the prescribed number of doses per day is inversely related to adherence, with adherence being significantly higher for once-daily versus 3-times daily and twice daily, versus 4-times daily, dosing (Claxton, Cramer, and Pierce, 2001). Simplifying the drug regime has some positive effect on adherence, with once or twice daily dosing producing higher levels of adherence compared with medicines taken three or four times a day (Fish and Lung, 2001). Moreover, although simplifying a complex regimen may facilitate adherence, there is little to support the notion that reducing from twice to once a day, as a single strategy, is a panacea for nonadherence (Claxton et al, 2001). Complexity *per se* is not the key issue but how well the treatment fits in with the individual patient's routine, expectations and preferences.

Socio-demographic variables

There are few consistent findings regarding the influence of patients' socio-demographic characteristics (eg, gender, ethnicity, socio-economic status or education) on adherence, with the effects of these characteristics mainly identified as weak and inconsistent (Ockene et al, 2002). Furthermore, these socio-demographic variables comprise a 'black box' in that they encompass a large number of possible influences rather than providing an explanation that can inform interventions. Relations between adherence and demographic variables can be used to target interventions but do not tell us about the content of the interventions. One of the stronger associations is between older age and nonadherence. People aged 75 years and over form a group of high medicine users, with four in five people aged over 75 years in the UK being prescribed at least one medicine and 36 per cent prescribed four or more medicines (Department of Health, 2001). Some research suggests that older people are more likely to keep to a regimen prescribed for them than are younger people (Park et al, 1999). However, a number of studies indicate that people aged 75 years and over are at increased risk of nonadherence. This is mainly due to them not understanding drug regimes and forgetting and is attributed to a greater prevalence of cognitive problems, multiple pathology and high rates of polypharmacy (Dunbar-Jacob and Mortimer, 2001). However, there is also evidence that elderly patients intentionally alter their medication regimes (Barber, Parsons, Clifford, Darracott and Horne, 2004; Cooper, Love and Raffoul, 1982).

Information and patient knowledge

The relationship between a patient's knowledge of their medication regimen and their adherence to it is not simple or clear-cut. Haynes (1976) in his classic review of the adherence literature, concluded that although 12 studies had demonstrated a positive association between knowledge and adherence, at least twice as many, more methodologically sound studies, had failed to demonstrate a link. Studies conducted since then generally reinforce the view that that associations between knowledge and adherence are at best small and inconsistent (Haynes et al, 1978; Lee, Wing and Wong, 1992; Eagleton, Walker and Barber, 1993) and that enhancing knowledge does not necessarily improve adherence (George, Waters and Nicholas, 1983).

Research focusing on knowledge as the primary determinant of adherence is flawed for two major reasons. First, many of the studies linking knowledge and adherence have used cross-sectional designs. This means that it is difficult to assign causality. Are patients less adherent because they lack knowledge or are nonadherent patients less interested in their treatment and so do not seek out information? Second, inconsistencies in the association between knowledge and adherence suggest that medication knowledge is not a unitary concept, and instead comprises different components. For example, patients may know how to take the medication but not know how to judge whether it is working or what the common side effects are (Ascione, Kirscht and Shimp, 1986). The observed inconsistencies in relations between medication knowledge and adherence may therefore be partially explained by variations in the way in which medication knowledge is conceptualised and measured.

The failure of research to identify strong or consistent links between knowledge and adherence does not mean that knowledge is

unimportant. Clearly, a certain level of knowledge about the treatment and how to use it is an essential prerequisite for appropriate usage (Raynor, Booth and Blenkinsopp, 1993). However, we should not assume that all we need do to prevent nonadherence is to give patients clear information about how to use their treatment. Adherence research which focuses only on patients' knowledge of the regimen fails to take account of the fact that nonadherence may arise from an active decision on the part of the patient and may not simply be due to a lack of competence or lack of knowledge about how to use the medication.

Memory and recall[8]

A study of patient recall of prescription instructions indicated that patients are able to recall less than 50 per cent of the prescription information presented (Anderson, Dodman, Kopelman and Fleming, 1979), a figure borne out in a review of a range of recall performance across patient groups by Ley (1988) that reported that between 35 and 53 per cent of material was not recalled by patients. Memory performance has been found to correlate with reduced adherence in patients with HIV infection (Hinkin et al, 2002), chronic obstructive pulmonary disease (Incalzi et al, 1997), elderly patients with type 2 diabetes (Vedhara et al, 2004), and generally among elderly patients (Isaac and Tamblyn, 1993). Accurate recall of instructions for medicine taking is a prerequisite for adherence (Kessels, 2003). Studies indicate that almost half of medicine taking information recalled by patients is incorrect. Whilse individual factors, such as intelligence (Ley, 1988), have been found to predict recall of medicine information, research has concentrated on the qualities of the information provided. Key factors relating to recall include primacy (Ley, 1972; 1982), with the information presented earliest being recalled most accurately; perceived importance (Ley, 1972); and simplicity (Ley, 1982), with the mean amount of information recalled decreasing as the amount of information presented is increased (McGuire, 1996).

However, poor recall of instructions is only one aspect of memory influencing adherence. A common barrier to adherence is simply forgetting to take the medication at the prescribed time. Unfortunately, existing research does not provide a clear indication of how to help patients overcome this barrier to adherence. The development of effective reminders is a key priority. Advances in automated telephone technology offer an interesting possibility. Automated calls with a telephone nurse follow-up, compared to usual care, improved self-care and glycaemia control among vulnerable patients with diabetes in a USA study (Piette, Weinberger and McPhee, 2000). However, further research is needed to evaluate the efficacy and patient acceptability of this method within the UK. (The development of adherence support technologies is included as a research priority in Chapter 6).

A possible area for future research relates to the concept of 'implementation intentions' or action plans (Gollwitzer, 1999; Gollwitzer

[8] We would like to thank Dr Ian Kellar (Centre for Health Care Research) for his help in compiling this section.

& Brandstatter, 1997). Implementation intentions tie specific behaviours to environmental cues by prompting the planning of when and how the behaviour can be carried out (eg, When I make my cup of tea every morning, I will take my anti-hypertensive medication). There is preliminary evidence that these simple plans can facilitate the adoption of health-related behaviours, such as resuming activities after joint replacement surgery and taking vitamin supplements (Sheeran and Orbell, 1999). Further research is required to investigate the effect of forming implementation intentions on medication adherence among clinical populations.

Prescription costs

Cost and access barriers are identified as important influences on the uptake of prescriptions and repeat medicines are of particular significance in health systems with a high cost of co-payments and deductibles (Mossialos and McKee, 2003). These factors have a particular influence on medicines use among more disadvantaged groups in situations where charges are levied. Research seems to suggest that it is not income *per se* that is important but the specific cost-sharing arrangements of different health systems which determine how much a patient has to pay in co-payments and deductibles for their specific medicine (Piette, Heisler, and Wagner, 2004). (The issue of prescription payments is discussed in more detail in Chapter 4).

Although cost to the payer has been found to be related to nonadherence in the United States of America (USA) (Piette et al, 2004), relatively little work has been done in the UK on this issue. A recent qualitative study involving 31 UK participants found that: 'the management behaviour of those participants who had to pay for their prescriptions, particularly those from less-affluent or deprived backgrounds, was influenced by cost. However, cost was not the overriding influence, with other factors, such as symptom or disease severity, effectiveness, or necessity of treatment, playing a more important part in participants' 'management decisions.'(Schafheutle, Hassell, Noyce and Weiss, 2002).

The effects of the healthcare system and economic environment on adherence are discussed in more detail in Chapter 4. These are important external factors influencing patients' decisions about starting and persisting with prescribed medication and their capacity to implement intention to take the medication. However, it is clear that these factors influence some patients more than others as there is wide variation in adherence among populations from a similar socio-economic background and type of health system.

Social support and adherence

A recent systematic review of 122 studies, published between 1948 and 2001, found significant relationships between adherence to medical treatment and social support. Several types of support were examined including practical, emotional, and uni-dimensional social support; family cohesiveness and conflict; marital status; and living arrangements of adults. Practical support had the highest correlation with adherence, with patients who received practical support being 3.6 times more likely to adhere than those who did not (DiMatteo, 2004a).

However, many questions about the relationship between social support and medication adherence remain unanswered. The DiMatteo review mentioned above was not limited to medication adherence but included studies investigating other behaviours such as adherence to appointments and dietary advice. Moreover, the authors point out limitations in the literature, such as wide variation in the definition and measurement of social support and the paucity of prospective studies making it difficult to establish cause and effect. Furthermore, we know little about the effects of social support across different diseases and treatments or about the moderators of the social support-adherence relationship. In conclusion, it seems that social support may help some individuals overcome the barriers to adherence. However, we know little about the type of support that is likely to be effective or how to match support to individual needs.

Depression and anxiety

A meta-analysis of 25 high quality studies investigating the relationship between depression (12 studies) and anxiety (13 studies) found that associations between anxiety and nonadherence were variable, and their mean effect sizes were small and non-significant (DiMatteo, Lepper, and Croghan, 2000). However, the relationship between depression and nonadherence to medication prescribed for chronic illnesses (other than depression) was substantial. The mean effect sizes were significant with depressed patients tending to be three times more likely than non-depressed patients to be nonadherent. The 12 depression studies were categorised into two groups: renal disease or renal transplant (six studies) and other diseases including rheumatoid arthritis, cancer and general medical care (six studies). The effects of depression on adherence were fairly uniform across the disease categories.

The available studies do not give a definite picture of causality. Depression may affect adherence in several ways. Depressed mood may accentuate concerns about the illness and treatment leading to intentional nonadherence. It may also lead to apathy and reduce patients' capacity to adhere to the regimes. Research using longitudinal designs is necessary to identify the mechanism underlying the observed relationship between depression and adherence and whether treating depression improves adherence.

Patients' beliefs

A range of studies of patients' beliefs and adherence have been published within the sociological and psychological literatures. These have been reviewed elsewhere (Horne, 1997 and Pound et al, 2005). We can separate out two major strands within this literature:

1 Studies of patients' perceptions of medicines. This has comprised qualitative approaches, largely from the sociological literature, identifying a range of lay beliefs about medicines which often appear to differ from the medical/scientific view. This work has been augmented by quantitative approaches, largely from the psychological literature, to develop valid and reliable methods for assessing the salient beliefs influencing adherence to medicines and encompass them within a parsimonious framework. A key aim of this research was to quantify, using statistical approaches, the relationship between medication beliefs and adherence, and to develop theoretical models of adherence.

2 Research aimed at understanding the broader context of patients' decisions about taking medication, which considers how people perceive and manage illness. This research has helped develop a more comprehensive framework for explaining adherence. This has improved our understanding of how we process and interpret information about illness and treatment and how this and other factors shape our views about medicines and our decisions about adherence.

We will now discuss each of these approaches in turn, synthesising the main findings from the sociological and psychological literature. Studies have employed both qualitative and quantitative approaches and have originated from both sociological and psychological theories. However, there is considerable consistency and synergy between the findings from these separate disciplinary approaches.

Patients' perceptions of prescribed medicines

Since the early 1980s a number of qualitative studies of patient groups have explored the reasons for patients' medication decisions. The aim was to examine the meanings that guide patients' actions rather than assessing and explaining deviation from some norm. Reviews of qualitative studies have demonstrated the existence of shared patterns of beliefs and practices across several medical conditions and across a range of locations and cultures (primarily within the USA, UK and Europe). These comprise both narrative reviews (Blaxter and Britten; 1996; Horne, 1997; McGavrock, Britten, and Weinman, 1996) and a recent synthesis by Pound et al (2005) of 38 qualitative studies undertaken using methods of meta-ethnography (Noblit and Hare, 1988).

Concerns about potential adverse effects

When asked to talk about medicines in qualitative studies, people often seemed to take the benefits for granted and express a variety of beliefs about the dangers of prescribed medicines (see Box 1 for a summary). In this representation, the harmful effects of medication are intrinsic, so that one cannot have the positive effects without the negative. Efficacy and toxicity somehow go hand in hand and that more effective medicines implicitly, have more side-effects (Lorish, Richards, and Brown, 1990).

Quantitative studies showed that these beliefs could be grouped under a single theme of *concerns* about medication (Horne, Weinman, and Hankins, 1999). For example, if people believe that medication could cause dependence they also tend to worry about long term effects and about the capacity of medicines to disrupt their lives. One obvious source of concern is the experience of symptoms as medication 'side-effects' and the disruptive effects of medication on daily living; but this is not the whole picture. Many patients receiving regular medication, who have not experienced adverse effects, are still worried about possible problems in the future (see Box 1). These core concerns seem to be fairly generic and relevant across a range of disease states and cultures, and they are typically endorsed by over a third of study participants (Horne et al, 1999 and Horne and Weinman, 1999). Other concerns are specific to the particular class of medicine (Horne and Weinman, 2002). For example, worries that corticosteroid inhalers prescribed for asthma will result in weight gain (Hand and Bradley, 1996) or that regular use of analgesic

medication now will make it less effective in the future (Gill and Williams, 2001).

Box 1 Beliefs about the harmful effects of medication: examples from qualitative research

Harmful side-effects. Fears of experiencing or the actual experience of harmful effects of prescribed medicines appear to be fairly universal and are associated with perceptions of the 'power' of medicines to do harm as well as good. There is some evidence that certain medicines, such as corticosteroids (Cochrane, Horne, and Chanez, 1999) and antiretrovirals may be perceived by the patients to be particularly 'risky' or dangerous (Siegel, Dean, and Schrimshaw, 1999), leading some patients to question whether it is worth starting (Cooper, Buick et al, 2002) or persisting with treatment (Siegel and Gorey, 1997).

Addiction and dependence. A recurring theme associated with negative attitudes to medicine is the notion that chronic use of medication carries the risk of dependence or addiction. It is difficult to pinpoint the precise meaning of these terms and they are often used interchangeably by patients. In a medical context, `addiction' is usually defined as a state of psychological and physical dependence. Relatively few medicines are thought to have this property which is generally limited to psycho-active/mood altering drugs. However, fear of becoming addicted or `too dependent' on medication has emerged in several qualitative studies of medical conditions including rheumatic diseases (Donovan and Blake, 1992), epilepsy (Conrad, 1985), asthma (Adams, Pill, and Jones, 1997) and hypertension (Morgan and Watkins, 1988). Notions of addiction or dependence seem to be linked to the perception of having to take medication as a `threat to self reliance.'(Conrad, 1985).

Immunity and tolerance. The notion of becoming `immune' to the beneficial effects of the medication has been noted among rheumatology patients in the UK (Donovan and Blake, 1992) and in the USA (Lorish et al, 1990), who were concerned that after regular use the medication would lose its analgesic effects.

Long-term harmful effects and accumulation within the body. This refers to general fears noted by a small number of studies that taking powerful drugs over a long period may lead to harmful effects that are as yet unanticipated (Morgan, 1996; Boath and Blenkinsopp, 1997).

Masking symptoms. A few studies of cancer and HIV, describe some patients as being concerned that the prescribed drugs may mask other symptoms that might indicate a more serious condition that they should be aware of (Boath and Blenkinsopp, 1997; Ersek, Kraybill, and Hansberry, 1999).

***Chemical vs natural*.** This representation relates to the perceived means of production of medicines. Although the term `natural' was not clearly defined, labelling of a treatment in this context was associated with a value judgement in which `natural' remedies were seen as safer than `unnatural' medicines, and that the dangerous aspects of medication were linked to their chemical/unnatural origins (Conrad, 1985; Gabe and Thorogood, 1986).

Necessity beliefs

Studies across medical conditions show that people prescribed the same medication for the same condition, differ in their perceptions of personal need for it (Horne et al, 1999). It is worth noting that perceived necessity is not the same as perceived efficacy. We might believe that a treatment will be effective but at the same time not see a personal need for the treatment. Conversely, we might perceive a strong need for a treatment that we believe to be only moderately effective, because we know that it is the only treatment that is available. Although views about efficacy are likely to contribute to perceived need, the constructs are not synonymous.

Public perceptions of pharmaceuticals

Perceptions of specific medicines are related to more general beliefs about medicines as a whole. Many people are suspicious about medicines perceiving them to be fundamentally harmful substances that are over-prescribed by doctors (Britten, 1994 and Fallsberg, 1991). This view is linked to wider concerns about chemicals in the environment (Gupta and Horne, 2001) and about scientific medicine, with a lack of trust in doctors (Calnan, Montaner and Horne, 2005) and an increasing interest in alternative or complementary health care. People with a more negative orientation to medicines in general tend to have stronger concerns about the potential adverse effects of prescribed medication and are consequently less adherent (Horne and Weinman, 1999).

Beliefs about medicines as a class of treatment are likely to influence a patient's expectations of a new prescription offered by the clinic, be they positive (eg, 'I think it will help and is just what I need') or negative (eg, 'I am likely to get side effects or encounter problems with this treatment'). These initial expectations influence how subsequent events are interpreted - for example whether symptoms are attributed to the illness or the treatment (Siegel et al, 1999). They may even influence outcome directly through the placebo/nocebo effect (see Di Blasi, Harkness, Ernst, Georgiou and Kleijnen, 2001, for a review of non-specific effects).

We can only speculate on the origins of this view. In modern society, the mass media is identified as a major vehicle for 'mediating' cultural meanings and depicts both the 'wonders' of modern medicine with its 'magic bullets' or 'miracle drugs', but also its risks that include the Thalidomide 'tragedy' of the 1960s, the effects of Opren among elderly people in the 1980s and a number of scares about oral contraceptives. The mass media thus both creates and conveys images of pharmaceuticals that may shape lay views and provide a critical 'frame' within which medicine itself and perceptions of health risks are interpreted and understood (Gabe, Gustafsson and Bury, 1991; Gabe and Bury, 1996). One possibility is that information about a particular medicine (eg, speculation in the press that anti-depressants are 'addictive') might feed into a 'general schema' and be extrapolated to mean that 'most medicines are addictive' (Horne, 2003).

Negative experiences with medicines in the past (self or significant others) are also likely to have an effect. Research examining the cultural meanings of medicines suggests that patients' beliefs about medicines are not purely derived in the health care arena, but are also influenced by prevailing cultural meanings as well as by their own personal

experiences of prescribed treatment and the experiences of members of their social network. Pound et al. (2005) suggest that for people who choose not to comply with prescribed medicines, their response to prescribed medicine is best captured by the concept of 'resistance.' The extent of resistance may vary among different groups of the population (Beck et al, 1999 and Morgan, 1996) and this will be discussed later in this chapter.

Negative beliefs about pharmaceuticals may bias the individual against prescribed treatments – even before they have experienced them (Cooper, Horne, Gellaitry, Lambert and Fisher, 2002). However, the converse may also be true. Overly positive views about medication may lead to inappropriate demands for prescriptions (Boath and Blenkinsopp, 1997). This could be particularly problematic in developing countries if expensive pharmaceuticals (such as antibiotics) are purchased for the treatment of routine or self-limiting conditions (such as uncomplicated diarrhoea) for which simpler and cheaper treatments are adequate (Haak, 1988).

Balancing perceived necessity and concerns

Studies involving patients from a range of illness groups including asthma (Horne and Weinman, 2002), renal disease (Horne, Sumner, Jubraj, Weinman and Frost, 2001), cancer and coronary heart disease (Horne and Weinman, 1999), hypertension (Ross, Walker and MacLeod, 2004), HIV/Aids (Horne et al, 2001), haemophilia (Llewellyn, Miners, Lee, Harrington and Weinman, 2003) and rheumatoid arthritis (Neame and Hammond, 2005) have found that low rates of adherence are related to doubts about personal need for medication and concerns about potential adverse effects. This suggests that simple benefit-risk models, such as the necessity-concerns framework, may be a potentially useful way of operationalising the key beliefs influencing adherence.

Evidence from these studies and the qualitative research described earlier are consistent with the notion that many patients engage in 'common-sense' medication use that involves minimising intake by reducing the dose and/or frequency of doses, taking drug 'holidays' or stopping altogether. These ways of adjusting (generally reducing) the drugs, are a rational and understandable action in the context of patients' own beliefs and experiences, the information available to them, and the wider social context, although often do not correspond with technical-biological knowledge. Central to patients' use of prescribed medicines is their judgement of their personal need for it. Moreover, treatment necessity is evaluated relative to concerns about potential and actual adverse effects (Horne and Weinman, 1999). This involves the use of experiential knowledge together with sources of information both within and outside the health care arena. The evaluation may be implicit as well as explicit.

Testing ongoing need for medication

Necessity beliefs may change over time as patients evaluate the effects of their medication (Cooper, 2004). Many patients prescribed long-term treatments 'test' their need for the medication, through altering the dose or stopping the medicine and observing or monitoring the effects (Pound et al, 2005). Testing may be an explicit or a subconscious act and has been described in relation to a wide range of medicines, including non-steroidal anti-inflammatory medicines for arthritis

(Donovan and Blake, 1992), anti-hypertensive medication (Benson and Britten; 2002; Britten, 1996), asthma inhalers (Buston and Wood, 2000) and antiretroviral therapy (Siegel, Schrimshaw and Raveis, 2000). However, people sometimes find it difficult to distinguish the effects of the medicine from the effects of their illness. For example, people taking anti-hypertensive medication often need to rely on blood pressure measurement as an objective indicator of whether the medicines are having the desired effect (Morgan, 1996).

Operationalising theoretical models of health-related behaviour

Several theoretical models have been developed to explain how people initiate and maintain actions to preserve or improve health status. These models, often collectively referred to as social-cognition models (SCMs), share the common assumption that the motivation to engage in and maintain health-related behaviours arises from beliefs that influence the interpretation of information and experiences and guide behaviour. Examples include the Health Belief Model (Rosenstock, 1990), Theory of Planned Behaviour (Azjen, 1985) and Leventhal's Self-regulatory Theory or Common Sense Model (Leventhal, Leventhal and Contrada, 1998). These models and their application to explaining health behaviours (Conner and Norman, 1996) and adherence to treatment (Horne and Weinman, 1998) are reviewed elsewhere. Relatively few studies have used these approaches to explaining adherence to medication in chronic illness or as a basis for developing interventions. However, the necessity-concerns framework might be used as a basis for operationalising some of the salient beliefs about treatment within these models. There is preliminary evidence that the necessity-concerns framework can be used to operationalise Leventhal's self-regulatory theory to explain nonadherence to medication in chronic illness (Horne, 2003; Horne and Weinman, 2002). A more detailed discussion of psychological theories relevant to medication adherence is presented in Appendix 4.

Symptom perceptions and beliefs about illness

Patients' expectations and experiences of symptoms influence both the initial perceptions of need for medication and subsequent appraisal of how well the treatment is working. The effect of symptom experiences on views about medication necessity may be quite complex. At one level symptoms stimulate medication use by acting as a reminder or by reinforcing perceptions of need. Conversely, the absence of severe symptoms often results in the perception that the illness is more benign than it actually is, leading to doubts about the necessity of continuous treatment (Morgan, 1996; Donovan and Blake, 1992; Usher, 2001). Symptom experience may also influence medication concerns if they are interpreted by the patient as medication side-effects (Cooper, Gellaitry, Fisher and Horne, 2003) or, alternatively, as evidence that the medication is not working (Leventhal, Easterling, Coons, Luchterhand and Love, 1986)***.***

Beliefs about illness Over the past decade or so, research has improved our understanding of how people think about illness and identified the importance of 'common-sense' beliefs. A fundamental response to the experience of symptoms or being told that we have a disease is the search for a coherent 'common-sense' model of the illness. This helps us to make sense of the illness and guides our actions in dealing with it. Common-sense models of illness include beliefs about the

symptoms, causes, personal consequences, timescale (eg, acute *vs* chronic *vs* episodic) and potential for control or cure (Cameron, Leventhal and Love, 1998; Horne, 2003). Beliefs about the illness influence perceptions of treatment necessity and adherence (Horne and Weinman, 2002; Ross et al, 2004).

Patients' beliefs about illness, although they may not accord with medical evidence, have an internal logic and coherence and are often strongly influenced by symptom experiences. This is illustrated by the example in Box 2. In this example of a quantitative study, valid and reliable questionnaires were used to assess illness and medication beliefs. However, similar logical relationships between illness and treatment beliefs have been noted in qualitative studies (Pound et al, 2005). For example, many people are reluctant to take medication on a long-term basis if they do not experience disruptive or distressing symptoms and instead take the medication to treat episodic symptoms (Morgan, 1996; Donovan and Blake, 1992; Usher, 2001).

Box 2: Illustrating the 'common-sense coherence' of illness and treatment beliefs: the example of adherence to inhaled corticosteroids (ICS) for asthma

A recent UK study of the impact of illness representations and treatment beliefs on asthma self-management (Horne and Weinman, 2002) showed that patients were significantly more likely to endorse the personal need for regular ICS if they shared the 'medical view' of asthma as an 'acute on chronic' condition (ie, it is a chronic disease which manifests as acute symptomatic flare-up or asthma attacks) with potentially serious consequences. These patients accepted that asthma remains a problem even when there are no overt symptoms of breathlessness. The rationale for the regular use of inhaled steroids (to prevent or at least lower the frequency of attacks) was easy to accept. In contrast, other patients' models of asthma were more closely linked to symptom experience. These patients did not perceive their asthma as a chronic condition with potentially serious consequences. Rather, they considered themselves to be well when asthma symptoms were absent and took ICS sporadically in response to symptoms. They doubted their personal need for preventer medication because the notion of asthma as a *chronic* condition, needing continuous treatment, was at odds with their experience of it as an *episodic* problem.

Self-identity in relation to illness and treatment In some conditions, notably HIV/AIDS, taking medicine is a reminder of illness and may therefore not accord with people's efforts to appear 'normal' and healthy (Cooper et al, 2002; Erlen and Mellors, 1999; Johnson, Roberts and Mann, 2000). In contrast, Prout, Hayes and Gelder (1999) observed, in relation to the management of childhood asthma, that the prescribed medicines were valued for their positive effects in controlling the child's asthma, with an important benefit being that this helped parents to maintain the 'ordinariness' of their child. Medication use, although involving acceptance of the illness, therefore had the positive effect for these families of enabling the child to participate in normal activities through controlling asthma symptoms.

People with epilepsy, schizophrenia and other mental health problems, HIV, depression and conditions that are viewed as stigmatising are often reluctant to take medicine for fear of disclosing their illness and marking themselves out as different (Cooper et al, 2002; Rogers et al, 1998;

Usher, 2001). However in contrast to this unwelcome effect, medicine use may have the positive effect of controlling the condition (eg, reducing risks of epileptic seizures) thus reducing the risks of stigmatised responses.

Peoples' evaluation of their personal need for medication may also be influenced by notions of self and 'hardiness.' There has been disappointingly little research in this area, but perceptions that one can resist the progress of disease by drawing on sources of 'inner strength', 'hardiness' or by keeping a 'positive outlook' emerged as reasons for rejecting HAART in interviews with over 100 HIV-positive men (V. Cooper, Buick et al, 2002).

Competing priorities and alternative resources

Using alternative resources People's decisions about medicines are influenced by their perceptions of the available alternatives. The prevalence of medical pluralism is well recognised with many patients using complementary medicine in parallel with prescribed treatments (V. Cooper, Buick et al., 2002). For example, about half the respondents in a study of rheumatoid arthritis used some sort of 'alternative remedy' (eg, cod liver oil, feverfew, dietary changes and homeopathy) either instead of or as well as the prescribed treatment (Donovan and Blake, 1992). Similarly, Morgan and Watkins (1988) found that many patients prescribed anti-hypertensive medication tried to control their blood pressure by avoiding stress and that large numbers of patients of Caribbean origin took herbal remedies both as a general tonic and to help with their blood pressure.

There is preliminary evidence that some patients explain their decision to delay accepting antiretrovirals for the treatment of HIV by citing a preference for non-pharmacological methods of treating HIV, including complimentary therapy and 'maintaining a positive attitude' (V. Cooper, Buick et al, 2002). Support for complementary and alternative medicine (CAM) is not simply based on a 'knee jerk' reaction from those who are anti technology. Rather, the public pragmatically assess different therapies and procedures on their own merits (Calnan et al, 2005).

Conflicts with other activities Nonadherence may arise in situations where use of the prescribed medicines conflicts with other aspects of patients' lives, such as requirements for eating with or before medicines or not taking medicines with alcohol (Chesney et al, 2000). Moreover, for some medicines such as HAART, the considerable demands of the medicine regime do not merely impinge on patients' daily routines but may have major impacts on social relationships and work.

Insights from psychosocial research into patients' beliefs

In summary, research into patients' beliefs about their illness and treatment has identified the following insights in explaining patients' nonadherence with prescribed medicines:

1. Patients' beliefs about their illness and treatment are logically coherent. Although patients' interpretation and ideas about their illness may appear mistaken from the medical perspective, they are 'common sense' interpretations based on their own understanding and experiences.
2. Patients' behaviour (eg, taking or not taking medication) may be more strongly influenced by their own 'common-sense'

interpretation of their illness and treatment than by medical advice or instructions.

3 Patients' common-sense interpretation may be based on potentially modifiable misconceptions about the nature of the illness and about the benefits and risks of the treatment.

4 Perceptions of the risks (and benefits) of medication are influenced by a range of factors including 'prototypic' beliefs about classes of treatments – such as general beliefs about pharmaceutical medicines as a whole, the past experiences of ourselves and others, social and cultural norms as well as the information we receive from various sources.

5 Medication use occurs in the context of everyday life and is influenced by the extent to which patients accept or deny their illness, the perceived value of medicine use in maintaining normal activities and self-presentation, and the availability of alternative treatments and ways of preventing or controlling symptoms.

6 The focus on patients' perceptions and common-sense reasoning has improved our understanding of the perceptual factors influencing people's motivation to take or not take medication. We now need more research into how these perceptual factors relate to and combine with the practical barriers to implanting decisions to take medication (eg, capacity and resource limitations such as forgetting or difficulties in administering medication).

7 The majority of studies have been cross-sectional and there is a need to understand how perceptions and medication practices change over time and influence perceived necessity and concerns in response to greater experience, increased knowledge and changes in illness experience.

Imposed compliance

So far this chapter has described medication use as an action over which patients have considerable autonomy. However, Usher (2001) in her qualitative study of medicine use by people with schizophrenia described a situation where patients are under considerable pressure from relatives or health professionals to take medicines as prescribed and sometimes only took medicine because they felt powerless to do otherwise. She described this situation as 'imposed compliance'. Rogers et al (1998) similarly described pressures of social sanctions experienced by patients in relation to neuroleptic medication. An extreme example of imposed compliance occurs where patients with mental illness receive their medicine administered by injection. More generally, this notion of imposed compliance draws attention to pressures that may be experienced to varying degrees by many patients, with this emanating from both social networks and health professionals.

Adherence in vulnerable groups

Children and adolescents

It is estimated that 200 million prescriptions were issued for children and adolescents in the UK during 2002. Children need to take long-term prescribed medicines for various reasons including asthma, epilepsy,

diabetes, severe allergy and Attention Deficit Hyperactivity Disorder (Costello, Wong and Nunn, 2004). However there is evidence that adherence with prescribed medication is lower among children and adolescents than in adults, with rates being particularly low for adolescents as they approach independence (Staples and Bravender, 2002). Estimates of nonadherence for children and adults generally range from 25 to 60 per cent (Costello et al, 2004). Children with learning difficulties are likely to be at particular risk of nonadherence, although little work has been done in this area (Costello et al, 2004).

In order to gain an impression of the size of the literature on children and adolescents, we conducted a search of papers using the Medline database. Using a search strategy derived from a series of Cochrane reviews (see Appendix 3), this search on Medline alone elicited 3003 papers on adherence and children, indicating extensive literature. However, a limited hand-search indicated little in the way of integrative commentary. Whilse an array of articles review literature within treatment conditions, such as ADHD (Thiruchelvam, Charach and Schachar, 2001), juvenile rheumatoid arthritis (Fine and Worling, 2001; Kroll, Barlow and Shaw, 1999), type 1 diabetes (Davis et al, 2001), HIV (Steele et al, 2001; Steele and Grauer, 2003), epilepsy (Mitchell, Scheier and Baker, 2000; Shope, 1988), and asthma (Divertie, 2002; Penza-Clyve, Mansell and McQuaid, 2004; Rand, 2002). Few reviews take a broader perspective, with several examining predictors of adherence (DiMatteo, 2004b; Eiser and Kopel, 1997; Fotheringham and Sawyer, 1995; Litt and Cuskey, 1980; Staples and Bravender, 2002), and a single key review of the efficacy of intervention strategies (Costello et al, 2004).

Traditionally studies of medicine use by children focused exclusively on parents' practices and reasons for nonadherence. However, it is now increasingly acknowledged that young children have their own beliefs and concerns and may influence medicines use through resisting medicines or taking responsibility for medicines use. This has led to a greater emphasis on involving children in medical consultations and as participants in research (Sanz, 2003; Gabe, Olurride and Bury, 2004). This is endorsed by the National Service Framework for Children (Department of Health, 2004), which advocates shared decision-making between parents or carers, children or young people, and professionals. This requires involving children and young people, as they develop, in discussions of risks and benefits of treatment, and taking into account their values and beliefs and the effects of the proposed treatment on daily living. It is also advocated that health professionals should assess, with each individual child, parents and/or carers when they can and want to be responsible for their own medicines. This child-centred approach identifies the need for an understanding of children's perceptions of medicines and the impact on their lives.

The small number of qualitative studies of children and adolescents suggest that these groups are less aware or worried about possible long-term harmful effects of medicines compared with adults, but are concerned about what they perceive as side-effects and dislike feeling dependent on medicines (Gabe, Bury and Ramsay, 2002; Kyngas, 2001; Fitzgerald, 2001). Problematic aspects of medicines use for younger age groups may also relate particularly to the psychosocial aspects of medicines use in terms of the feeling of being different from their peers because of their medical condition and possibly restricted in normal activities. Positive effects of the medicines are therefore to promote

normality. Negative psychosocial aspects include fears of stigma and labelling associated with taking medicines.

Another key issue highlighted by The National Service Framework for Children and Young People (Department of Health, 2004), is the use of medicines in schools. Despite issuing guidance to schools, there is evidence that many teachers have not read the guidance and implementation is poor (Wong, Awolowo, Gordon and Mo, 2004). Access to medicine at school is therefore variable and for some children forms an important barrier to appropriate medicines use.

Older people

Medicines use is relatively high among older people, with four in five people over 75 prescribed at least one medicine and 36 per cent prescribed four or more medicines (Department of Health, 2001). There is conflicting evidence as to whether older people are more or less likely to be nonadherent than members of other age groups (Carter, Taylor and Levenson, 2003). However, it is known that adverse reactions to medicines are relatively high among this age group and are implicated in between five and 17 per cent of hospital admissions.

Factors associated with high risks of unintentional nonadherence are particularly prevalent among older people aged 75 years and over (Carter et al, 2003). This includes taking multiple medicines with high dose frequencies, decreasing dexterity and/or cognitive function and high rates of living alone (Department of Health, 2001).

However, many elderly people also engage in intentional nonadherence and make decisions to change or stop their medicine without professional advice. Important factors include their experience of the medicines in terms of side effects, adjustments made in response to symptom changes, and the perceived inefficacy of treatments prescribed (Lowe, Raynor, Purvis, Farrin and Hudson, 2000).

The National Service Framework for Older People (Department of Health, 2001) has identified medicines review and adherence as particular issues in promoting the health and effectiveness of care for elderly people. However, there is a need to establish the prevalence of intentional and unintentional nonadherence, the extent to which elderly people in private households rely on others for medication administration, problems of accessing prescriptions and needs in terms of communication.

Ethnic minorities

The 2001 census identified 7.9 per cent of the UK populationas members of ethnic minority groups. However, only a few UK based studies have examined beliefs and practices in relation to prescribed medicines. These provide evidence of the significance of cultural traditions and experiences for medication use. A survey of undergraduate students in the UK of Asian and European cultural backgrounds identified differences between groups in beliefs about medicines (modern pharmaceuticals) and personal sensitivity to the adverse effects of taking medicines (Horne et al, 2004). Students of Asian cultural background were significantly more likely to perceive medicines as intrinsically harmful, addictive substances that should be avoided and less likely to endorse the benefits of modern medicines. This relationship between cultural

background and beliefs about medicines in general was maintained after controlling for potential confounding variables.

An in-depth study of hypertensive patients comprising first generation migrants from the Caribbean and a group of white patients from the same socio-economic background also identified greater concerns about possible harmful effects of prescribed anti-hypertensive medicines among first generation Caribbean migrants and lower adherence (Morgan and Watkins, 1988). These patients remained under treatment because of their worries about the risks of high blood pressure but nonadherence was high, with respondents frequently only taking the anti-hypertensive medication 'as necessary' when they felt or were told there blood pressure was 'high' (intentional nonadherence). This difference in meanings and responses was attributed to the greater familiarity with herbal remedies among the Caribbean patients. These remedies were obtained locally and provided an additional resource to treat high blood pressure. Secondly, the perception of herbal remedies as 'weak' medicines served as a framework that influenced Caribbean patients' perceptions of the 'power' of prescribed medicines to exert both beneficial and adverse effects, and led to their questioning the appropriateness of taking such remedies long-term. They therefore often 'left off' the prescribed medicine if they thought their blood pressure was controlled and that the anti-hypertensive medicines were therefore not 'necessary' (Morgan, 1996). A recent study that revisited the use of anti-hypertensive medicines among Caribbean patients in south London has produced similar findings of patients' reasoned decision-making and assessment of their 'need' for the medicines, often leading to practices that diverged from recommended medicine taking (Connell, McKevitt and Wolfe, 2005).

Although there is some evidence of cultural differences in beliefs about medicines among ethnic minorities in the UK, these do not form homogeneous groups. Differences exist both between and within ethnic groups in terms of cultural background, education and socio-economic status. For example, language difficulties and the need for interpreters experienced by some members of minority groups may result in less adequate consultations and higher rates of unintentional nonadherence. There is therefore a need for further UK based studies to examine the variability in beliefs within and between groups, to inform prescribing-related consultations and the provision of patient information on medication.

A model for guiding interventions

A recent conceptual distinction that brings together the findings of different types of research and explanations of patients' medication use is that of 'unintentional' and 'intentional' nonadherence (see Figure 1).

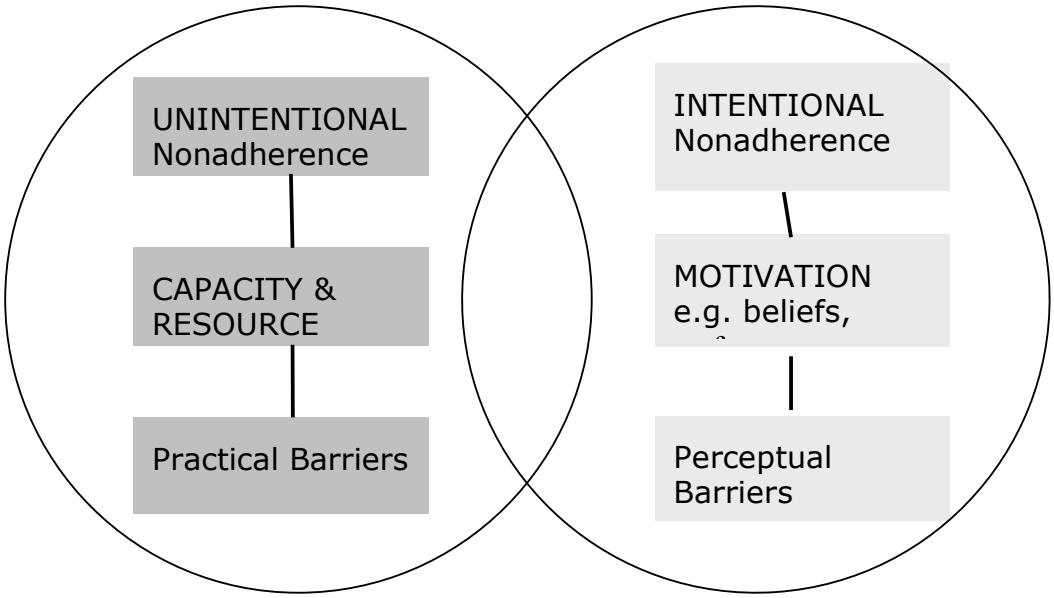

Figure 5. Model of adherence

Unintentional nonadherence - refers to barriers to patients taking medicines as prescribed. Barriers arise from capacity and resource limitations on the part of the patient. Capacity and resource limitations might include deficiencies in memory (eg, forgetting instructions or forgetting to the take the medication), dexterity (eg, difficulties in opening medication containers or using medication devices such as inhalers or injections) or knowledge (eg, being unaware of the need to obtain a repeat prescription) or difficulties with disruptions to normal routine.

Intentional nonadherence – describes the way in which patients may take deliberate decisions to adjust their own medication use and comprises both 'rejectors' who do not take the medicines at all (absolute noncompliance) and 'modifiers' who alter the dose or frequency of the medicines or only take the treatment 'as necessary' (partial noncompliance). Intentional nonadherence is thus an intentional action that is rational in terms of patients' beliefs, circumstances, priorities, preferences and experiences, although these perceptions and actions may differ from medical expectations and rationality. Barber (2002) has proposed using a theory of human error in organisations to explain both intentional and unintentional nonadherence. This approach embraces the intentional and unintentional acts of the patient, and local and organisational factors which may have caused the nonadherence. This approach is explained more fully in Appendix 4.

There is currently little known about the extent of intentional and unintentional nonadherence. However, Barber and colleagues (Barber et al, 2004) examined patients' reported problems with medication prescribed for one of five common chronic conditions. In the sample of 226 adults aged 75 and over, approximately 30 per cent reported nonadherence over the first four weeks of treatment, of which 45 per cent reported intentional nonadherence and 55 per cent reported unintentional nonadherence. Practical aspects leading to unintentional

nonadherence included; the tablets being difficult to swallow, hard to remember to take medication, complicated regime, having to take half a tablet and difficulty in breaking the tablet accurately. This study indicates that intentional and unintentional nonadherence are both common.

Different causes of nonadherence require different responses. This identifies a need for further data regarding the prevalence of intentional and unintentional nonadherence among different patient groups, types of treatment, and in relation to different stages of medication use. Moreover, it might be expected that unintentional factors, such as forgetting to take the medicine, will assume greater significance when motivational factors are low. In contrast, constraints may often be overcome where motivational factors are high.

This chapter has focussed on nonadherence as a behaviour that varies within and between individuals and that may be unintentional or unintentional. Although the focus of this chapter has been the individual, it is important to recognise that both intentional and unintentional adherence occur within, and are to some extent a consequence of, a particular environment. Subsequent chapters will explore the external influences on adherence-related behaviours focussing on patient-provider interactions and communication in Chapter 3 and on societal policy and practice in Chapter 4. It is important to recognise this because the solution to the problem of nonadherence may, in part, lie outside the patient.

Outstanding research questions,

Patients' perceptions of medicines

Studies conducted across a range of chronic illnesses and involving patients from different countries and cultural groups and using qualitative and quantitative methods have consistently found that adherence is related to the way in which patients judge their personal need for treatment, relative to their concerns about potential adverse effects.

Moreover, research suggests that that the way in which individuals balance perceived necessity against their concerns relates to the appraisal of the effects of medicines, to perceptions of illness, as well as to social representations of medicines in general and the perceived availability of alternatives. These factors relate to one another in a way that often has a strong internal logic, although this may be inconsistent with the scientific evidence or the medical view.

Further primary research is now needed to assess whether these insights can be used to model interventions to help patients make adherence decisions that are informed by realistic assessments of the likely benefits and risks of treatment and are not based on mistaken premises or misplaced beliefs about the illness and treatment.

The following are examples of specific research questions:

1 How do patients judge their personal need for medication in different situations and stages of illness?

2 How do perceptions of medication change over time and in response to information and experience of the treatment?

3 How do patients' expectations, experiences and attributions of symptoms (eg, to medication or illness) influence perceptions of and adherence to prescribed medication?

4 How do patients interpret and act on different types of information about the potential benefits and risks of medication? How does this influence perceptions of need and concerns and the 'trade off' between perceived necessity and concerns?

5 Theory development – What is the utility of the necessity-concerns framework and other methods of operationalising the salient attitudes to treatment within established theoretical models of health-related behaviour? Are there other theoretical constructs that could be used in place of, or in addition to this framework to provide a better understanding of adherence and how to enhance it?

6 How do emotional states (eg, depression and anxiety) influence perceptions of and adherence to medication? How can these effects be moderated? (eg, by social support and other factors).

7 How do patients perceive, evaluate and respond to information about medicines from different sources?(e.g. doctors, pharmacists, pharmaceutical industry, media)

8 What do patients value about alternative and complementary therapies relative to medication? Can this help us understand how to improve communication about medicines?

9 How do ethnicity and social disadvantage influence patients' perceptions, assessments and medication behaviours?

10 How do the perceptions and life circumstances of different age groups (children, young adults and elderly people) influence adherence and what are the implications for interventions?

Modelling intentional and unintentional nonadherence

11 What are patients' perceptions of adherence and its importance to their goals? Do perceptions vary for different treatments prescribed for multiple pathologies?

12 What is the contribution of intentional and unintentional factors to rates of nonadherence? How does this change over the course of illness and how does it vary for different conditions and treatment regimens?

13 What are the perceptual and practical barriers to medicines use for patients with multiple pathologies or psychiatric conditions and for their families?

14 What are the main barriers to patients implementing their intensions to adhere to prescribed medication? How might these be overcome?

15 What are the effects of enforced compliance (eg, in mental illness as a result of assessment of risks to the public associated with nonadherence) on the individual?

Methodological developments

16 Can different indicators of adherence (eg, self-report, prescription redemption rate) be used in combination to produce better assessments of adherence for use in intervention studies?

17 How should we assess whether individual patient's adherence decisions are 'informed'?

Adherence and clinical outcome

18 There is need for a tertiary review to develop a framework to identify clinical priorities for adherence interventions on the basis of efficacy of medication and importance of adherence in attaining benefit.

Change over time

19 We need to understand more about how adherence and its determinants change over time as this will tell us when as well as how to intervene to support appropriate prescriptions. Recent research has improved our understanding of the key perpetual and practical barriers to adherence in many of the disease and treatment categories where adherence matters most. However, many of the available studies are cross-sectional meaning that we cannot be certain about causality and have little insight into how adherence and the determinants of adherence change and interact over time. A key priority therefore is for prospective studies to answer these questions. This is important to inform not only how we intervene but when.

Adherence in vulnerable groups

Consideration of vulnerable groups cuts across the explanatory themes and is relevant for most research questions, regardless of whether research is targeted at explaining individual behaviour, investigating communication in healthcare, societal policy and practice or evaluating interventions. The issue is also relevant for the normative questions. Work in this area requires systematic reviews of the available literature followed by empirical studies. Specific questions are:

1 What are the effects of social disadvantage and ethnicity on accessing prescriptions and adherence to prescribed medication?

2 How do the perceptions and life circumstances of different age groups (children, young adults, elderly people) influence adherence and what are the implications for interventions?

3 What are the particular barriers to medicines use for people with multiple pathologies (and their informal carers) and what interventions are required?

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Section 4 Patient provider interaction and health care communication

John Weinman & Rob Horne

Introduction

The consultation between the patient and the health care professional (HCP) lies at the centre of health care and is an obvious starting point for investigating medication taking and prescribing behaviour. The development of relatively unobtrusive audio and video-recording techniques has allowed researchers to investigate the consultation and many studies have analysed the process of the consultation and attempted to relate process variables or characteristics to a range of outcomes, including treatment adherence.

The information which is transmitted during the consultation is central to the formulation of diagnoses and in the delivery of treatment. Effective communication is necessary to ensure not only that the patient's problems and concerns are understood by the HCP but also that relevant information, advice and treatment is received and acted upon by the patient. Over the past thirty or so years there has been considerable research on the medical consultation prompted to a large degree by the fact that there has been consistent evidence that not only do patients often report dissatisfaction with the process and outcome but also there is widespread nonadherence with subsequent treatment recommendations. Moreover, the consultation is often considered to be the primary influence on patients' medication-taking behaviour, as well as the most obvious setting for delivering interventions for promoting better use of medicines.

Although most research on health care communication has focused on the HCP-patient interaction, the impact of other modes of communication has also been investigated. There have been a large number of studies investigating the efficacy of written information on a range of patient outcomes, including adherence, and there is a growing literature on the impact of the internet in communicating health and treatment related information.

The empirical evidence: what we know

Studies of HCP-Patient interaction

There are a plethora of studies on HCP-patient communication, most of which focus on doctors and the medical consultation. At least three distinct aspects of the consultation can be distinguished:

- Context – the setting in which the consultation takes place, and its primary function (eg, primary care *v* secondary care; initial *v* follow-up consultation, etc.)
- Process – the manner in which the consultation is conducted (ie, style of consultation: doctor-centred; patient-centred; shared decision making, etc.)

- Content - what is discussed (not discussed) (eg, does the doctor elicit patients' beliefs, attitudes, preferences?; is adherence discussed? ,etc.)

From a literature search of Medline and PsycLIT, looking for reviews and primary research linking HCP-patient interactions with adherence/compliance, there are three broad categories of research:

Descriptive studies

These have involved the development of a wide range of methods for describing the content and process of the consultation. A number of systems have been developed to measure aspects of the doctor-patient relationship (Stewart, 1995). One of the broadest distinctions made has been between consultations which are described as patient-centred and those which are HCP-centred, reflecting the extent to which the HCP or patient determines what is discussed (Grol, de Maeseneer, Whitfield and Mokkink, 1990). HCP-centred consultations are those in which closed-questions are used more often and the direction is determined by the HCP, typically with a primary focus on medical problems. In contrast, patient-centred encounters involve more open-ended questions with greater scope for patients to raise their own concerns and agendas (Bower and Mead, in press). Related to this are consistent differences in the extent to which the HCP responds to the emotional agendas and the non-verbal cues of the patient (Roter, Stewart, Putnam and Lipkin, 1997).

A meta-analysis of HCP–patient communication studies found that the many different elements of communication measured in the studies fell into five broad categories: information giving; question asking; partnership building; rapport building; and socio-emotional talk (Hall, Roter and Katz, 1988). Information provision has been found to have clear influences on health outcomes, particularly when accompanied by emotional support, resulting in reduced psychological distress, enhanced symptom resolution and reduced pain. Physicians asking about patients' understanding, concerns and expectations were also important in achieving these outcomes. Using cluster analysis, Roter and colleagues (1997) identified five patterns of relationship in primary care consultations: narrowly biomedical; biomedical (in transition); biopsychosocial; psychosocial; and consumerist.

A very different approach to process analysis can be found in the studies of Ley and colleagues (Ley, 1988), who have concentrated on the informational content of the consultation and the quality of information provided by the doctor. In particular, they have analysed the content in terms of its level of complexity, comprehensibility and the extent to which the information is organised. They and others have found that medical information may be too detailed or complex with the result that important information may not be understood or retained by the patient (see below). The implication of discrepancies in doctor and patient understanding of anatomical and other medical terms have been explored in a number of studies of doctor-patient communication (Gibbs et al, 1987; Thompson and Pledger, 1993). Negative effects have been found on patient understanding and satisfaction following the consultation. Moreover, recent evidence shows that when doctors' and patients' vocabulary for anatomical and other terms are matched in the consultation, then significant gains are found in overall satisfaction with the consultation, as well as with specific components of it, such as

rapport, communication comfort and compliance intent (Williams and Ogden, 2004).

Correlational/Explanatory studies

These studies have examined the effects of the different content and/or process variables (outlined above) on a range of outcomes, including understanding, knowledge, satisfaction and treatment adherence.

Studies, which have assessed how much patients are able to recall from consultations, have shown that about half the information is retained but there is considerable range. This variation partly reflects the type of setting and sample used and partly the method which is used to test for recall. There are a number of other factors involved, including the content of the information, patients' prior knowledge and their level of anxiety. With regard to the content and structure of the message, information which is presented early in the consultation is recalled better (the primacy effect) as are statements which are perceived as being important or relevant.

One very obvious explanation for unintentional nonadherence arises from the poor cognitive outcomes outlined above, particularly poor understanding and recall of information presented in the consultation. Many patients lack basic knowledge about their medication but the relationship between this and their adherence is quite complex. In a systematic review of the adherence literature, Haynes (1976) concluded that, although 12 studies had demonstrated a positive association between knowledge and adherence, there were more that had failed to demonstrate a link. Studies conducted since then generally indicate that associations between knowledge and adherence are at best small and inconsistent (Eagleton, Walker and Barber, 1993) and interventions which enhance knowledge do not necessarily improve adherence (Haynes et al, 1978).

The most common outcome which has been used in studies of healthcare communication is patient satisfaction, which has been investigated as an endpoint in its own right,as well as a possible mediator of more distal outcomes including treatment adherence and health. Fitzpatrick (in press) maintains that the concept of patient satisfaction is important because it focuses on the need to understand how patients respond to health care. As a result, it is increasingly being assessed in surveys of health care settings, as a marker of quality of care, along with other such dimensions of quality as access, relevance to need, effectiveness, equity and efficiency. Patient satisfaction is a multidimensional concept since patients have been found to have differing views about different aspects of their health care, such as the HCP's behaviour towards them, the information provided, the technical skills of the HCP and the access to and quality of the health care setting. Despite this there is evidence that the behaviour of the HCP during the consultation is the critical determinant and one which can significantly influence ratings of all the other aspects of health care.

There is also increasing interest in the role of patient satisfaction as a mediator between information provision, recall and adherence. Dissatisfaction with attributes of the practitioner or the amount of information and explanation provided may act as a barrier to adherence by making the patient less motivated towards treatment (Hall et al, 1988) and may therefore influence both intentional and unintentional aspects of nonadherence.

However, very few studies have looked directly at effects of consultation on medication-taking behaviour; recent work by Jenkins et al (2003) is an interesting exception. Studies have linked variables above (eg, patient recall, understanding and satisfaction) to adherence but there is little empirical evidence about the direct effects of consultation on adherence and the extent to which changes in consultation (process and content) can affect changes in medication taking behaviour.

Intervention studies

These have primarily focused on changing the skills and competence of the HCP to improve the outcomes outlined above but there are also intervention studies which have been aimed at patients, to improve their experience of the consultation. Both types of intervention study will be briefly reviewed.

For many years communication skills training has been a core component in medical and other healthcare professional education, and evaluation studies of these provide consistent evidence that consulting behaviour can be improved in both routine and specific (eg, giving `bad news') consultations. Skills that facilitate the effective communication of information include using language that is readily understood, presenting information in a way that takes account of the patient's beliefs and checking understanding of any information that has been given (Ley, 1988).

Video recordings of consultations show that these skills are frequently absent in routine consultations (Braddock, Fihn, Levinson, Jonsen and Pearlman, 1997; Campion, Foulkes, Neighbour and Tate, 2002). Thus, for example, recording of consultations conducted by primary care physicians in the USA revealed that just 2 per cent were direct questions asked of the patient to check understanding (Braddock et al, 1997). Similarly, in an analysis of videotaped consultations selected by candidates as part of a qualifying examination for membership of the Royal College of General Practitioners, checking patient understanding was evident in just 20 per cent of the consultations (Campion et al, 2002).

A recent Cochrane review of interventions to increase patient-centeredness in consultations showed that these are generally successful in modifying HCP styles of communication and increasing rates of patient satisfaction (Lewin, Skea, Entwhistle, Zwarenstein and Dick, 2004). However, the evidence was much less convincing as to whether these interventions result in improvements in either adherence to treatment or advice, or in more positive health outcomes. Moreover, some studies (Kinmonth et al, 1998) have shown negative effects and this has led to a more critical approach to this area (Michie, Miles and Weinman, 2004) and the proposal that facilitating patient adherence and/or behaviour change needs to involve the use of motivational strategies as well as patient-centred communication skills.

A number of studies have evaluated training packages for patients prior to medical consultations with the aim of helping patients to be clear about their needs and to maximise the chances of achieving these. While early studies provided some encouraging findings, particularly for health outcomes (Greenfield, Kaplan and Ware, 1985), the results have been equivocal. Just as with training interventions for HCPs, the evidence indicates that while specific behaviours (eg, question asking) can be modified, the impact on adherence and health outcomes is less

clear (Harrington, Noble and Newman, 2004), and there is considerable scope for further research on this.

Studies of other communication methods

Written information

There has been a great deal of research investigating the value of providing patients with written information, either on its own or as an adjunct to the consultation (Weinman, 1990; Noble, in press). While most of the studies have investigated the information provision and behaviour change aspects of written information, a small number have explored the extent to which written information can take account of patient priorities and facilitate active participation in decision making (Dixon-Woods, 2001).

Reviews of written information about a variety of health topics reveal several common problems, including the use of inaccurate information, missing information and text that is too complex to be understood by the majority of the intended audience (Ley, 1988; Slaytor and Ward, 1998; Coulter, Entwistle and Gilbert, 1999).

Evaluative studies of written information have investigated effects on a wide range of outcomes including knowledge, recall, satisfaction, mood and adherence (Johnson, Sandford and Tyndall, 2003), and generally show that it is valued by patients and is helpful when it is provided in addition to routine care. There have also been attempts to provide patients with audio or videotapes of consultations, particularly those which might be problematic for patients, and these have been found to promote better recall and understanding (Scott et al, 2003). A smaller number of studies have investigated the efficacy of written information designed to increase patient involvement in the consultation (see above) and, while these can have small effects, they are generally less successful than face-to-face interventions (Harrington et al, 2004).

Internet use

One very obvious recent addition to sources of healthcare communication has been the access to health information on the world wide web (Eysenbach, Powell, Kuss and Sa, 2002), as well as the possibility of on-line access to medical expertise (Umefjord, Petersson and Hamberg, 2003). Access to the internet has provided a major resource for patients to learn about their illness and treatment (Benotsch, Kalichman and Weinhardt, 2004) and there is evidence that the majority of internet users have carried out searches for medical information (Fox and Fallows, 2003). This is clearly going to be a very fruitful area for future research and development, particularly to evaluate the extent to which the internet can be used to facilitate improved self-management in chronic disease (Bull, Gaglio, McKay and Glasgow, in press).

Communicating with different groups

There are ethnic and social inequalities in health care and health outcomes, and there is some evidence to show that the quality of health care professionals' communication with these groups may contribute to these inequalities (Cooper and Roter, 2002). Ethnic minority patients report less involvement in consultations and lower levels of satisfaction

with care, and patients from lower socio-economic groups are given less information in consultations. Cooper and Roter (2002) recommend that communication skills training programmes need to be more broadly based to train health care practitioners to communicate in a culturally more sensitive way, and that strategies are needed to empower patients across ethnic and social groups to participate more in their care. Communicating effectively with those with low levels of literacy and those from minority ethnic groups requires some different considerations to those that govern communication with those who are literate and those from dominant ethnic groups.

With patients from different backgrounds, HCPs also need to be aware of possible differences in their beliefs about illness and treatment. Since these beliefs are very likely to play a major role in patients' evaluation of and use of treatment (see Chapter 2), effective HCP communication will need to incorporate the elicitation and acknowledgement of patients' beliefs as a fundamental part of the consultation.

The role of prescribers' beliefs

There is now accumulating evidence of significant differences in patterns of prescribing and of variation in adherence to recommended good practice among health care practitioners (O'Brien, 1997). This includes not only differences in what is prescribed for the same condition, but also in the amount and level of information which is provided about prescribed medications. These differences are consistent with a much broader research litereature which has demonstrated very clear variation in many aspects of health care professional practice (Marteau and Johnston, 1990). This literature is also showing that an important determinant of this variation are the differences in attitudes and beliefs which are held by health care practitioners. There are now a number of studies which have shown that prescribers' beliefs about quite specific aspects of a treatment are related to prescribing patterns for a wide range of clinical problems, including HIV (Horne and Fisher, 2005), persistent non-cancer pain (Hutchinson et al, in press), atrial fibrillation (Pradhan and Levine, 2002), heart failure (Horne et al, 1999) and angina pectoris (Beaulieu et al, 2005). Thus there is considerable scope for future research to examine the role of prescribers' beliefs on the process and outcome of the consultation in order to ascertain the extent to which they subsequently impact on the patient's evaluation of and adherence to the treatment.

Research agenda

The prescribing consultation is often considered to be the source and potential remedy for adherence problems. It provides the focus for the concept of concordance and remains a focus for debate about medication-taking. However, our review of the empirical evidence identified very few studies that systematically evaluate the effects of the prescribing consultation on adherence behaviour. Of course, this does not mean that the consultation is unimportant or that we should not strive to improve consultation as a 'good' in its own right. However, it does identify the need for further basic research to clarify the effects of the consultation on medication adherence. The priority research questions are:

Effects of the consultation on adherence

1 What are the direct and mediated effects of the consultation on short and longer-term patterns of treatment adherence?

2 What are the key aspects of the consultation that influence medication taking behaviour? For example, using the Roter Interactional Analysis System (RIAS) – we urgently need systematic evidence about the possible direct and indirect effects on adherence of the different categories and styles of communication defined by the RIAS.

3 Following on from the above, to what extent is adherence a function of these more global styles or are other factors more salient when considering the specific outcome of medication taking behaviour? - eg, shared decision making, eliciting beliefs, concerns, identifying and dealing with practical issues in taking medication (eg, forgetting, difficulties with packaging, etc)

Practitioner perceptions and behaviours

4 How do patients' preferences, beliefs and expectations and patient style affect prescriber behaviour?

5 What are the effects of 'training' and other interventions on practitioner and patient attitudes, behaviour and skills related to prescribing and communication about medicines?

Shared decision-making

6 What are prescribers' and patients' attitudes to shared decision making, partnership and other models of consultation?

7 What joint decision-making processes are possible? What do real world practices that approximate to joint decision-making look like? What are the strengths and weaknesses of different such practices seen from the vantage point of various stakeholders (eg, prescribers, patients, funders)?

8 Are there practical mechanisms in place (or available to put in place) that could re-distribute accountability more from prescribers to patients (eg, waivers)? What are the legal, policy, practical and psychological implications of trying to share accountability differently?

9 How can clinicians and patients be supported to deal with the cognitive and emotional challenges of prescribing consultations designed to promote informed choice and adherence to medication?

10 What are the effects of coercion on patients?

New prescribers

11 There is a new and growing agenda relating to non-medical prescribers (pharmacists, nurses, etc) This is a key context issue and there are range of questions relating to patient perspectives on new prescribers and to new prescribers' perceptions and skills. The effects of new prescribers on patient adherence to medication should be included in any research agendas designed to evaluate new prescribers.

12 In what ways is it possible to supplement the activities of the NHS workforce in facilitating optimal medication usage through other,

complimentary approaches (eg, the use of 'expert patients,' family support etc).

Facilitating communication of adherence

13 How can we facilitate the honest disclosure of medication-taking behaviours within prescribing-related consultations and medication-use reviews? How can we equip health practitioners to respond appropriately and effectively?

14 How can we enable new and existing prescribers to identify patients at risk of nonadherence or who are a priority for medication-review and adherence support and how can we provide it – new methods, new practitioners ?(eg, health trainers)

15 How can we support prescribers to meet the challenges of quality frameworks relating to medication-usage as a component of self-management?

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Section 5 Societal policy and practice

Rachel Elliott

This chapter examines how adherence and society interact with one another. The first section of this chapter presents the evidence for the impact of nonadherence on society, in terms of societal economic burden. There have been many attempts to quantify the potentially substantial burden of nonadherence. The quality of the evidence is discussed. The ability of this evidence to support the case for initiatives to improve adherence is considered.

The second section examines the impact of societal level policies on adherence. The evidence for impact on both health and cost to society is presented. Areas where additional evidence is required are highlighted. Recommendations for designing studies to measure the impact of policies are made.

What is the 'impact' of non-adherence?

Potential consequences of nonadherence can be divided into:

- health benefits forgone (human cost, opportunities lost);
- productivity costs (personal and social economic burden).

Health benefits forgone have been discussed elsewhere in this report. The wider societal burden of nonadherence, if it exists, arises from morbidity associated with sub-optimal drug use, and includes:

- cost to the patient (such as loss of health and subsequent loss of income);
- cost to the health care provider (downstream costs of treating morbidity);
- cost to society (such as productivity losses).

In an environment of constrained health care resources, allocation of those resources should be efficient (maximum outcome for a given level of resources), equitable and patient-centred. The allocation of resources to interventions or policies to improve adherence can only be justified if we know, with some level of certainty, that:

- nonadherence has negative health and economic consequences that are alterable by intervention;
- the interventions and policies to improve adherence are effective at a given level of resources (`technical efficiency');
- more benefit cannot be obtained from allocating those resources elsewhere in the system (`allocative efficiency,).

Most countries spend a lot of their health care budget on drugs, a lot is also spent on Research and Development for new drugs, but in reality, the most efficient use of resources could be to improve use of existing drugs through better quality prescribing and optimising patient adherence.

Measuring societal impact of nonadherence

The burden of nonadherence depends on the perspective used (patient, health care provider, society). Direct costs are incurred by the health care provider or patient, during treatment of consequences of nonadherence. Indirect costs or productivity costs (`friction costs') are incurred by the patient and society because of lost or impaired ability to work or to engage in leisure activities due to morbidity and lost economic productivity due to death (Drummond, O'Brien, Stoddart, & Torrance, 1997).

The costs associated with nonadherence can be estimated using the same methods used to assess the societal economic impact of illness in general, that is, the 'cost of illness' (COI). The most commonly used COI methods attempt to identify and measure all costs of an illness (direct, indirect and intangible), and to express, in monetary terms, the burden to society (Byford, Torgerson and Raftery, 2000). Other less-commonly used COI valuation methods include:

- willingness to pay to avoid an illness (contingent valuation);
- averting behaviour approach (preventative methods or investments used to avoid or mitigate the effects of a disease).

COI studies tell us how much a country is spending on a disease, for example, coronary heart disease costs the UK £7.06bn per year (Liu, Maniadakis, Gray, and Rayner, 2002). However, COI studies point to the areas of greatest economic burden but they cannot suggest the most efficient way to reduce it. We do not know what proportion of that £7.06bn per year is preventable. Also, they can also suggest some sort of competition between diseases (does diabetes have a higher COI than heart disease, and if so does this make it more important?) (Laupacis, 2002). Diseases that do not make the 'Top 20' may be the ones with highest preventable morbidity, such that allocating resources to them would lead to a bigger societal benefit. COI studies alone are probably inappropriate for setting priorities and making choices between alternative courses of action.

The COI method itself has some obvious limitations. The indirect costs (productivity losses) usually dominate all other costs, yet it is the part of the estimation method with least theoretical and methodological consensus. The methodology for estimating productivity losses, though well established, does not necessarily provide a reliable estimate in times of high unemployment. The true cost of lost productivity can only be assessed by detailed surveys of industry productivity and labour participation. Also, most countries have less than 100 per cent employment so there may not be productivity losses at all (Laupacis, 2002). Therefore, theoretical cost of illness may not translate into actual cost of illness.

Wide variation in COI methodology means that the quality of published studies is variable. A recent review found that 80 per cent of 1725 studies had insufficient cost data (Bloom, Bruno, Maman, and Jayadevappa, 2001). This raises concerns about comparability, accuracy, validity and usefulness.

The evidence for the economic impact of nonadherence is presented in the next section, with these methodological limitations presented as a key modifier in interpretation and use.

Evidence for the societal impact of nonadherence

The evidence around the societal consequences of nonadherence is poor, disparate, variable and non-existent in many therapeutic areas and patient groups. COI methods are employed, but the methods used are variable. The societal impact of nonadherence has never really been quantified other than through 'top-down' approximations. This method estimates economic cost by using aggregate data on mortality, morbidity, hospital admissions, primary care, disease related costs and other health-care relevant data (Liu et al, 2002). The advantage of these studies is the ready availability of national data.

On review of the literature, six studies were found that report national `top-down' estimates of economic impact of nonadherence (see Table 1). It can be seen that estimates of economic impact of nonadherence are generally large.

Most studies estimated the numbers of hospital admissions due to nonadherence, and estimated economic impact from this (see Table 1).

Table 1: Estimates of societal economic impact of nonadherence

Study	Methods	Results
(Levine, 1984) **USA**	Cardio-vascular patients Methods not known (original work unobtainable)	National estimate for cardiology patients (USA): 125,000 deaths per year leading to a societal cost of 20 million lost work days and $1.5 billion lost earnings
(Col, Fanale, & Kronholm, 1990) **USA**	11.4% of 315 elderly admissions due to nonadherence Used hospital charges to calculate cost	Local estimate for elderly patients (USA): $77,000 ($2150 per admission)
(Sullivan, Kreling, & Hazlet, 1990) **USA**	From a meta-analysis, 5.5% hospital admissions (1.94 million admissions) due to nonadherence ($8.5 billion)	National estimate (USA): Hospital admissions due to nonadherence: $8.5 billion

(Task Force for Compliance, 1993) **USA**	National estimates, assumed: 10% hospital admissions due to nonadherence 10% nursing home admissions due to nonadherence Method of allocation of indirect costs not reported	National estimate (USA): Total direct costs: >$30 billion Total indirect costs: >$50 billion Total costs: >$100 billion
(Dartnell et al., 1996) **Australia**	14/965 admissions due to nonadherence Attached costs to bed-days caused by drug-related admissions and extrapolated to one year	Local estimate (Australia): Total direct costs: AUS$953,715
(Coambs et al., 1998) **Canada**	National estimates, assumed: 6.5% hospital admissions due to nonadherence ($1.78 billion) 23% nursing home admissions due to nonadherence ($0.66 billion) 10% GP visits due to nonadherence ($1.09 billion) Direct costs ≡ indirect costs	National estimate (Canada): Total direct costs: $3.53 billion Total indirect costs: $3.53 billion Total costs: $7.06 billion

This method presents only a partial handling of direct costs to the health care provider, as all other costs (primary and other care or interventions, downstream costs) were not included. Some studies attempt to estimate indirect costs, which immediately inflates values. These estimates have limited usefulness because they use unclear or poor methodology in estimation of both direct and indirect costs, are based on major assumptions and give very unstable results.

Costing nonadherence as a ubiquitous phenomenon across population groups and disease states does not encourage anyone to do anything about it, or policy-makers to direct resources to it. These estimates do not tell us what proportion of that cost is due to waste or is preventable.

Patient-based estimates of economic impact

'Bottom-up' or patient-based estimates of economic impact of nonadherence use information on disease treatment and follow-up, usually from epidemiological data. This method is more complex than the 'top-down' approach but is able to give more specific estimates of costs by disease and patient type. This type of study may provide information on how costs may be affected by a particular intervention or policy in a disease or patient group.

Searching the literature has found few studies that provide patient-based estimates of economic impact of nonadherence, and none from the UK. Specific areas include hypertension (McCombs, Nichol, Newman, and Sclar, 1994), oral contraceptives (Rosenberg, Waugh and Long, 1995), schizophrenia (Weiden and Olfson, 1995), hormone replacement therapy (Hurley, Frost, Trinkaus, Buatti and Emmett, 1998) and diabetes (Gilmer, O'Connor, Manning and Rush, 1997; Hepke, Martus and Share, 2004) (See Table 2). Some studies have carried out modelling studies (Rosenberg et al, 1995; Weiden and Olfson, 1995). There are very few studies that use prospective patient-linked data in a real cohort of patients (Hepke et al, 2004; Hurley et al, 1998). These studies did not examine outcomes so do not provide information on economic impact, only financial impact.

The need for further research

It is clear from the evidence found that the societal impact of nonadherence is not well characterised. However, all studies suggest an increased burden to patient, health care provider and society with nonadherence. Better research is needed in this area to identify the societal impact of nonadherence and present a coherent business case for interventions and policies to improve adherence. Evidence is required to persuade policy-makers that addressing nonadherence is integral to successful and efficient health care policy. Priority areas are diseases that have a known high morbidity associated with nonadherence, which may be preventable, such as diabetes, hypertension, hypercholesterolemia, asthma, depression, schizophrenia and organ transplant.

There is extensive literature on costing methodology and relatively standard approaches to costing and cost analysis should be used (Drummond et al, 1997; Johnston, Buxton, Jones and Fitzpatrick, 1999; Weinstein et al and 1997). Nonadherence may not lead to morbidity, and associated costs, for many years, so cost must be measured at appropriate points, longitudinally, in the progression of the disease, allowing an appropriate time interval after nonadherence begins. Otherwise, changes in cost caused by nonadherence cannot be identified, not due to lack of association, but due to bad study design (Hepke et al, 2004; Billups, Malone and Carter, 2000).

The economic impact of 'nonadherence' cannot be quantified until we are clearer about its definition, process and outcome.

Table 2: Estimates of disease-specific economic impact of nonadherence

Study	Methods	Results
(McCombs et al., 1994) **USA** **Hypertension**	Used individual patient inpatient and outpatient claims data in a regression analysis of 6419 Medicaid patients over 40 years of age, to identify increased health service costs associated with interruptions in therapy	Local estimate (USA): Patients with interrupted antihypertensive therapy consumed $281 less in medicines costs, p<0.0001, and $873 more in other health care costs, p<0.0001 ($637 due to increased hospitalisation, p<0.0002)
(Rosenberg et al., 1995) **USA** **Oral contraceptives**	Decision analytic model: Examined cost of 1 million unintended pregnancies related to OC use	National estimate (USA): Total cost: $2.6 billion
(Weiden & Olfson, 1995) **USA** **Schizophrenia**	Used national mental health costs and monthly relapse rate for nonadherent 'neuroleptic-responsive multiple-episode schizophrenic outpatients' to model impact over 2 years	National estimate (USA): Direct costs of relapse due to nonadherence over two years: $0.64 billion
(Gilmer et al., 1997) **USA** **Diabetes**	Used 3017 HMO patients with diabetes' individual patient inpatient and outpatient claim data and national unit costs, in a regression analysis to	Local estimate (USA): Over 3 years, medical care costs increased significantly for each 1% increase in HbA_{1C} above 7%. 6→7% HbA_{1C}: 4% increase 6→8% HbA_{1C}: 10% increase

	assess whether increases in HbA_{1C} were associated with increased direct costs	6→9% HbA_{1C}: 20% increase 6→10% HbA_{1C}: 30% increase
(Hurley et al., 1998) **USA** **Hormone replacement therapy**	1158 women on HRT, individual patient inpatient and outpatient claim data, national unit costs	Local estimate (USA): Total direct costs for 18 months: Cost per low complier: $1935 Cost per high complier: $1874
(Hepke et al., 2004) **USA** **Diabetes**	57687 Medicare patients with diabetes, individual patient inpatient and outpatient claim data, national unit costs	Local estimate (USA): Reduced medical costs with adherence, but increased drug costs

Impact of societal policies on adherence

Societal policies can affect adherence to medicines through a range of mechanisms. Briefly, policies can:

- change financial access to medicines, through changes in cost of drugs to the patient, prescriber or third party payer;
- change demand, such as allowing or banning direct-to-consumer advertising (DTCA) of prescription only drugs;
- affect supply of:
  - medicines, such as deregulation of medicines from prescription-only (POM) status, to 'over the counter' (OTC) status, or use of restrictive formularies;
  - prescribers, such as expansion of prescribing rights to nurses and pharmacists.

There is an implicit assumption that policy-induced changes in medicines-taking will be appropriate, for example:

- Changes in financial access are intended to reduce non-essential consumption;
- Banning DTCA is intended to reduce inappropriate demands for branded prescription drugs;
- Deregulation and formularies are intended to reduce costs to health care providers and reduce inappropriate prescribing.

However, policies are often shown to have much more wide-ranging effects than this, and can cause both wanted and unwanted changes in medicines-taking. These intentional and unintentional effects are discussed in the next sections.

In the UK, there has been limited emphasis on adherence in health care policies and there are very few policies that explicitly deal with patient adherence to medicines. Recent UK DoH plans for future roles for pharmacists, who are most closely involved with medicines-taking, do not refer to adherence, other than indirectly through medication reviews (Department of Health, 2003b). National Service Frameworks and clinical guidelines do not all address adherence issues.

Two national initiatives are the Expert Patient Program and Medicines Partnership. The Expert Patient Programme (2001) deals specifically with the long term management of chronic illness. Medicines Partnership is unusual in that it deals specifically with medicines-taking behaviour, utilising both the concepts of compliance and concordance.

There are also wider influences on adherence. Any policy change that affects any part of the prescribing process, such as primary care funding, GP availability, loss of GPs from the workforce, pharmaceutical industry pricing controls and controls on parallel imports, or any policy causing insidious erosion in health care provision integration and communication, are likely to affect adherence. In fact, in the USA, adherence has been used to assess the impact of primary care delivery on patient outcome (Safran, Taira, Rogers, Kosinski, Ware and Tarlov, 1998). It is used as a marker of a 'successful' patient-prescriber relationship. The ongoing and wide-ranging systems reform proposed for the NHS is likely to affect health care provision, particularly for patients with long-term conditions (Department of Health, 2004d). Careful examination of key changes such as the introduction of community matrons, increased numbers of foundation trusts and increased plurality of service provision may influence access to, and uptake of, medicines.

Furthermore, the general trend towards individualism in health policy, and a 'personalised NHS' where patient choice is the emphasis, may impact on adherence, but it is not clear whether policies that increase choice and patient autonomy will increase or decrease adherence. Furthermore, this trend may conflict with public health policies where the emphasis is on collectivism, such as those around vaccination, which are likely to fail if they do not take into account nonadherence. In particular, immunisation policy, which largely assumes the passive compliance of populations, has been shown to fail when this passive compliance does not occur (Vernon, 2003).

UK (and EU) policies that may be most likely to affect medicines adherence are:

1 Drug cost sharing (`prescription charges');
2 Industry-targeted price-controls;
3 Direct-to-consumer advertising of prescription only drugs;
4 POM-P switch (deregulation of medicines);
5 Expansion of prescribing to 'non-medical' prescribers;
6 National service framework medicines-taking quality initiatives;
7 Expert Patient Programme;
8 Medication use reviews.

Evidence for impact on medication adherence, and associated societal impact, was examined for each of these areas and is reported below. Key questions for future research are proposed.

Societal impact of drug cost sharing policies

Costs to patients of prescription drugs are the principal area where there is evidence for impact of societal policies on adherence.

Cost-sharing by patients has two functions: to produce revenue for the payer, and to reduce inappropriate demand ('moral hazard'). Methods used to limit drug spending are:

- Preferred drug lists (PDL) or formularies;
- Prior authorisation requirements for prescribing (PA);
- Limited numbers of prescriptions in a time period (`cap');
- `Fail first' requirement (an alternative [usually cheaper] has to be shown to fail before prescribing of the requested drug is allowed);
- Drug category reimbursement exclusions:
  - branded or combination products (such as Valium™);
  - limiting of `me-too' drugs in a class (such as proton-pump inhibitors);
  - banning entire categories (such as amphetamine appetite-suppressants);
- Patient cost sharing through fixed or variable co-payments;
- Reference pricing, where the cost of lower-price medicines in a therapeutic class is covered (below a 'reference price') but patients are charged for the extra cost of higher-price products;
- Limited financial coverage for medicines in a time period.

Cost-sharing mechanisms vary between and within countries, so making comparisons between systems is complex.

Impact of drug cost sharing policies from other countries

There is a large body of research in the USA and Canada linking patient cost-sharing, such as prescription co-payments, to reduced drug use, increased morbidity such as hospitalisation, and increased costs to health care providers. A recent review summarises the 'best' of these (Lexchin and Grootendorst, 2004). Nearly all of the 24 studies show a negative impact on drug use and health outcomes in the chronically ill and the chronically ill poor following increased patient cost-sharing. Policies that decrease established drug benefit coverage or increase patient cost-sharing consistently reduce use of appropriate and essential medicines such as thiazide, diuretics and psychotropic agents (eg, antidepressants), along with reducing inappropriate use and drug costs. Patients, forced to reduce medication use because of cost, may not make what would be considered a medically `rational' choice – choosing non-essential medications with symptomatic benefits (eg, nonsteroidal anti-inflammatory drugs) while forgoing essential medications that prolong life and prevent morbidity (eg, antihypertensive agents).

Up to 46 per cent reductions in use occur for both ineffective and effective medicines if drug co-payments are introduced (Soumerai, Avorn, Ross-Degnan and Gortmaker, 1987; Tamblyn, Laprise, Hanley, Abrahamowicz, Scott, Mayo et al., 2001). People on lower incomes wait until their condition is more serious before consulting a doctor (Strickland and Hanson, 1996). They reduce costs by not filling prescriptions, reducing intake and haggling about price (Cox and Henderson, 2002). This behaviour is reported by up to 70 per cent of patients (Cox and Henderson, 2002), but is generally not discussed between patients and prescribers (Piette, Heisler and Wagner, 2004).

There is a large body of research in the USA and Canada linking prescription co-payments to reduced drug use, increased morbidity such as hospitalisation and increased costs. Nonadherence in elderly, disabled and low-income groups in the USA is often linked to lack of prescription drug insurance (Kennedy and Erb, 2002). In Canada, increased cost-sharing by patients led to a 15 to 22 per cent reduction in essential drug use among the poor and elderly (Tamblyn et al, 2001). There was an 88 to 117 per cent increase in serious adverse events and 43 to 78 per cent increase in emergency department visits, associated with decreases in the use of essential medicines. Even small changes can have surprisingly large health effects on vulnerable populations. The chronically mentally ill are particularly susceptible to reimbursement changes; they may reduce the use of essential medications if there is any co-payment at all, even if it is as low as 50 cents (Soumerai, 2003). Those with mental health comorbidities (ie, psychoses, bipolar disorders, anxiety) reduce essential medication use when drug cost-containment policies are introduced to a greater extent than do those with somatic illnesses (Fortess, Soumerai, McLaughlin and Ross-Degnan, 2001). For example, when the USA state of New Hampshire limited Medicaid drug-reimbursement to three medications a month, patients with schizophrenia reduced their use of essential psychotropic agents by 15 to 39 per cent. Visits to community mental health centres rose by 43 to 57 per cent. Withdrawal of this policy led to a resumption in baseline levels of medication use (Soumerai, McLaughlin, Ross-Degnan, Casteris and Bollini, 1994). Elderly mentally ill patients were the most likely to reduce prescription filling when faced with increased cost-sharing (Fortess et al, 2001).

Methods to restrict the prescribing of high cost medicines are often used, sometimes called 'prior authorisation'. An empirical study of a prior authorisation policy in benzodiazepines demonstrated reductions in non-problematic use (short-term use of low doses of medication) in patients for whom they are known to be effective and essential, without substituting alternative medications (Ross-Degnan, Simoni-Wastila, Brown, Gao, Mah, Cosler et al, 2004). When the USA state of New York sought to limit the prescribing of benzodiazepines by introducing triplicate prescription programs the result was to reduce use by 48 per cent among Medicaid patients with chronic psychiatric disorders and by 60 per cent in patients with seizure disorders (Simoni-Wastila, Ross-Degnan, Mah, Gao, Brown, Cosler et al (2004). There were larger reductions in non-problematic than problematic use in this study.

Many studies link negative health effects to cost-related under use of medicines. Heisler, Langa, Eby, Fendrick, Kabeto and Piette, (2004) concluded that presence of cost-related medication restriction among middle-aged and elderly Americans is associated with a larger reduction in health status (adjusted odds ratio (AOR): 1.76 (95 per cent CI: 1.27-2.44); increased rates of angina (11.9 per cent *vs* 8.2 per cent; AOR: 1.50 (95 per cent CI: 1.09-2.07) and higher rates of nonfatal myocardial infarction or stroke (7.8 per cent *vs* 5.3 per cent; AOR: 1.51 (95 per cent CI: 1.02-2.25).

A study from Japan suggests positive economic incentives have limited, but positive, effects on adherence, in an elderly population with up to 100 per cent subsidy of prescription costs (Hagihara, Murakami, Chishaki, Nabeshima and Nobutomo, 2001)

There is a small amount of equivalent research in Europe (Lundberg, Johannesson, Isacson and Borgquist, 1998; Krobot, Miller, Kaufman,

Christensen, Preisser and Ibrahim, 2004). In Sweden, Lundberg *et al.* reported that the young, those with poor health status, low education and low income were mostly likely to decrease use of prescription drugs when user charges were increased (Lundberg et al, 1998). In Germany, poorer insurance coverage has been shown to reduce use of migraine medicines (Krobot et al, 2004).

Impact of drug cost sharing policies from the UK

The co-payment on prescriptions in England is currently £6.65, which is three times the maximum co-payment proposed for brand medicines ($5.00) under new USA federal legislation (Henry J Kaiser Family Foundation), and thirty times higher than the 50 cents reported to reduce adherence in a USA study (Soumerai, 2003). This is also a higher 'fixed' co-payment than Austria or Germany (Noyce, Hutten, Atella, Brenner, Haaijer-Ruskamp, Hedvall et al, 2000). Denmark, Finland, France, Italy and the Netherlands use graduated charges, depending on pack size or drug cost (Noyce et al, 2000). Not only is the English prescription charge very high and likely to lead to cost-related under use of medicines, it also has an illogical and inequitable exemption system. Some chronic conditions, such as diabetes and epilepsy, are exempt, but others are not, such as asthma and schizophrenia. All people over 60 are exempt, as are expectant and new mothers, irrespective of income, but only 20 per cent of people between 18 and 60, including those claiming income support, are exempt (Phelps, 2001). About 85 per cent of prescriptions filled in England per year are exempt from charges, and this statistic can be interpreted incorrectly to suggest that there is little cost-related under use of prescription medicines. However, this figure tells us nothing about the prevalence of unfilled prescriptions for essential medicines, or the influence of the prescription charge as a deterrent to visiting a GP.

There is some evidence that medicine costs incurred by patients affect adherence in the UK (Schafheutle, Hassell, Noyce and Weiss, 2002; Schafheutle, 2003a; Schafheutle, 2003b). Research suggests that, in fact, as many as 750,000 people in England and Wales may not be filling prescriptions due to cost (Phelps, 2001) and patients' cost reduction strategies are similar to those in the USA (Schafheutle et al, 2002). Patients do not talk to their doctors about cost and there was a low awareness of prepayment certificates (Schafheutle, 2003a; Schafheutle et al, 2002). There is no UK evidence available on the effects of this cost-related under use on patients' health.

Costs incurred by patients affect GPs' prescribing decisions (Hassell, Atella, Schafheutle, Weiss and Noyce, 2003). British GPs have been reported to try to reduce patients' cost-sharing by recommending OTC medicines; increasing quantity prescribed; prescribing for a family-exempt member; writing fewer prescriptions and prescribing 'stronger' medication (Hassell et al, 2003).

Perversely, in the UK, there is a perception that nonadherence is increased by patients not paying for their prescriptions (Senior, 2001), which is not borne out by evidence from the UK and other countries. Recent reports by the Royal Pharmaceutical Society of Great Britain (RPSGB) and the British Medical Association (BMA) condemning the prescription charge goes some way to calling for evaluation of impact of prescription charges on adherence and associated morbidity (Harrison, 2005; British Medical Association, 2005). A more logical and less harmful

approach to raising revenue from prescription taxes is unlikely to occur without the types of analysis carried out routinely in the USA and Canada.

In Wales, prescription charges have been abolished for everyone under the age of 25. The cost of a prescription for everyone else is £3 (from April 2006) and prescriptions will be free by 2007 (British Medical Association, 2005). The rationale for selecting this initiative over other alternative prescription co-payment schemes has not been made clear. The impact of this policy change on overall medicines revenue for the Welsh Assembly or on patient adherence does not appear to have been evaluated.

Impact of industry-targeted price-controls

Different countries exert different levels of price-controls on medicines. Very few countries allow manufacturers to set their own prices. Countries can directly control prices using a range of criteria. These include assessing the therapeutic value of the drug (Belgium, France, Italy and Sweden); referencing the price to existing products (Belgium and France); reference to international comparisons (Canada) and contribution of pharmaceuticals to the economy (UK and Spain) (Ess, Schneeweiss and Szucs, 2003). Indirect controls include reference pricing, where drugs are only reimbursed to the level of the 'reference drug' for a class (Canada and Germany); generic substitution (Germany, Denmark, the Netherlands, Switzerland), profit control (UK) and price freezes (UK, Germany, Switzerland, Italy, Greece, Spain) (Ess et al, 2003). The impact of industry-targeted price-controls on patient adherence has not been widely investigated. The impact will be affected by whether the patient is exposed to the 'true' cost of the drug, or not. It is likely that increased prices, where the patient is exposed these prices, will reduce adherence to both essential and nonessential medicines, in the same way as other cost-sharing mechanisms.

Industry-targeted price-controls increase the complexity of assessing impact of cost-sharing policies on adherence. The real costs for medicines paid by patients in different countries will be affected by divergence in drug prices and patient cost-sharing mechanisms. Very high drug prices in countries such as Germany, may not translate into high overall costs for patients (Noyce et al, 2000). British patients have among the lowest drug prices in Europe in many cases, but, if paying the prescription tax, may pay more than the actual price of the drug, and thus incur among the highest costs (Noyce et al, 2000). However, in the UK, under current patient cost-sharing arrangements, patients are protected from industry-targeted price-controls and adherence should not be affected by them.

Impact of direct-to-consumer advertising of prescription medicines

The USA and New Zealand are the only industrialised countries that allow DTCA. Legislation is being reviewed in Europe, Canada and Australia. The European Public Health Alliance suggests the following arguments for and against DTCA (European Public Health Alliance, 2002):

What are the arguments in favour of DTCA?

- People want and need information on medicines;

- Advertisements will help people to get needed medical care at an earlier stage;
- Advertisements will lead to better adherence;
- A doctor's prescription is needed, so the patient is protected.

What are the arguments against DTCA?

- Prescription drugs are not like other consumer goods. Even when used properly, they can cause serious harm;
- People are vulnerable when they are ill;
- Advertisements aim to stimulate sales. They cannot provide impartial, objective information;
- Advertising increases pressure from patients to their doctors for reasons unrelated to medical evidence;
- Advertising promotes the consumption of medicines;
- The cost of an increased consumption of prescription medicines puts further pressure on the sustainability of national health care systems.

DTCA leads to increased requests for advertised medicines and more prescriptions, despite physician ambivalence about treatment choice (Mintzes et al, 2003). In the USA, where DTCA has been allowed since 1997, there is evidence to suggest that DTCA has significant effects on prescribing and taking of medicines (Rosenthal, Berndt, Donohue, Frank, and Epstein, 2002; Hotton, Larson, Koepsell and Downer, 2003). DTCA tends to focus on diseases where patients themselves can identify their own symptoms, such as allergies, arthritis and depression. Patients with diabetes, depression, hypercholesterolaemia, arthritis and allergies were more likely to persist with therapy for six months when they had asked for the medicine with prompting from a DTCA (Pfizer Inc and RxRemedy Inc, 2001).

DTCA may improve adherence to the products advertised. However, this may be associated with inappropriate prescribing. The strengths of DTCA are likely to be informing and empowering patients, destigmatising diseases like depression, and increasing awareness of underdiagnosed and undertreated diseases. However, these objectives could be met through processes other than DTCA. The ability of patients to access American websites with information on medicines via the internet may yet attenuate European legislation preventing DTCA.

Impact of deregulation of medicines

Deregulation of medicines from prescription-only (POM) to a pharmacy (P), or over the counter (OTC) medicine has the potential to transfer drug costs to the patient from the health care provider, as well as providing increased availability to patients. It may be predicted that patients' use of OTC products will be affected, not only by patient characteristics, such as self-efficacy, but also by the cost they incur for that product.

Medicines available without a prescription can be recommended by clinicians, pharmacists or lay significant others. The definition of adherence where the patient follows recommendations from one of these sources, or can effectively self-prescribe, requires clarification. There is some work on the impact of deregulation on adherence. In the USA,

prescribing in areas such as anti-histamines and H_2-receptor antagonists is reduced after deregulation, but it is not clear if this affects overall use of the medicines (Tasch, Goeree, Henke and O'Brien, 1996; Andrade, Gurwitz and Fish, 1999). In Sweden, utilization of medicines deregulated increased after deregulation, suggesting that 'adherence ' to a product increased (Carlsten, Wennberg and Bergendal, 1996). It was not clear whether use was appropriate. In the UK, deregulation of H_2-receptor antagonists did not lead to an increase in OTC sales, but to an increase in GP prescribing levels (Furler, Rolnick, Lawday, Mak and Einarson, 2002). This suggests that patients in the UK are more deterred by direct costs, have lower levels of information, use initial experience of OTC medicines to request subsequent prescriptions, or are subject to other barriers to use of deregulated medicines. Research has shown that, in the UK, patients already paying prescription charges and those who are most happy to self-medicate are most likely to use OTC medicines (Payne, Ryan-Woolley and Noyce, 1998).

This evidence does not tell us if utilisation is appropriate, or if the patient is adhering to a course of action decided upon by themselves or with the support of a health care professional. USA work carried out around the impact of deregulation of second-generation (`non-drowsy') anti-histamines suggests that patients revert to the cheaper product, in this case, a sedating anti-histamine. Some of the savings made by the health care provider from limiting spending on the second generation anti-histamine were lost due to the cost of loss productivity associated with use of sedating anti-histamines (Sullivan and Nichol, 2004).

Impact of non-medical prescribers

Supplementary prescribing rights have been granted to nurses and pharmacists in the UK, and recently, independent prescribing rights have been introduced for this group. The impact of the patient-prescriber relationship on adherence is discussed in Chapter 3, and is known to be influential in adherence. Increasing the numbers of prescribers and changing the nature of that relationship through the use of different professional groups is likely to affect adherence (Nolan, Bradley and Carr, 2004).

Impact of National Service Framework medicines-taking quality initiatives

While use of medicines is an integral component of each of the National Service Frameworks (NSFs), the 'coverage' of adherence to medication is variable across the NSFs. Most notable is the focus given to adherence related issues in the NSF for Children, Young People and Maternity Services (Department of Health, 2004a; Department of Health, 2004b) and the NSF for Older People (Department of Health, 2001b; Department of Health, 2001a). There is also relatively good coverage of medication related behaviour and issues around self-management in the NSFs for Diabetes, Renal Services and Long-Term Conditions (Department of Health, 2003a; Department of Health, 2004c; Department of Health, 2005). Encouragingly the NSF for diabetes has drawn on the Expert Patient Program for recommendations on how to enable patients to get the most out of their medicines (Department of Health, 2003a). The importance given to adherence to medication in the NSF for Coronary Heart Disease (CHD) and the NSF for Mental Health seems to be somewhat lacking (Department of Health, 1999; Department of Health,

2000a). Within the NSF for Cancer and the NSF for Paediatric Intensive Care, the scope for discussion of patient adherence to medication has obvious limitations (Department of Health, 1997; Department of Health, 2000b).

Self-management features highly in most of the NSFs, with training programmes for patients, recommendations for increased information about treatment and use of compliance aids. It is not evident from the literature that medicines-taking quality initiatives that may have been developed from these NSFs and supporting documents have been implemented or evaluated.

Impact of the Expert Patient Programme

Recognition of the need to treat patients with chronic illness differently from those with acute illness (Holman and Lorig, 2000) led to the Expert Patients Task Force and subsequent development of the Expert Patient Programme (Expert Patient Task Force, 2001). This aims to encourage patients to play a greater role in decisions about their illness, which may affect subsequent adherence to medicines. This programme will be rolled out throughout the NHS by 2008 (Department of Health, 2004d). It is not evident from the literature that the Expert Patient Programme has been evaluated.

Impact of medicines use reviews

The role of the pharmacist in optimising medicines use through medication use review has been widely researched (examples of UK studiesinclude Zermansky et al, 2001 and Krska et al, 2001) and a full review of this literature is not appropriate here. `Medicines use review and prescription intervention service (MUR)' came into effect as an advanced service to be provided to the NHS in England and Wales by pharmacy contractors in April 2005 (see Box 1) (Prescription Pricing Authority, 2005). Pharmacy contractors can undertake up to 400 MURs in any one year and the current reimbursement is £25 per MUR.

It is not clear how pharmacists are conducting these MURs, how many are being carried out and in which patient groups. Also, it is not evident from the literature that the impact of MURs (as defined in the Drug Tariff) on adherence has been evaluated.

Box 1: Medicines use review and prescription intervention service

`The underlying purpose of MUR services is, with the patient's agreement, to improve his knowledge and use of drugs by in particular:

- establishing the patient's actual use, understanding and experience of taking drugs;
- identifying, discussing and assisting in the resolution of poor or ineffective use of drugs by the patient;
- identifying side effects and drug interactions that may affect the patient's compliance with instructions given to him by a health care professional for the taking of drugs; and
- improving the clinical and cost effectiveness of drugs prescribed to patients thereby reducing the wastage of such drugs.'

(Prescription Pricing Authority, 2005)

Measuring policies' impact on adherence

There is a danger that policies that affect adherence intentionally or unintentionally may be introduced on the basis of assumptions about adherence alone, as a reaction to increased drug costs, or without consideration of wider implications of the change. However, it is possible to use evidence to support policy formulation. Furthermore, it is possible to evaluate the impact of policies on adherence.

Study design in policy analysis

Any policy that may affect medicines adherence is likely to affect patient health and overall costs to the health care provider, the patient and society, so should be evaluated. Evaluation of policies is a complex process and often cannot use the same study design as a randomised controlled trial for a medicine. Also, policies are very often introduced as a political imperative, removing opportunity to assess the 'baseline' situation.

Interrupted time series studies in medication use policy research

Interrupted time series analysis is a method increasingly used to examine the cost and outcomes of educational, administrative and policy interventions in medication use research (Wagner, Soumerai, Zhang and Ross-Degnan, 2002). This is a quasi-experimental design to evaluate longitudinal effects of these interventions. It allows the quantitative assessment of how much an intervention changes an outcome of interest, immediately after the change (such as a policy change), over time, whether there was a delay in effect, whether the effect is transient or not, and whether factors other than the intervention could explain the change. Rather than use a control group of patients, it relies on comparing the experiences of a group of patients affected by the policy versus the (counterfactual) experience of the same patients if the policy had not been implemented (Schneeweiss, Maclure, Soumerai, Walker and Glynn, 2002). Counterfactual experiences cannot be observed, so it is assumed that the counterfactual is correctly described by extrapolating from the same population's previous experience. This method was used in the USA state of New Hampshire to examine the impact of the introduction of a policy to limit Medicaid drug-reimbursement to three medications a month (Soumerai et al, 1994). Monthly doses for the cohort affected by the policy change were examined before the cap was introduced, during the period when the cap was enforced, and then during the period after the cap was removed. To test the validity of the assumptions around counterfactual experience, these data were compared with a control cohort from New Jersey. This method enabled the researchers to identify the negative impact of the policy on prescription-filling behaviour, and associated increases in other health care consumption (Schneeweiss, Maclure, Walker, Grootendorst and Soumerai, 2001).

Randomized controlled trials in medication use policy research

There are very few well-designed observational evaluations of medication use policy. Many studies are seriously confounded by unmeasured characteristics and patient selection bias. These problems can be controlled by using a randomised trial design, but this method is rarely used in evaluations of medication use policy (BMJ, 2004). One rigorous example of this approach is the evaluation of the cost and

clinical outcomes associated with restricting reimbursement for nebulised respiratory therapy in Canadian adults (Schneeweiss, Maclure, Carleton, Glynn and Avorn, 2004). This study used the prescriber as the unit of randomisation to minimise contamination, prescription filling as a proxy for adherence, clinical outcomes, and direct healthcare costs. Moderate net savings and no increase in unintended health outcomes from the policy were found. This method was compared with an interrupted time series analysis and found concordant results.

Conclusion

Should we evaluate policy?

It is not a responsible use of public resources to fund initiatives and policies that are introduced solely on the basis of ideology, reaction or evangelism. Specific initiatives to improve adherence, whilse laudable, are costly, divert resources from elsewhere in the NHS and we do not know if they are working. Methods are available to assess the impact of medication use policy and evaluations should be employed alongside policy change.

Which policies need to be evaluated?

Policies or initiatives that purport to change funding arrangements for medicines or prescribers; educate or empower patients; educate stakeholders (such as physicians and pharmacists); affect the prescribing process or affect communication should be evaluated for impact on adherence. We recommend assessment of policies or initiatives that have the potential to either advertently or inadvertently change adherence, and work overseas has shown this can be done. Stakeholder analysis and early involvement of those stakeholders may produce more insightful policies around medicines use.

Barriers to evaluations of medication use policy

Policy evaluation will continue to be hampered by lack of data until strategic efforts are made to increase the quantity and quality of patient-specific data collected routinely within the NHS. Minimum data requirements to assess the impact of policies on adherence are: patient demographics; diagnoses and co-morbidities; prescribing and prescription-filling behaviour; laboratory tests ordered and returned and clinical indicators (such as weight and blood pressure); all health service contacts (primary and secondary care) and health outcomes.

Priority research questions

What is the economic impact of nonadherence in diseases where nonadherence has been proven to have clinical consequences (such as diabetes, asthma, HIV infection, cancer, cardiovascular disease, severe mental health problems, organ transplantation etc)? This evidence needs to be supplemented by an assessment of the level of preventability of nonadherence in each group studied and associated economic impact. Patient groups within disease types likely to incur the greatest increases in morbidity due to nonadherence need to be identified (such as patients with multiple co-morbidities).

1. Are data routinely collected and readily available that can be used to allow assessment of impact of nonadherence, and if not, how can these minimum datasets be developed?
2. How does the prescription charge system in England, Wales and Scotland, affect prescription filling for essential and non-essential medicines, subsequent patient health, present and future health service and societal cost?
3. How effective, equitable, timely, patient-centred and efficient are national and regional adherence-enhancing policies and initiatives?
4. Does the use of medicines change because of deregulation and is this change in use appropriate or inappropriate? Does deregulation lead to financial barriers that reduce use in some groups?
5. Does the introduction of supplementary and independent prescribing rights for non-medical prescribers create a welcome or confusing plurality of service provision, and how does this impact on medicines-taking behaviour?
6. How are pharmacists carrying out medicines use review (MURs), do they affect patients' beliefs, medicines-taking behaviour or health, and how can pharmacists optimise the MUR process to support informed choice about medicines?

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Section 6 Unpicking the philosophical and ethical issues in medicines prescribing and taking

Alan Cribb & Nick Barber

In this Chapter we look 'behind' and 'beyond' the terms compliance, adherence and concordance in order to focus upon the fundamental questions these concepts raise about the acts of prescribing and medicine taking. In particular, we emphasise the importance of scholarship into what should be done – ie, the central importance of asking questions, not just about what actions are taken by prescribers or patients, but also asking about what actions ought to be taken. To help open up this field of inquiry we identify some of the core values underlying the domains of medicines prescribing and taking, and the major ethical conflicts that arise in these domains. Finally, we sketch out fundamental research questions in this area.

Terms, concepts and models

Compliance, adherence and concordance mean different things, and are used (separately or in combination) to do different kinds of jobs. Roughly speaking, compliance refers to the extent to which patients follow doctors' prescriptions about medicine taking; adherence - although it is often used interchangeably with compliance - refers to the extent to which patients follow through decisions about medicines taking (ie, leaving open the question of who makes these decisions or how they are made); and concordance refers to the extent to which patients are successfully supported both in decision making partnerships about medicines and in their medicines taking.

In order to make sense of the complex sets of issues associated with the three title terms we think it is useful to make two sets of distinctions. First, there is the distinction between medicines prescribing and medicines taking. Although for certain purposes it is necessary to consider these two things together (eg, to understand any effects that different models of prescribing have on medicines taking), the two should also be considered separately, not least because professionals and patients are situated differently with respect to these two domains. Second, there is the distinction between two different kinds of questions that can be asked about medicines prescribing and taking – scientific and normative[9] questions. By 'scientific' we mean questions about the description and explanation of medicines prescribing and taking processes and practices and the factors that influence them. By

[9] These might also be referred to as 'ideological' questions - the usage adopted where these issues were introduced in Chapter 1. The project team used these terms interchangeably, ie, simply using 'normative' or 'ideological' to mean 'questions about values' and indicate a contrast with scientific questions.

'normative' we mean questions about what medicines prescribing and taking should take place.

There are a range of normative questions in play here – for example, we can ask what medicines prescribing and taking practices are desirable, what are the respective responsibilities or obligations of different agents in this sphere, what medicines prescribing and taking practices ought to be promoted and, in turn, what forms of 'promotion' (support, encouragement, persuasion, etc) are ethically acceptable?

Our argument here is that:

In using concepts such as concordance, adherence and compliance it is essential to bear these two distinctions in mind. One implication of taking these distinctions seriously is to note that specific concepts, interpretations or definitions of concepts, are not always equally useful in each of these domains.

The scientific and normative agendas are both important and are mutually implicated – research is needed into both. The normative agenda relating to the field of concordance, adherence and compliance is both rich and highly contested. In the area of medicines prescribing and taking there are a broad range of values 'at stake' that need to be distinguished and explained so that the tensions and priority relationships between values can be acknowledged and addressed (that is to say it is often not possible to secure all of the values deemed desirable so we need to think about what matters most). These value tensions call for ethical judgement and give rise to ethical dilemmas in the area.

The value debates and ethical issues at stake in the domains of medicines prescribing and taking should help to frame the scientific research agenda and can also be illuminated by it. Some key questions for the research agenda emerge from taking the normative dimension seriously.

Our primary concern in this Chapter is to stress the normative agenda because otherwise there is a risk that research will be directed at questions like 'does A increase B' without any account of whether A or B are the right thing to do. This is far from a purely academic consideration: there are some very real ethical judgements to be made and defended in this important policy area.

Different concepts, different uses

The terms compliance, adherence and concordance are different concepts that can be useful in different ways. Concepts with a narrower range tend to be easier to operationalise for scientific research. In this sense 'compliance' is a useful term – useful because it has a relatively determinate scope. However, saying this is quite separate from saying that compliance is the norm which ought to govern medicine taking. Indeed, the genesis and construction of the concept(s) of concordance reflects to a large extent the foregrounding of certain value questions and in particular the rejection of compliance as a norm, ie, it reflects a move away from a simple emphasis on biomedical knowledge and authority and of paternalistic assumptions about the relationships between professionals and patients. So whereas 'compliance' lends itself to scientific uses, 'concordance' is manifestly a normative concept.

Before explaining this in more detail, it is first worth spending more time clarifying the concept of concordance, as it has had two related, but distinct definitions. When this matters in this Chapter we will distinguish them by subscripts 1 and 2. The first definition derives from the document in which concordance was formally proposed: 'From compliance to concordance' in 1997, the second refers to the definition currently found at www.concordance.org, which is now the Medicines Partnership web site.

Concordance$_1$ is:'an agreement reached after negotiation between a patient and a health care professional that respects the beliefs and wishes of the patient in determining whether, and how, medicines are taken.' If the prescriber and patient cannot reach agreement, then the patient's view should have precedence.

Concordance$_2$ is described by a sentence and a diagram. The sentence is: `Concordance is a new way to define the process of successful prescribing and medicine taking, based on partnership.' The diagram is a roof supported by three columns. The roof states that: `Concordance is a process of prescribing and medicine taking based on partnership.' The content of the three columns is:

`Patients have enough knowledge to participate as partners' and `Health professionals are prepared for partnership'

`Prescribing consultations involve patients as partners'

`Patients are supported in taking medicines'

Each of these goals is supported by more detailed statements.

There is no official statement about how these two versions of concordance are related. The original concordance document suggested that the concept would need to be developed. Specific statements, made in the context of the first definition, about respect for beliefs and wishes, and about the patient's view taking precedence if there is no agreement, are not visible in the second definition. However, the goal of patient involvement, and the linking of prescribing and medicine taking, remains constant.

It is plausible to argue that the concept of concordance has the opposite characteristics to compliance as summarised above, ie, concordance may be useful as a normative or aspirational term but is arguably insufficiently defined in scope (at least considered on its own) to be easily operationalised for scientific purposes.

Box 1: Illustration of the different uses of the terms

	Prescribing	**Medicines taking**
Used as normative statement (What ought to be done)	Concordance$_1$ Concordance$_2$	Concordance$_2$
Used for scientific measurement		Adherence Compliance

These uses of the terms are illustrated in Box 1 (above). This indicates where we are suggesting the terms 'fit best'. However, it is vitally

important to see that the normative agenda is inescapable whatever terms are used. Any policy or analysis which relies on the concepts of compliance or adherence will inevitably give the impression that these refer to some good thing - ie, that, roughly speaking, more adherence is inherently better than less adherence - unless it explicitly says otherwise (eg, sets out a more qualified normative position). Those people who research compliance/adherence cannot evade normative agendas, they can only fail to address them explicitly. The great advantage of the concept of concordance is that it explicitly wears its 'value-laden' nature on its sleeve. Its weakness, we want to suggest here, is that it tries to do rather too much. As things stand, the concept of concordance lacks the degree of specificity that is useful in both scientific and normative analysis. In the remainder of this section we will begin to indicate our reservations about placing too much weight on the concept of concordance given this comparative lack of specificity.

It is hard to evaluate concordance against the broader healthcare literature because to do so requires some decisions about what concordance is – for example, is it a whole philosophy of care, or is it a concept focussed on the nature of decision-making about medicines? We go into this further in the next section, however, we can illustrate some of the issues by relating concordance to the wider literature on medicines decision-making. First, we explain the dominant models.

Currently, there are four frequently discussed models of patient-doctor decision-making about treatment: Paternalistic decision-making, interpretive decision-making, shared decision-making and informed decision-making (Emanuel and Emanuel, 1992; Laine and Davidoff, 1996). There is no universally agreed definition of these models and what they include. On the contrary, there is much confusion and overlap in how these models are understood (Charles, Gafni and Whelan, 1997). Furthermore, there is considerable debate about what the application of these models would involve.

Generally, decision-making models vary in the respective roles that doctors and patients take in the final selection of treatment. From the point of the patient this means the models differ according to the degree to which patients are able to take part in, and perhaps shape, choices about their treatment. In the paternalist model, practised over centuries, the doctor chooses the treatment. In the interpretive model (Emanuel and Emanuel, 1992), the doctor decides about a treatment plan, but does so by taking the values and preferences of the patient into consideration. Shared decision-making means that the doctor and patient take steps to participate in the process of treatment decision-making, they share information and a treatment decision is made to which both parties agree (Charles et al, 1997). Finally, in the informed decision-making model the patient decides on his or her own, after the doctor discloses information, about benefits, risks and alternative treatment options.

The model of decision-making found in concordance$_1$ seems to be closest to, but distinct from, the shared decision-making model. It is different in the assertion that the patient's view should have precedence and because it allows for the patient to delegate the decision-making authority to the doctor (Pollock, Belnkinsopp and Grime, 2002). By contrast, in the shared decision-making model, delegating the decision-making authority to another party is seen as actually falling outside shared decision-making. The suggestion that the patient's decision should predominate if there is disagreement moves the model nearer to

an informed decision-making model, however, it does not specify the information transfer that must occur, in the way the informed patient models require. Thus, if we confine our attention just to this area of understanding medicines-related decision-making, we can see that there are a range of interpretations of what exactly is required by 'concordance' with (a) different emphases on the scope and significance of patient autonomy, and (b) different assumptions about what specific processes and outcomes need to be in place for concordance to be achieved.

Fundamentally, however, this is not simply an issue of conceptual or definitional clarity. The point is that concordance is a normative concept; it is a statement about appropriate or desirable values (we unpick these in the next section) but it is a statement that was introduced in what was essentially a scientific context. That is, it was introduced as part of the 1997 document, cited above, that presented an excellent analysis of the literature on nonadherence and its causes, including patient beliefs. The problem is not merely that statements of values cannot be derived from statements of fact, but also that statements of value themselves require the same degree of careful analysis and elaboration that are routinely applied in scientific research. Without this level of normative analysis and elaboration, value statements are bound to lack specificity. What is needed is a normative account that helps us to see the range and combinations of things that 'matter' and that also helps us to recognise (and deliberate about) situations in which different valuable things come into conflict.

Compliance, adherence or concordance – why do they matter?

In this section we look 'behind' the three title terms to identify the key sets of values they embrace. There are four broad (sets of) values in the area. Within each of these four categories there are different, and sometimes competing, values or interpretations of values.

The categories are:

A. Following through decisions over time

Including: A1. The following through of professional recommendations about treatments/action and/or A2. The following through of patient informed choices about treatments/action. (Following through here means carrying out and/or appropriately reviewing).

B. Good quality decision making

Including: B1. The supporting of informed patient choice (patient education, understanding, decision-making involvement, responsibility) and/or B2. The supporting of informed professional choice (knowledge of patient specificities, perspectives and preferences).

C. Good quality healthcare relationships

Including: C1. Broader and deeper communication and/or C2. Mutual respect and/or C3. (Elements of) partnership working.

D. Good outcomes

Including: D1. Patient satisfaction with medicine taking and/or D2. Optimal health gain for individuals and/or D3. Promoting cost-effective use of treatments and/or D4. Stewardship - avoiding the waste of (often collective) resources (e.g. medicines, consultation time) and/or D5. Public health.

This kind of analysis could obviously be further extended, refined and debated but the key point is that A, B, C and D – and the components thereof – represent different valued things. The danger is that unless they are separated out in this kind of way they will be fudged together with results that are both scientifically and ethically unhelpful. The risks of fudging together different values can be illustrated by returning to the example of concordance.

The concept of concordance explicitly encompasses A, B, C and D with a particular emphasis on the role of a good relationship (C) in influencing decision making (B) and thereby following through actions (A) to deliver good outcomes (D). As with compliance and adherence, the relevant purposes or outputs are not explicitly built into the definition of concordance but they are never far beneath the surface. For example, the introduction of `From Compliance to Concordance' states: `The aim of concordance is to optimise health gain from the best use of medicines, compatible with what the patient desires and is capable of achieving'. This all-embracing character of concordance, that is the fact that it draws attention to all of these elements, makes it a worthwhile reference point for thinking about the domains of medicines prescribing and taking. However, this 'all embracing' character can also be a serious limitation in practice.

The problems of operating with a very broad ideal such as this one – i.e. the dangers of 'fudging'- can be raised in the form of a question: When we advocate concordance (or when we try to determine how far concordance is being achieved) how should we weight the various elements mentioned in the concordance literature? What should we do when and where the various elements conflict? An 'all embracing' account can easily slide into a 'have it all' account and serve to obscure the many questions of priority as well as the tensions and dilemmas inherent in medicines prescribing and taking. Of course, the extent to which the various elements of concordance are, or are not, in tension in practice is largely an empirical question. But it seems wiser to assume that the fit will be less than perfect than to assume the opposite. To be fair to the advocates of concordance, the existence of potential tensions and dilemmas is to some extent acknowledged in the fuller accounts from which the above extracts are drawn. And, what is more, it is even highlighted in the above quote about the aims of concordance$_1$ which spells out that the aim is not to optimise health gain *per se* but to do so in a way that is consistent with patient desires. In this case the potential conflict between patient wants and health gain is clearly signalled and the straightforward priority of the former is asserted.[10]

[10] Although it is not clear whether this priority is still present in concordance$_2$.

Now we must stress that although we have concentrated our 'critical' attention on the concept of concordance, this is not because the concept of concordance is particularly weak from a normative perspective. If anything the opposite is true – the point is the literature on concordance recognises the centrality of value judgements in the area and advocates for a particular, and broadly 'reforming' agenda in the relationship between prescribers and patients. It is this fact that allows us to raise concerns about its comparative lack of specificity. By contrast, the scientific literatures on compliance or adherence adopt a 'value-neutral' face. Yet this means that they simply fail to contribute to the normative agenda. To the extent that these literatures remain focused on measurement, description or explanation they tell us nothing, in themselves, about what medicines prescribing or taking ought to take place. Even worse – as we signalled above – they may indirectly serve to sustain or reinforce certain value positions (eg, that more compliance is always a good thing) by default.

In this section we have listed 12 'values' related to compliance, adherence and concordance (under the four categories A to D, above) that deserve consideration, a range of values that all need to be balanced together. This list is not meant to be either definitive or exhaustive but simply to indicate the complexity of the domain. In the next section we focus on some of the central dilemmas and balancing acts facing policies on prescribing and medicine taking. These balances may be different in different health systems; however, we will focus on the NHS.

Ethical Issues - patient autonomy, paternalism and the public good

Arguably the central ethical issue in the field of medicines prescribing and taking is the right balance between patient autonomy, on the one hand, and paternalism or other countervailing goods on the other. Concordance, and most other decision making models, respect the patient's right to autonomy; the models are structured to bring various degrees of patient autonomy into the prescribing decision.

Paternalism is often portrayed as an undesirable aspect of the practice of medicine, however, this need not be so – it has an important role. There is nothing necessarily bad about being paternalistic, which simply involves limiting people's freedom of choice or action on the grounds that it is in their interests to do so. We can always separate out the two questions – (i) Is this a case of paternalism? and (ii) Is paternalism ethically justifiable in this case?

It should be noted that the whole of our medicine decision-making framework is broadly paternalistic. This is certainly true of the NHS but it is also true, albeit sometimes in different ways, in any context where access to medicines is controlled for health protection reasons. The fact that, under the Medicines Act and other legislation, there is not open access to all medicines (or at least a free market for all who can afford to buy them) is routinely explained by the need to protect individuals from taking risks with their own health and lives or with the health and lives of others. The former reason is a classic example of paternalism and the latter is an example of a utilitarian or broader 'public good' justification. If we believe that these are both good reasons then we believe that the medicines decision-making framework of the NHS represents a case of justifiable paternalism. Within this framework, doctors play a crucial part

in the 'filtering' or 'gatekeeping' mechanisms that limit patients from having direct access to medicines simply on the basis that they want them and/or can afford to buy them. It is a context which is so-to-speak framed by paternalism and thus the question becomes not 'paternalism or patient autonomy' but rather 'how far should paternalism extend and when and how should it be balanced by respect for patient autonomy?'

Hence circumscribing patient choice might, in principle, be justifiable for:

1 Broadly paternalistic reasons, such as:
   - Patient harm minimisation (an aspect of beneficence or non-maleficence) – ie, the need to balance autonomy with independent, knowledge-based judgements about patient welfare and the relevant costs, benefits and risks of decisions.
   - The underpinning of trust or care (another aspect of beneficence or non-maleficence) – ie, working in partnership is only one relevant good in healthcare relationships, in many instances it needs to be balanced against other relationship related goods.

2 Broadly public good reasons - such as:
   - Stewardship – the effective use of shared resources.
   - Fairness – the need to consider the interests of everyone affected by medicines decisions, including, in a system such as the NHS, the need to protect roughly equal access to treatments on the basis of need.
   - Public health (and other collective goods) – the potential effects of medicines use (or non use) on public health is clearly a relevant factor and obviously so in certain areas, such as infectious disease control. There are also many other social or collective consequences of medicines policies and strategies which have potential relevance here – including, the direct effects of medicines on the environment or more diffuse effects, such as changes in the cultural climate.

It is useful to distinguish between medicines prescribing and medicines taking in this respect. As far as medicines taking is concerned, patients' wants and choices are, of course, fundamental because – in the normal case – taking medicines is 'up to' patients. To say that circumscribing patient choice may be justifiable for various combinations of these reasons is only to begin the argument. Each context and case has to be considered on its own merits. But this list reminds us that even in the area of medicines taking there can be good reasons to circumscribe or constrain patients' freedom of choice or action with regard to medicines (eg, in cases of infectious disease or mental ill-health where public health or safety is potentially at risk). In the area of prescribing it is, by contrast, routine for patients' wants to have to be balanced against what is suggested by the doctor's evidence base on the one hand and population-oriented or public good on the other. This is, in part, what underpins the prescriber having a gate-keeping role.

Research questions and research priorities

The fundamental normative questions raised by this field - the questions which we are suggesting must inform the setting of research priorities – can be expressed, in simple terms, as follows – What is good prescribing? What is good medicines taking? In other words, what goals and ideals should inform policies and practices in these domains? As we have argued, most existing literatures do not even attempt to address these questions because they are concerned with more scientific

(descriptive or explanatory) questions. And, to the extent that they do address these questions, existing literatures do not – perfectly understandably - engage with the level of analysis or argument that might be expected in ethical debate. Nonetheless, these literatures do provide some bearings on how we might begin to answer the normative questions and represent a useful starting point on which to build a normative analysis and research agenda.

Good prescribing

The literature on good prescribing is curiously sparse, considering medicines are the most common method of treatment in industrialised countries. There are three strands to this literature. The first defines good prescribing pharmacologically, and is usually used as a way of identifying 'poor prescribers'. A second strand deals with prescribing in challenging circumstances in which specific ethical conflicts are at play, such as prescribing for the terminally ill. A third strand of literature explores the ideal type(s) of decision-making about treatment between doctor and patient. These have been described earlier in the Chapter. There has, however, been little work on what factors should be considered in the prescribing process or on how these factors should be deliberated about. We have previously proposed three elements that need to be balanced together (Cribb and Barber, 1997):

1. The patient's wants.
2. Technical properties of the drug – by which we mean its pharmacology and other properties, such as its form (liquid, tablet etc) and cost.
3. The general (or collective) good.[11]

(The ethical relevance of these elements was illustrated in the previous section).

By what process ought these elements to be brought together to make a decision? The decision-making models that are proposed, such as shared decision-making and informed decision-making, all offer elements of choice to the patient, however these models - like concordance – are not designed to, and cannot do everything. Some important questions, which are key to defining good prescribing, remain to be addressed (Wirtz, Cribb and Barber, 2005). In particular:

The models do not address how the option set ought to be generated; ie, how the potential treatment options to be offered to the patient might be constructed, eg, whether patients have a role in constructing the option set.

Although the decision-making models state what sorts of information should be considered in the decision (such as values, beliefs, preferences), they do not state how all the information should be brought together to make a final decision. Umbrella phrases such as 'mutual discussion' or 'negotiation' are used, which are open to wide

[11] Some corroboration of the practical relevance of this model comes from a review of the literature on appropriateness (Buetow, Sabbald, Cantrill and Halliwell, 1997).

interpretation. There is a need for a better description of the full process of dialogue and deliberation. Nor has there been any careful analysis of the relative importance of the intrinsic and instrumental reasons for dialogue.

The significance of the accountability of the health professional is not fully recognised in the models. The deep seated ethical and legal differences between professional and lay patterns of accountability may well be the fundamental limitation of models of patient involvement, yet this has not been addressed.

In summary, the concept of good prescribing is underdeveloped. The most developed aspect – patient involvement in decision-making – is in any case rarely used in practice, and this may well reflect the need for significant normative work to develop this concept and to integrate it with other aspects of good practice.

Good medicine taking

Once again, the normative question about the nature of `good medicine taking' is not directly addressed in the literature. The two concepts that bear upon and help to illuminate this area are concordance and 'informed adherence' (Horne and Weinman, 2004).

Concordance$_2$ states that the patient should be supported in medicine taking, and this is illustrated by four statements about: reviewing medicines, discussing medicines and medicine taking with patients, dealing with patient's practical difficulties in medicine taking, and professionals sharing relevant information with each other. This is essentially a professionally focused concept; the patient's full role and responsibilities are not richly elaborated.

Weinman and Horne have proposed 'informed adherence' as a practical ideal (Horne and Weinman, 2004). They build on a psychological model of informed choice (Michie, Dormandy and Marteau, 2003). Their goal is that patients are informed about the evidence base of their medicines, and that the patient's choice is not encumbered by false beliefs or understandings about their condition or the medicine. This is a carefully defined model that enhances the narrow assumptions of 'compliance models' with an acknowledgement of the importance of the patient's perspective and the reasons for adherence. It thereby does some important normative work whilst remaining sharp enough for use in rigorous scientific studies.

These two concepts, concordance and informed adherence, both give useful pointers towards the foundations of good medicines taking, but are simply not designed, in themselves, to illuminate all of the relevant issues and cases which could arise when asking the question:`What is good medicines taking in this instance?'

For example: (a) If a patient has tuberculosis and is treated by medicines, should the prescriber just provide information relevant to the patient's own health, or should they also provide information about the wider societal consequences of not taking the therapy, ie, infecting others? How far should people who are taking medicines be 'given' responsibility, or held responsible, for the social effects of their choices? (b) How should we deal with patients who have their values or beliefs altered by mental illness, or who have significant competence limitations? ie, When should we encourage, or even put pressure, on

patients to take medicines and focus much less on their own understanding or reasons for acting? (c) Patients may also face difficult ethical decisions about medicines taking in their own lives. A medicine may adversely affect the person's performance at work. What should a patient do in this situation? There are complex loyalties, responsibilities and accountabilities at play in these cases which transcend the question of their understanding of their health conditions and medicines.

In short, much work needs to be done to answer questions about what prescribers and patients ought to do with medicines. Some of these unresolved questions are very fundamental generic ones about, for example, the right balance of roles and responsibilities. However, there are, in addition, a multitude of more specific questions which arise from the sheer diversity and complexity of practice.

Emerging research priorities

The ethical agenda of balancing respect for patient autonomy with paternalistic and public good considerations, and the fundamental questions about the nature of good prescribing and medicines taking, give rise to crucial normative research questions that overlap with, and must be fed into, the agenda setting for scientific research.[12] We will summarise these normative research questions below and also indicate examples of some of the linked empirical research questions, investigation of which we suggest would be useful to support this normative research programme.

For each of these four research agendas, we would expect answers to vary according to circumstances and cases, ie, they all need analysing both generically and also through an empirically informed consideration of contrasting cases.

1 What joint decision-making processes are ethically acceptable? What would be the ideal nature of the communication and the forms of reasoning or deliberation that make up patient-doctor joint decision-making? There are innumerable complications in operationalising this idea, including the critical questions about health professionals balancing their educational and protective roles with roles as advocates or 'partners'.

   Linked empirical questions - What joint decision-making processes are possible? What do real world practices that approximate to joint decision-making look like? What are the strengths and weaknesses of different practices seen from the vantage point of various stakeholders?(eg, prescribers, patients, funders) (see Chapter 3)

2 How far, and in what ways and instances, should medicines taking policies and strategies be framed around choice rather than 'compliance'? (eg, What forms of encouragement or 'pressure' can be acceptable to get people to take medicines?)

   Linked empirical questions - When, where and why do different forms of 'pressure' produce adherence in medicines taking and when, where and why are they counter-productive?

[12] We have argued for some of these at greater length elsewhere (Wirtz et al, 2005).

3 How should patients' reasons and/or motivations for taking medicines influence the way we judge the success of compliance/adherence policies and strategies? Does it matter why people adhere to recommended regimes (eg, informed choice, exaggerated fear?) or only that they adhere – and where these diverge how should they be balanced together?

Linked empirical questions - How do different kinds of rationale and emotions shape adherence? When are 'good reasons' less (or more) effective in producing adherence than other kinds of motivation?

4 How should differences in forms and levels of accountability for professionals and patients determine the degrees and kinds of patient influence in medicines decision-making? This, we would argue, is a critical issue, and one which is closely entangled with the other three just listed. Professionals have structured forms of accountability to employers, professional bodies, other patients, as well as broader populations. They are thus legally, as well as ethically, required to pay attention to the various balancing acts summarised above. By contrast, patients' responsibilities are less formalised, broad in scope and complex. Under these circumstances how far, and in what respects, does it make sense to treat patients as 'equal partners' in medicines decision-making?

Linked empirical questions - Are there practical mechanisms in place (or available to put in place) that could re-distribute accountability more from prescribers to patients (eg, waivers)? What are the legal, policy, practical and psychological implications of trying to share accountability differently? (see Chapter 3).

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Section 7 Interventions to facilitate adherence

Rob Horne & Ian Kellar

Introduction

This section deals with interventions to facilitate adherence to medication; examining the evidence for what works and why. Many research studies have examined the effects of a wide range of interventions designed to facilitate adherence. Literature searches show that over 120 articles reporting unconfounded randomised controlled trials have been published since 1972. This literature has been subjected to a series of systematic reviews (Haynes, McKibbon and Kanani, 1996; Roter et al, 1998; McDonald, Garg and Haynes, 2002; Peterson, Takiya, and Finley, 2003) including a Cochrane systematic review (Haynes, McDonald, Garg and Montague, 2002).

As a means of synthesising the existing literature, this chapter draws upon the results of systematic reviews by Roter et al (1998), Peterson et al (2003), and a Cochrane review by Haynes and colleagues (2002). These are the key reviews in this literature and are distinct in limiting their approach to examining the efficacy of interventions to facilitate adherence, in contrast, for example, to reviews that seek to account for variation in adherence due to moderating effects of physician behaviour (DiMatteo, Sherbourne, Hays and Ordway, 1993), or individual (DiMatteo, Lepper and Croghan, 2000) and social factors (DiMatteo, 2004).

As part of our scoping exercise, we extended the scope of the Cochrane review by including studies that met the stringent quality criteria, but were not eligible for inclusion in the Cochrane review because they had measured adherence but not clinical outcome. We do not dispute the Cochrane reviewers' rationale that improving adherence is only valuable if it brings clinical benefits to the patient. However, we wanted to examine whether including studies that had measured adherence (but not clinical outcome) might provide valuable information about how to change adherence behaviours. The method and results from this extended review are presented later in this chapter.

Evidence from systematic reviews- what works and why

Roter review

Roter et al (1998) reviewed studies from English-speaking journals that reported systematic attempts to influence adherence to medical regimens. The review did not look exclusively at adherence to medication but also included adherence to other self-management behaviours (such as self-monitoring of blood glucose in diabetes).

Inclusion criteria for studies were a controlled design (not necessarily randomised) where adherence was measured, and with a sample size greater than ten.

The review identified and classified 152 studies conducted between 1979 and 1994. They coded the type of interventions used into four categories:

- *Educational (information)* - impart information, typically via written and/or audiovisual information.
- *Behavioural (skills)* – attempt to improve patients' capacity to deal with the 'practicalities' of taking medication as recommended through skills building or by making the regimen easier through simplification and by issuing reminders.
- *Affective (motivational)* – attempt to change emotional or social influences on adherence by means of counselling or social support.
- *Provider Support (clinician-focused*) – attempted to use educational or behavioural strategies, but directed them at physicians, nurses or pharmacists.

Of the 152 interventions categorised, 102 were single component interventions. Of these, there were 50 behavioural; 43 educational; four affective; and five provider interventions. The 50 remaining studies utilised a combined programme. Of these, there were 32 educational and behavioural; 13 affective, educational and behavioural; and five provider, educational & behavioural interventions. It was reported that each category of intervention was associated with a significant effect upon adherence, with all categories of intervention except behavioural conferring at least a 20 per cent added benefit. However, the review did not detail which studies were and were not effective within each category, and no significant difference between separate categories of interventions was found. Indeed, the effect sizes suggested that the most effective approaches appeared to combine two or more of the approaches. Generally, however, Roter et al (1998) concluded that: `no single intervention strategy appeared consistently stronger than any other… there is no obvious superiority of one strategy with any other.' This review showed that it is possible to influence adherence behaviours but could not establish which components of interventions were effective or why some interventions worked and others did not.

Peterson review

This was a meta-analysis of interventions promoting prescription medication adherence, and which were evaluated in a randomised controlled design with a sample size greater than ten (Peterson et al, 2003). The review identified 95 studies from 61 articles published between 1971 and 2000. Interventions were coded into three categories.

- *Educational (information)* – attempted to impart information, typically via written and/or audiovisual information.
- *Behavioural (skills)* – attempted to change or influence specific patient behaviours related to adherence, typically by reminder or skill building, or dosage scheduling.
- *Combined* – a mixture of both approaches.

Of the 95 identified, there were 41 behavioural; 22 educational; and 32 combined interventions. In similar findings to those of Roter et al. (1998), each category was associated with modest significant overall

effects upon adherence (4 to11 per cent), but within each category, no single intervention approach was more efficacious than the rest, with the exception of a mail reminder where this was included in a combined approach. The review did not detail which studies were or were not effective within intervention categories. However, overall it was concluded that: `there were no significant differences among the educational, behavioural, and combined groups.'.

Haynes review

Similar to Peterson et al (2003), Haynes et al (2002) focused exclusively on interventions that attempted to affect adherence to prescribed, self-administered medication, tested in a randomised controlled trial setting. Studies were excluded if follow-up was less than six months, or where clinical outcome was not reported.

The search strategy resulted in 145 relevant studies, but only 35 papers were included for review (1972- 2001), with limited length of follow-up, unacceptable levels of attrition, and non-reporting of treatment outcome being the main reasons for exclusion. The review examined a broad array of strategies to enhance adherence, highlighting the prevalent approaches as: provision of written information (12 studies), counselling (five studies), family-centred interventions (five studies), and reminders (four studies). However, no tests of between-category differences were performed.

The overall conclusion of this review was that: 'complex strategies for improving adherence with long-term medication prescriptions are not very effective despite the amount of effort and resources they consume.' Even successful interventions have modest or short-lived effects. Moreover, the general quality of research is 'surprisingly weak,' with relatively few rigorous trials of adherence interventions.

Systematic review following Haynes et al., 2002

Rationale for the SDO augmented systematic review

The Haynes et al (2002) review could justifiably be described as the 'gold standard.' By specifying intervention studies that exclusively target adherence to prescription medication, where the interventions were assessed within a randomised controlled trial design, the literature is both more relevant and more effectively evaluated than that within the Roter et al review (1998). Moreover, by excluding studies with excessive dropout, and those which used only a short evaluation period for long-term treatments, conclusions drawn on the basis of these interventions are from a more rigorously evaluated literature than the Peterson et al (2003) study. Consequently, we have taken as our 'gold standard' the Cochrane systematic review of adherence interventions, most recently updated in 2002.

The Haynes review excluded studies if they did not include clinical outcome measures. This is, in one sense, appropriate, since enhancing adherence is only relevant (and justified) if it improves clinical or patient

outcomes, such as quality of life. However, papers that use adherence as the only outcome variable can still inform us about behaviour change. Excluding these papers risks omitting studies which improve our understanding of how to change adherence behaviour.[13]

Aim

To extend the Haynes et al (2002) review to include studies that assessed adherence as a behavioural outcome but did not assess clinical outcome.

Method

We extended the Haynes et al (2002) systematic review to include papers that used adherence as the only outcome measure. To do this we repeated the search strategy developed by Haynes and colleagues but omitted the 'clinical outcome measure' exclusion (see Appendix 5). Moreover, it was decided to exclude studies that purely focused on changing treatment, either via provision of alternative medication or dosing regimens, as these approaches substantively alter the behavioural goal, rather than the means by which it is attained. Additionally, due to resource constraints, we elected to only include English language articles. As a result, five studies from the Cochrane Review (Haynes et al, 2002) were excluded.[14]

Classification of interventions

The following categories were used to code the intervention approaches:

- *Perceptual (motivational)* – attempts to influence motivation by changing knowledge, beliefs, or attitudes, typically via written and/or audiovisual information.
- *Practical (capacity and resources*) – attempt to change or influence specific patient behaviours, typically by reminder or skill building, removing barriers to performance, or by dosage scheduling.

Combined – a mixture of both approaches.

Rationale for classification of interventions

The perceptual category contains studies that try to change beliefs and knowledge. Most rely on the provision of information. Such interventions

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[13] Our extended review is limited by the fact that we chose to adopt the Haynes exclusion of six month follow-up. It could be argued that excluding studies if they did not follow-up patients for six months or more may have missed studies that could have contributed new knowledge about how to change adherence, albeit in the short-term. Inclusion of short-term follow-up studies in the augmented review would have meant changing the Haynes search strategy. This would have resulted in a significant increase in the time and resources needed to complete the review, placing it beyond the scope of the current project. It was our view that this was not a priority as all interventions that produce sustained behavioural change are likely to improve health outcomes.

[14] The augmented review was conducted by Ian Kellar with assistance from Keri Peters, Rhian Parham and Jo Novis.

are often labelled 'educational.' However, it is our view that this label is too generic and does not adequately describe the scope of the information provided. Information alone does not change behaviour, and the knowledge–action gap is well recognised in health services research. An intervention may be effective at improving knowledge yet not affect behaviour change, because it fails to impinge on the beliefs that influence the motivation to start and continue with treatment. Thus effective educational interventions need both components. However it is important to be specific and distinguish between the components in order to identify the key targets of the intervention (knowledge, beliefs or both) and to establish the efficacy of the intervention in affecting the specific processes: improving knowledge or influencing beliefs.

Results of the augmented review

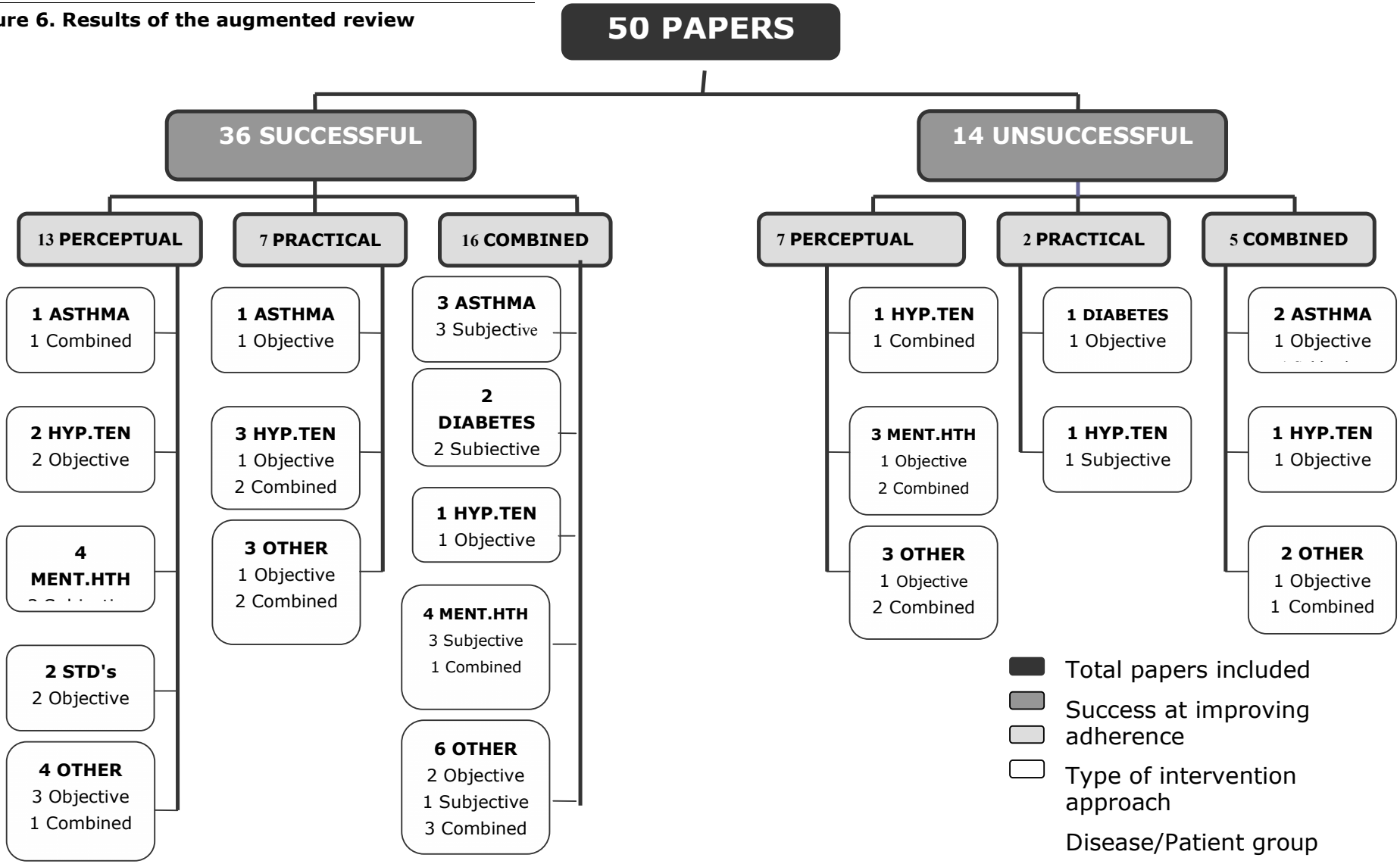
The augmented review identified 30 papers included by Haynes et al (2002)[15] and reviewed a further 20 studies that attempted to bring about change in adherence to prescription medication (see Appendix 6 for details of the studies reviewed). Subsequently, a total of 50 articles were reviewed.

Figure 1 provides a breakdown of the included studies on basis of study outcome (successful *vs* unsuccessful), content of the intervention (whether it addressed perceptual factors (eg, beliefs, knowledge) or practical barriers (eg, capacity or resources limitations) or used a combined approach), disease category and method of adherence assessment (subjective *vs* objective).

Of the studies reviewed, 20 took a perceptual approach, nine targeted practical barriers, and 21 combined strategies (see Figure 1, level 3). In total, 36 resulted in significant changes in at least one adherence-related outcome measure (see Figure 1, level 2). Of the 36 successful interventions, 13 addressed perceptual barriers, 7 targeted practical barriers, and 16 utilised a combined strategy (see Figure 1, level 3). Of the unsuccessful studies, 7 were perceptual, 2 were practical, and 5 were combined in approach (see Figure 1, level 3). Classification of intervention was not associated with success (Chi-square=.818, p=.664), indicating that, as yet, no approach can be determined to be more successful that the others. However, a 2-tailed, z-approximation test indicated that the observed proportion of successful versus unsuccessful studies was significantly better than chance ($p<0.005$). However, we cannot rule out the possibility of selection bias in that successful interventions may be more likely to be published.

[15] Five papers included in Haynes et al 2002 were excluded from our SDO review because the 'intervention' was limited to changing the medication or dosage regimen.

Figure 6. Results of the augmented review



Summary and synthesis across the reviews

A cross-comparison of the results of the search strategies and inclusion criteria of the Roter et al (1998), Peterson et al (2003), and Haynes et al (2002) studies indicated limited overlap. Of the 153 studies included by Roter et al (1998), just 20 were included by Peterson, five by Haynes and nine in our augmented review. This is unsurprising, as the strategy did not exclude non-randomised allocation and was not restricted to adherence to medication. Of the 61 studies reviewed by Peterson, eight were reviewed by Haynes et al (2002) and 19 were included in our augmented review. This may be due to the high standard required by Haynes et al (2002) with respect to both attrition rates (<20%) and length of follow-up (>6months) in studies of long-term treatments.

The findings of the SDO augmented systematic review were consistent with the results of Roter et al (1998), Peterson et al (2003) and Haynes et al (2002); that interventions to promote adherence are broadly efficacious. Although we did not conduct a meta-analysis, the effect sizes of successful interventions were of a similar order to those found in the meta-analysis of Peterson et al (2003) which found that interventions increased adherence by between 4 and 11 per cent, and Roter et al (1998) which reported moderate effects. It seems therefore that although adherence behaviour can be increased, there is considerable room for improvement. The findings of our augmented review were consistent with Haynes' view that: `complex strategies for improving adherence with long-term medication prescriptions are not very effective despite the amount of effort and resources they consume' (Haynes et al., 2002).

Our review identified serious weaknesses in both the content of interventions and in the way that they were developed and tested. These are summarised below:

Limitations of adherence interventions research

Following the augmented review, a consistent set of conclusions can be drawn from the literature regarding the inefficacy of the research to direct future intervention content. The following weaknesses provide insight into the limited development within this field.

Content

1 *Narrow focus for intervention* Most interventions are not sufficiently comprehensive. Relatively few appear to consider both the practical and perceptual barriers to adherence. The majority have addressed unintentional nonadherence with an implicit assumption that adherence can be improved through more effective communication of instructions, by better patient education or by addressing non-volitional barriers such as forgetting (by issuing reminders), poor recall of instructions or by addressing failure to make plans when attempting to adhere to a complex regimen. Although this approach may be helpful for many patients, its efficacy is likely to be limited because it fails to address the causes of intentional nonadherence. Interventions are likely to be more effective if they also address the perceptual barriers (eg, beliefs and attitudes underpinning patients' motivation to initiate and maintain taking prescribed medication as recommended).

2 *'One-size fits all' approach* Few interventions could be described as 'patient-centred.' They fail to elicit and address the specific reasons for nonadherence in individual patients.

Development and testing

3 *Failure to specify the content of the intervention* Studies typically failed to detail the content of the intervention material, providing little indication why the intervention worked or did not work. This prevents us from generalising across context (such as patient groups, disease states, treatment types).

4 *'Black-box' evaluation* Most studies assessing complex interventions did not evaluate the separate intervention components. Consequently, we remain uncertain about what was effective and whether all elements of the intervention were required.

5 *Lack of theoretical framework* Few interventions have targeted proven determinants of adherence. Instead they typically use *ad-hoc* approaches that are not well described or standardised. This is missing an opportunity to build a knowledge base of interventions that might be generalisable across different contexts (eg, diseases, treatments and cultural groups).

6 *Little or no process evaluation* Changes in antecedents of adherence were rarely investigated, and where these precursors where reported, the question of whether they mediated the effects of the intervention on adherence was not examined. Similarly, the extent to which interventions were properly implemented was not evaluated.

Because of the limitations in the way that previous adherence interventions have been developed and tested, it is not clear why one intervention works and another, apparently similar intervention, does not. This point is illustrated in Boxes 1-3 below. Each box profiles two interventions (one successful, the other unsuccessful) from each of three types of intervention categorised according to content: whether the intervention had targeted practical barriers (capacity and resource limitations), perceptual barriers (eg, knowledge, beliefs, etc) or used a combined approach in which both perceptual and practical barriers were targeted.

Box 1: Interventions addressing practical barriers (limitations in capacity and resources)

Successful (Linkewich, Catalano and Flack, 1974)

This study aimed to enhance adherence in hospital pharmacy patients with a prescription for potassium phenoxymethyl penicillin tablets.

Patients in Group 1 (control) received their penicillin in the standard vial with a standard label; the pharmacist read the physicians' directions with no further instruction. Group 2 patients received their penicillin in a standard vial but also received a calendar prepared with therapy dates and administration times. It was suggested that these patients keep this calendar with their medicine and that doses should be checked off as they were taken. Group 3 patients received 40 unit dose packaged penicillin tablets in 10 strips of four tablets (one day of therapy in each strip). Patients in Group 4 received a 'Wyeth QID Strep-Pak' (tablets laid out in pre-packed 'diary chart' showing day of treatment and the time of day the tablet is to be taken). All 'intervention' patients received their medication with a standard label and an instruction card which emphasised the importance of completing treatment.

Adherence to medication was significantly higher in the intervention groups compared to the control group.

Unsuccessful (Becker et al,1986)

This randomised controlled trial aimed to improve blood pressure control in a sample of hypertensive patients aged between 20 and 80 years.

Patients in the control group received all of their antihypertensive medications in the traditional pill vials (separate vials for each pill that were labelled with the drug name, the dosage, the medication instructions, and the physician's name), whereas patients in the experimental group received all their medications in a special packaging format. The packaging device placed all pills that were to be taken together in a single plastic blister sealed with a foil backing, on which was printed the day of the week and the time of day at which each medication was to be taken.

No significant differences were found between the experimental and control group on either patient self-reports of adherence or pill counts.

Box 2: Interventions addressing perceptual factors influencing motivation

Successful (Friedman et al, 1996)

This study aimed to enhance adherence to antihypertensive medication. Participants were hypertensive patients who were 60 years or older.

Participants allocated to the control group received usual medical care, while those in the intervention group used a computer-controlled telephone system in addition to their usual medical care. The Telephone-Linked computer (TLC) system converses with patients in their homes between visits to their physicians. Participants called the TLC weekly to report their self-measured blood pressures, knowledge and adherence to antihypertensive medication regimens and medication side effects. In addition to questioning the patients, the TLC provided education and motivational counselling to improve medication adherence.

Results indicated that antihypertensive medication adherence improved by 17.7 per cent for telephone system users and 11.7 per cent for controls ($P = 0.03$).

Unsuccessful (Brown et al., 1987)

This randomised controlled trial involved a sample of patients aged at least 18 years old who were diagnosed with schizophrenia or schizoaffective disorder, according to DSM-III criteria. All participants had been receiving neuroleptics for at least one month.

Patients were randomised into one of four groups: (1) verbal instruction about medication and minimum information about side effects, (2) written and verbal instruction about medication and minimum information about side effects, (3) verbal instruction plus maximum side effect information, and (4) written and verbal instruction plus maximum side effect information. Verbal instructions were supplied by a psychiatrist and covered medication, its purpose, directions for use, side effects and interaction with alcohol. Written instructions were delivered in pamphlet form and were consistent with the verbal instructions. Minimum side effect information was a general description of adverse reactions while maximum side effect information added more specific information.

No change in medication adherence was found.

Box 3: Intervention addressing both perceptual and practical barriers

Successful (Morisky et al, 1990)

This study aimed to improve adherence to anti-tuberculosis medical regimens in both active tuberculosis patients and preventative patients (those with no active disease).

Patients in the 'special intervention' (SI) group received ten minutes of (behaviourally oriented) educational counselling consisting of tailored educational messages. SI patients received written instructions about the regimen, educational reinforcement about TB and the enlistment of family and friends support. Patients in the SI group also received positive verbal reinforcement and cash incentives for adherence to the regimen. A booklet providing information about TB, the importance of treatment and possible side effects was given to all intervention patients at their initial session. The results of diagnostic tests, the patients' medications and ways to remember medications and future appointments were recorded in the booklet and discussed at each visit. Those in the control group received usual care.

SI patients had significantly higher levels of adherence to their medical regimen compared to those in the control group.

Unsuccessful (Brus et al, 1998)

This study aimed to improve medication adherence rates in patients suffering from Rheumatoid Arthritis (RA).

Intervention group patients attended six patient education meetings; these focused on adherence with sulphasalazine therapy, physical exercises, endurance activities, advice on energy conservation, and joint protection. Four (two hour) meetings were offered during the first months and reinforcement meetings were given after four and eight months. During the meetings patients were provided with information on RA, attendant problems, and basic treatment. The related beliefs of the patients were discussed and, when necessary, corrected. If patients anticipated problems with the applications of any of the treatments, these were discussed, including possible solutions. Patients were encouraged to plan their treatment regimens and their intentions were discussed. Patients made contracts with themselves regarding these intentions. The control group received a brochure on RA which gave comprehensive information on medication, physical and occupational therapy.

Adherence with sulphasalazine was evaluated at three, six and 12 months and was found to exceed 80 per cent, with no differences between groups.

Conclusion

Multi-component interventions seem to provide the most reliable approach to improving adherence (Roter et al, 1998; McDonald et al, 2002). However, because few papers specify or evaluate the specific components it is not possible to tell which are most effective. The

interventions summarised in Boxes 1-3 above illustrate this weakness within the literature. Many of the interventions considered in our systematic review are surprisingly complex. Unfortunately, in a review of 39[16] unconfounded interventions, Haynes et al (2002) identify just a single multi-component intervention which evaluated separate and combined effects of the constituent intervention components (Johnson, Taylor, Sackett, Dunnett and Shimizu, 1978) and no studies examined whether sources of variability in intervention delivery moderated intervention effects. Our confidence in the veracity of this conclusion is reinforced by the similarity of findings between the three published systematic reviews, and our own augmented review, conducted as part of the scoping exercise, and by the overlap in the studies included in the reviews.

There have been no large scale systematic reviews of the intervention literature since 2003 and it is possible that more effective interventions may have emerged since then. However, neither the Project Team nor our Consultation Groups and Expert Panel were aware of a significant body of studies to contradict our analysis of the interventions literature, based on published systematic reviews.[17]

Should we give up on adherence interventions?

A synthesis of evidence presented in a systematic review conducted as part of this SDO scoping exercise, a previous Cochrane review and other authoritative reviews (Haynes et al, 1996; Roter et al, 1998; McDonald et al, 2002; Peterson et al, 2003), paints a picture which at first sight looks fairly bleak. There appears to be little evidence that adherence to medication for long term conditions can be improved in a way that can be sustained within the resources that are typically available in clinic settings.

However, this does not mean that improving adherence is a lost cause. On the contrary, our analysis provides clear insights into, not only *why* previous interventions have met with limited success, but also *how* they might improve in future.

The search for effective interventions to facilitate optimum adherence to appropriate prescriptions remains a high priority for the management of chronic diseases. Nonadherence is thought to compromise the efficacy of most self-administered treatments and optimising adherence to efficacious treatments is likely to pay large dividends to individuals and society. At a time when new pharmacological moieties are relatively scarce and very expensive, improving adherence to appropriate prescriptions of existing efficacious treatments may represent the best investment for improving the self-management of long-term medical conditions (World Health Organisation, 2003).

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[16] The 35 papers reviewed by Haynes et al (2002) tested 39 unconfounded interventions.

[17] We understand that the Haynes group are currently updating their Cochrane review – Haynes personal communication to Ian Kellar.

Research priorities

The main priority for research is to develop effective, equitable and efficient interventions to facilitate optimal adherence[18] to appropriate prescriptions where adherence matters most.[19] These can be defined as:

1 Conditions where there is strong evidence supporting the benefits of medication, above other treatment options and over doing nothing.

2 Treatments where there is strong evidence that high levels of adherence are essential to ensure efficacy or prevent problems, such as the emergence of treatment-resistance.

Although more work is needed to develop a framework for adherence priorities, we can immediately identify examples that seem to fit the criteria. These might include: highly active anti-retroviral therapy for HIV, pharmacological treatment of diabetes, immunosuppressant medication following transplantation, preventer medication in asthma, medicines for severe mental illness, medication for prevention of cardiovascular disease, anti-tuberculosis treatment and anti-cancer agents.

The key question here is:-

What are the most effective methods for changing the cognitive (ie, beliefs; attitudes), emotional and capacity (ie, memory limitations; changes in routines/habits, etc.) factors, which result in reduced adherence to appropriate medication?

Our analysis of the literature on the causes of nonadherence and our assessment of the reasons for the limited success of interventions provide clear pointers to improving content, development and testing of interventions. The main lessons are:

Content Interventions should be tailored to meet the needs of patients taking account of the particular perceptual (eg, beliefs and preferences) and practical (eg, capacity and resources) factors influencing intentional and unintentional nonadherence for that individual.

Development and testing Interventions should be developed using an appropriate theoretical framework with a phased approach to testing that includes assessment of process (ie, the things that are targeted for change) as well as outcomes. The MRC framework for complex interventions to effect behaviour change may be useful in this respect

These are discussed in more detail below.

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[18] We recognise that adherence is not always a 'good' thing, as a prescription may be inappropriate or not reflect the patient's changing needs. We assume that adherence is appropriate and beneficial if it follows a process that allows patients to influence the decision making if they wish, and an appropriate choice of medicine is made by the prescriber.

[19] How we define an 'appropriate' prescription may vary according to individual circumstances, and this needs to be addressed within a normative research agenda. However, the essence of appropriate prescribing is the application of the scientific evidence base to the unique needs and preferences of the individual, taking account of their desires and capacity for involvement in the decision.

Lessons for the content of interventions

In Chapter 2, we presented a model to inform the design of future approaches to adherence interventions. This conceptualises nonadherence as unintentional and intentional behaviours with internal and external determinants.

Unintentional nonadherence can be understood in terms of capacity and resource limitations that prevent patients from implementing their decisions to follow treatment recommendations. Intentional nonadherence is best understood in terms of the beliefs, attitudes and expectations that influence patients' motivation to begin and persist with the treatment regimen.

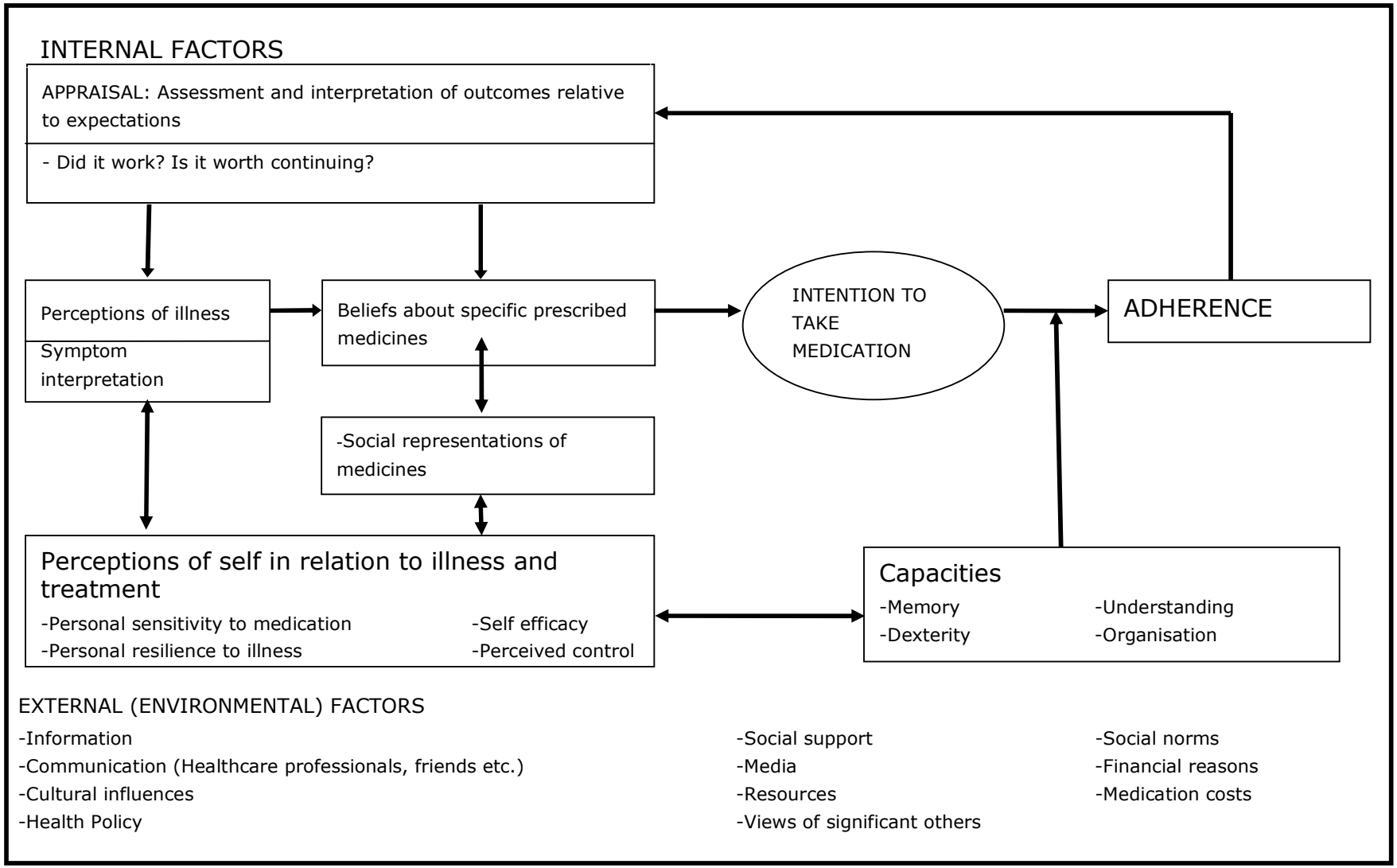
The 'internal' factors influencing motivation and capacity may be moderated by 'external' variables, such as the quality of communication between the patient and healthcare provider (as discussed in Chapter 3) and by information received from other sources (eg, the internet, friends, family and other patients), as well as by the wider societal contexts (eg, access to resources and societal policy and practice as outlined in Chapter 4). These factors are illustrated in Figure 2.

The available evidence from systematic reviews of adherence interventions presented in this chapter suggest that more comprehensive interventions that address both unintentional and intentional causes are likely to be more effective than single strand interventions that address one cause.

Developing interventions to facilitate informed choice and adherence to appropriate medication is the overriding priority for an empirical research agenda. Interventions will need to address three stages:

1. Initiating treatment for newly prescribed medication.
2. Maintenance of appropriate adherence patterns- how do we keep people doing the right thing? – preventing sub-optimal adherence.
3. Changing sub-optimal adherence, once patterns have developed.

Figure 7. Map of determinants of adherence



Interventions can be developed at several levels:

1. Interventions targeted at the individual patient level such as cognitive behavioural approaches. The available evidence suggests that these are likely to be more effective if they address both motivational factors and capacity limitations (the perceptions and practicalities approach).
2. Interventions focusing on others. For example, changing the behaviour of healthcare practitioners (eg, providing adherence support training for clinicians), facilitating support from non-professional helpers (eg, the Expert Patient programme; http://www.expertpatients.nhs.uk/) or targeting the household unit.
3. Organisational or service modification such as introducing an additional 'medicines-management' consultation with a pharmacist as part of programme of care for elderly patients.
4. Population level interventions, such as media-delivered information or behaviour change campaigns often known as social marketing.

Developing technologies for behaviour change

We need to develop interventions of varying complexity from simple minimal interventions targeted to all patients through to more comprehensive interventions targeted to patients most at risk of nonadherence.

We need to develop and evaluate 'technologies' for behaviour change and adherence support. These might include apparently 'non-technical' solutions, including cognitive-behavioural approaches, such as adherence therapy (see Appendix 7). One possible avenue of investigation is to examine whether more general strategies for facilitating self-management of illness might offer potential for adherence support (see Appendix 8).

A further avenue for investigation relates to innovative applications of existing and new technologies such as computers and mobile phones.

This is likely to require collaborations across the range of disciplines that have contributed to adherence research but might also draw on other disciplines that have yet to be become extensively involved, such as ergonomics. Specific initiatives may be required to promote interactions between the NHS and the UK science, engineering and technology base and industry to develop technologies to facilitate informed adherence to appropriate prescriptions. The Faraday Partnerships may offer a model for consideration (http://www.faradaypartnerships.org.uk/).

Applying the MRC framework for complex interventions to adherence

It is important that interventions are developed in a systematic way with staged studies accumulating increasing evidence for what might work and why. This is necessary to ensure that not only the interventions, but also the way they are evaluated, is efficient and represents 'value for money'.

The randomised controlled trial remains the definitive evaluation method for a fully-developed intervention. However, full-scale RCTs are expensive and time-consuming. Before committing to this, preliminary development work is necessary to identify the components of the

intervention, and the mechanism by which they will influence adherence and to evaluate the feasibility of the protocol.

The MRC recently published a framework for the development of complex interventions to effect behaviour change (Campbell et al, 2000). The MRC Framework for the evaluation of complex interventions sets out five stages in this process (see Figure 3):

1. Preclinical to explore relevant theory and identify potential confounders
2. Phase 1: Modelling - identify intervention components and mechanisms
3. Phase 2: Exploratory trial - explores feasibility
4. Phase 3: Full RCT- a definitive RCT with appropriate statistical power
5. Phase 4: Long-term implementation - assesses replication in uncontrolled settings

This framework may be applied to adherence interventions. It provides guidance of how to develop and evaluate behavioural interventions in a way that avoids the pitfalls that have led to the current situation where we have little indication of what works or why in terms of adherence interventions.

The analysis of previous interventions presented in this chapter suggests that one of the main reasons that we do not know what interventions work best and why, is that most previous studies have not developed the intervention systematically as suggested in the MRC framework. Most notably, there seems to be little evidence that previous interventions were systematically modelled or evaluated in an exploratory trial before moving to full scale trial.

The MRC framework, with its emphasis on the need for a strong theory base and systematic development, may be used as a basis for assigning priority to research ideas in adherence. The research priorities identified in our individual themes of patient behaviour, patient-provider communication and societal policy and practice are relevant at different phases of the MRC framework from the development of theory and modelling the intervention through to implementation.

Many of the key questions relating to the development of interventions to facilitate adherence in long-term illness are located at the early stages of development (corresponding to the first three stages of the MRC).

The immediate priority is for studies at the earlier stages of development of interventions to facilitate informed adherence to appropriately prescribed medication in areas where adherence matters most (eg, in HIV, transplantation, severe mental illness, moderate-severe asthma diabetes and secondary prevention of cardiovascular disease).

These studies would entail the modelling of interventions at Phases 1 and feasibility studies at Phase 2 of the MRC framework. The MRC framework has yet to be fully operationalised in relation to adherence interventions but shows promise in this respect. Small-scale studies in the early phases of development of the intervention could be used to assess whether certain components of the intervention change 'process' variables, such as informed choice and patient beliefs, as well as adherence behaviour. Interventions developed through this route could progress to full-scale evaluation in RCTs in which behavioural and clinical outcomes are measured.

Efficiency of interventions

Testing interventions at the latter stages of the MRC framework should include assessment of cost-effectiveness (efficiency). A cost-effective intervention to enhance adherence is one that is effective in reducing the burden of illness associated with nonadherence, at an optimal level of resource use. Many interventions are very resource-intensive and, if implemented widely, would divert large amounts of resources from other aspects of health care.

Better use of existing technologies, such as medicines, is likely to be a more cost-effective use of NHS resources than many new technologies. However, existing evidence about the efficiency of adherence-enhancing interventions is poor (Elliott, Barber and Horne, 2005). If we are to be able to demonstrate the cost-effectiveness of an intervention, we must develop interventions with a theoretical basis, as outlined in Themes one and two, and evaluate these interventions using study designs that fulfil MRC complex interventions study design requirements, as outlined above, and meet standard economic evaluation study design criteria (as outlined in Appendix 9).

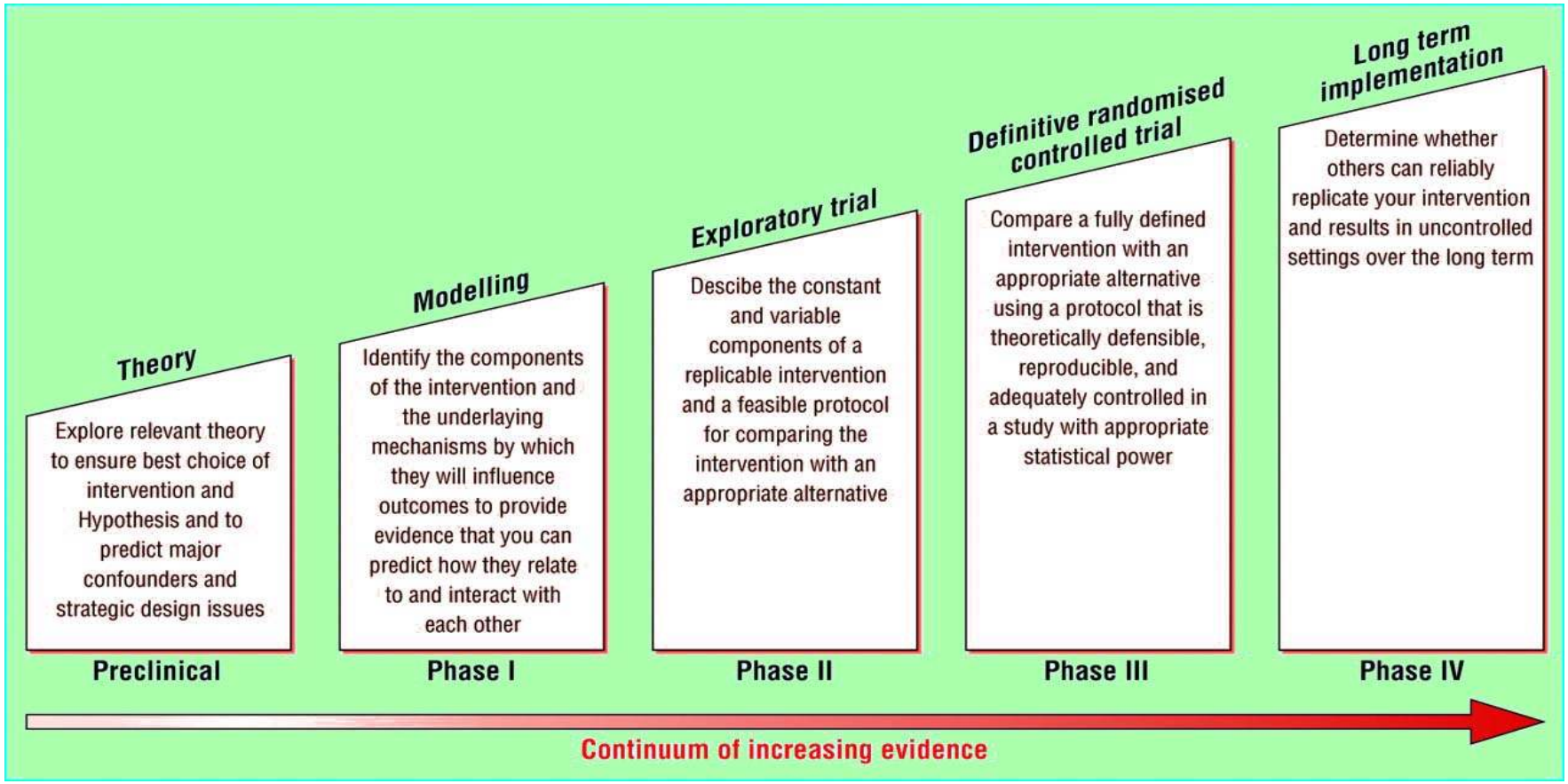


Figure 8. MRC Framework for evaluation of complex interventions (from Campbell et al., 2000)

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Section 8 Research priorities and conclusions

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This section pulls together the research priorities identified in Chapters two to six, spanning our four themes of explaining patient behaviour, patient provider interaction and healthcare communication, societal policy and practice and interventions to facilitate adherence. It also presents the emerging research questions from consideration of the normative questions relating to what is good prescribing and medication-taking in Chapter 5. The present chapter amalgamates the outstanding research questions from previous chapters in one, for ease of reference.

This research agenda is highly relevant to the NHS SDO research priorities of patient choice, access and continuity of care, workforce, e-health, methodological research and governance20. We have mapped the key research questions relating to facilitating informed choice and optimal adherence to appropriate prescription onto the NHS SDO priorities at the end of the present chapter.

Getting the best from medicines: an agenda for behaviour change

The translation of scientific advances in medicines development into improvement in the quality of life of individuals is dependent on the behaviour of prescribers and patients. Efforts in the basic and clinical sciences to develop and test novel pharmaceutical compounds and initiatives to promote evidence-based prescribing are wasted if the patient fails to benefit because of nonadherence.

Nonadherence may therefore be thought of as a failure in the implementation of basic scientific research. To close the gap between scientific advances (eg, new and effective medicines) and optimum outcomes (eg, patients with improved quality of life and satisfaction with their care), we need a clear understanding of the factors influencing medication-taking behaviour and how we might intervene to change practitioner and patient behaviour to improve outcomes.

In this sense the challenges for a research agenda in medication adherence are similar to those for other health-related behaviours, such as smoking cessation, exercise and diet: how to influence and change behaviour. The importance of the behaviour-change agenda in health is now well recognised, with initiatives such as the National Prevention Research Initiative (NPRI; http://www.dh.gov.uk/) supported by the Medical Research Council and other research funding bodies.

[20] http://www.sdo.lshtm.ac.uk/commissioninggroups.htm

There are, of course, important contextual differences between disease-prevention and treatment, but this core similarity offers the potential for synergy across initiatives.

Our approach to this scoping exercise was informed by the concept of adherence as a variable behaviour and the notion that any improvement in the current situation is dependent on behaviour-change.

The structure of the report derives from this approach. The extensive literature on adherence is separated into four themes. Theme 1 focuses on patient medication-taking behaviour and summarises current knowledge about the determinants influencing patients' adherence. This is the largest chapter matching the volume of research. Themes 2 and 3 summarise research into the contextual factors within which medication-taking occurs. Theme 2 examines interactions between patients and healthcare providers and Theme 3 focuses on societal policies and practices. The final theme looks at interventions and summarises our knowledge about how adherence behaviour can be changed.

Research priorities: an empirical and normative agenda

The development of effective, equitable interventions to prevent the high individual and social costs of nonadherence is the overarching priority for research.

However, medication carries the potential for harm as well as benefit and this raises the question of when it is 'right' to intervene to encourage adherence. At a basic level, adherence interventions are only 'right' if the prescription was appropriate for the individual. In Chapter 1 we acknowledged that, in most cases, there is a degree of uncertainty about the best prescription and the optimum level of adherence for a given patient.

The philosophical and ethical dilemmas inherent in the adherence debate are summarised in Chapter 5, which considers questions about the nature of good prescribing and medication-taking. The concept of concordance was an early attempt to address some of these questions, but many remain unresolved.

There are therefore two aspects to a future research agenda on adherence: *empirical* and *normative*. The empirical programme investigates the determinants of nonadherence and how these might be influenced by intervention. A fundamental question in this agenda is: 'How can we influence adherence behaviour?' The normative agenda deals with ethical and philosophical issues and a fundamental question here is: 'What is the right thing to do?'

In an ideal world, normative questions would be resolved first and the answers would inform the empirical research to design interventions to optimise adherence behaviours. However, the potentially high costs of nonadherence to the individual and healthcare system make imperative the pursuit of an empirical agenda to address the fact that many medicines are being prescribed and not taken appropriately. For this reason, the empirical and normative agenda will need to progress in parallel and can be mutually informative. But where do we start? How can we intervene before we know what is the right thing to do? We suggest that the answer to this dilemma is to separate out different streams of work on the basis of scientific/clinical evidence.

For some diseases, treatments and situations, there is more supporting evidence for the concept of adherence as 'good' than in others. These can be defined as:

1 Conditions where there is strong evidence supporting the benefits of medication, above other treatment options and over doing nothing.

2 Treatments where there is strong evidence that high levels of adherence are essential to ensure efficacy or prevent problems, such as the emergence of treatment-resistance.

Although more work needs to be done to develop a framework for adherence priorities, we can immediately identify examples that seem to fit the criteria. These might include: highly active anti-retroviral therapy for HIV, pharmacological treatment of diabetes, immunosuppressant medication following transplantation, preventer medication in asthma, medicines for severe mental illness, prevention of cardiovascular disease, anti-tuberculosis treatment and anti-cancer agents.

These examples do not, of course, constitute a comprehensive list but are mentioned to illustrate the type and range of conditions where there is a strong case for moving forward with an immediate empirical research agenda to develop interventions to facilitate informed choice and optimal adherence to appropriate prescritions. For medicines that do not match this criterion, the normative questions are more complex. Here, the imperative to intervene before clarification of what constitutes 'good medication prescribing and taking' is less clear, as discussed in Chapter 5.

The empirical agenda: developing effective interventions to facilitate informed adherence

The main priority for research is to develop effective, equitable and efficient interventions to facilitate informed adherence where adherence matters most. Our analysis of the causes of nonadherence and of why previous interventions have had only moderate effects provides insights into how we might develop more effective interventions, as discussed in Chapter 6.

The available evidence suggests that more comprehensive interventions, that address both unintentional and intentional causes, are likely to be more effective than single strand interventions that address one cause. We have presented a model to inform the design of future approaches to adherence interventions. This model conceptualises nonadherence as unintentional and intentional behaviours with internal and external determinants.

The 'internal' factors influencing motivation and capacity may be moderated by 'external' variables, such as the quality of communication between the patient and healthcare provider, as discussed in Chapter 3, and by the wider societal contexts, such as access to resources and societal policy and practice, as outlined in Chapter 4.

Specific research questions to inform the design of interventions

The following section lists specific research questions that we have identified as the main priorities within each of the scoping exercise themes.

Theme 1: Explaining patient behaviour

Chapter 2 summarised the many causes of nonadherence and showed that they fall into two overlapping categories: intentional and unintentional. Unintentional nonadherence occurs when the patient's intentions to take the medication are thwarted by barriers, such as poor recall or comprehension of instructions, difficulties in administering the treatment, or simply forgetting. Deliberate or intentional nonadherence arises when the patient decides not to follow the treatment recommendations. Adherence/nonadherence can therefore be understood as the product of individual *motivations* and *capacities*. It follows that interventions are likely to be more effective if they address both the *perceptual* factors (beliefs and expectations and experiences) influencing the motivation to begin and persist with the medication, as well the *practical* barriers (eg, forgetting or difficulties developing a routine) that affect the patient's capacity to implement their intentions to follow the agreed treatment plan.

Patients' perceptions of medicines

Studies conducted across a range of chronic illnesses and involving patients from different countries and cultural groups (and using qualitative and quantitative methods) have consistently found that adherence is related to the way in which patients judge their personal need for treatment, relative to their concerns about potential adverse effects.

Moreover, research suggests that the way in which individuals balance perceived necessity against their concerns relates to their appraisal of the effects of medicines and their perceptions of illness, as well as to social representations of medicines in general and the perceived availability of alternatives. These factors relate in another way that often has a strong internal logic, although this may be inconsistent with scientific evidence or the medical view.

Further primary research is now needed to assess whether these insights can be used to model interventions to help patients make adherence decisions that are informed by realistic assessments of the likely benefits and risks of treatment and are not based on mistaken premises or misplaced beliefs about the illness and treatment. The following are examples of specific research questions:

1. How do patients judge their personal need for medication in different situations and stages of illness?
2. How do perceptions of medication change over time and in response to information and experience of the treatment?
3. How do patients' expectations, experiences and attributions of symptoms (eg, to medication or illness) influence perceptions of and adherence to prescribed medication?
4. How do patients interpret and act on different types of information about the potential benefits and risks of medication? How does this

influence perceptions of need and concerns and the 'trade off' between perceived necessity and concerns?

5 Theory development – What is the utility of the necessity - concerns framework and other methods of operationalising the salient attitudes to treatment within established theoretical models of health-related behaviour? Are there other theoretical constructs that could be used in place of, or in addition to, this framework to provide a better understanding of adherence and how to enhance it?

6 How do emotional states (eg, depression and anxiety) influence perceptions of and adherence to medication? How can these effects be moderated? (eg, by social support and other factors).

7 How do patients perceive, evaluate and respond to information about medicines from different sources (eg, doctors, pharmacists, pharmaceutical industry, media)?

8 What do patients value about alternative and complementary therapies relative to medication? Can this help us understand how to improve communication about medicines?

9 How do ethnicity and social disadvantage influence patients' perceptions, assessments and medication behaviours?

10 How do the perceptions and life circumstances of different age groups (children, young adults and elderly people) influence adherence and what are the implications for interventions?

Modelling intentional and unintentional nonadherence

11 What are patients' perceptions of adherence and its importance to their goals? Do perceptions vary for different treatments prescribed for multiple pathologies?

12 What is the contribution of intentional and unintentional factors to rates of nonadherence? How does this change over the course of illness and how does it vary for different conditions and treatment regimens?

13 What are the perceptual and practical barriers to medicines use for patients with multiple pathologies or psychiatric conditions and for their families?

14 What are the main barriers to patients implementing their intensions to adhere to prescribed medication? How might these be overcome?

15 What are the effects of enforced compliance on the individual? (eg, in mental illness as a result of assessment of risks to the public associated with nonadherence).

Methodological developments

16 Can different indicators of adherence (eg, self-report, prescription redemption rate) be used in combination to produce better assessments of adherence for use in intervention studies?

17 How should we assess whether individual patient's adherence decisions are 'informed'?

Adherence and clinical outcome

18 There is need for a tertiary review to develop a framework to identify clinical priorities for adherence interventions on the basis of

efficacy of medication and importance of adherence in attaining benefit.

Change over time

19 Recent research has improved our understanding of the key perpetual and practical barriers to adherence in many of the disease and treatment categories where adherence matters most. However, many of the available studies are cross-sectional meaning that we cannot be certain about causality and have little insight into how adherence and the determinants of adherence change and interact over time. A key priority therefore is for prospective studies to answer these questions. This is important to inform not only how we intervene but when.

Theme 2: Patient-provider interactions and healthcare communication

The prescribing consultation is often considered to be the source and potential remedy for adherence problems. It provides the focus for the concept of concordance and remains a focus for debate about medication-taking. However, our review of the empirical evidence identified very few studies that systematically evaluate the effects of the prescribing consultation on adherence behaviour (Chapter 3). Of course, this does not mean that the consultation is unimportant or that we should not strive to improve consultation as a 'good' in its own right. However, it does identify the need for further basic research to clarify the effects of the consultation on medication adherence. The outstanding research questions are:

Effects of the consultation on adherence

1 What are the direct and mediated effects of the consultation on short and longer-term patterns of treatment adherence?

2 What are the key aspects of the consultation that influence medication taking behaviour? For example, using the Roter Interactional Analysis System (RIAS) – we urgently need systematic evidence about the possible direct and indirect effects on adherence of the different categories and styles of communication defined by the RIAS.

3 Following on from the above, to what extent is adherence a function of these more global styles or are other factors more salient when considering the specific outcome of medication taking behaviour? - eg, shared decision making, eliciting beliefs, concerns, identifying and dealing with practical issues in taking medication (eg, forgetting, difficulties with packaging, etc)

Practitioner perceptions and behaviours

4 How do patients' preferences, beliefs and expectations and patient style affect prescriber behaviour?

5 What are the effects of 'training' and other interventions on practitioner and patient attitudes, behaviour and skills related to prescribing and communication about medicines?

Shared decision-making

6 What are prescribers' and patients' attitudes to shared decision making, partnership and other models of consultation?

7 What joint decision-making processes are possible? What do real world practices that approximate to joint decision-making look like? What are the strengths and weaknesses of different such practices seen from the vantage point of various stakeholders? (eg, prescribers, patients, funders)

8 Are there practical mechanisms in place (or available to put in place) that could re-distribute accountability more from prescribers to patients? (eg waivers) What are the legal, policy, practical and psychological implications of trying to share accountability differently?

9 How can clinicians and patients be supported to deal with the cognitive and emotional challenges of prescribing consultations designed to promote informed choice and adherence to medication?

10 What are the effects of coercion on patients?

New prescribers and other members of the healthcare team

11 There is a new and growing agenda relating to non-medical prescribers (pharmacists, nurses, etc) This is a key context issue and there are a range of questions relating to patient perspectives on new prescribers and to new prescribers' perceptions and skills. The effects of new prescribers on patient adherence to medication should be included in any research agendas designed to evaluate new prescribers.

12 In what way is it possible to supplement the activities of the NHS workforce in facilitating optimal mediation usage through other, complimentary approaches? (eg, the use of 'expert patients', family support, etc)

Facilitating communication of adherence

13 How can we facilitate the honest disclosure of medication-taking behaviours within prescribing-related consultations and medication use reviews? How can we equip health practitioners to respond appropriately and effectively?

14 How can we enable new and existing prescribers to identify patients at risk of nonadherence or who are a priority for medication-review and adherence support and how can we provide it – new methods, new practitioners?(eg, health trainers)

15 How can we support prescribers to meet the challenges of quality frameworks relating to medication-usage as a component of self-management?

Theme 3: Societal policy and practice

The impact of nonadherence at a societal level is probably substantial, but existing data in the UK are too poor to fully characterise this, possibly because, until recently, the management of adherence has not featured strongly in NHS policy. However, several core policy initiatives such as the Expert Patient programme, National Service Frameworks and Medicines Use Reviews (MURs) now place patient self-management and involvement in decisions at the forefront of healthcare delivery. These offer strong incentives and provide an excellent context for the development of interventions to help patients with long term illnesses to get the best from medicines. However, it is essential that that these policy initiatives are based on effective interventions.

Key policies that are predicted to affect medicines-taking behaviour are the prescription tax system, deregulation of prescription only medicines and expansion of prescribing rights. The accelerated rate of deregulation of medicines in the UK needs to be assessed: does use of medicines change and is this change in use appropriate or inappropriate? Does deregulation lead to financial barriers that reduce use in some groups? The recent introduction of supplementary and independent prescribing rights for non-medical prescribers has generally been welcomed by health professional groups. However, it is not clear whether patients will perceive this development as a welcome or confusing plurality of service provision, or how this might impact on medicines-taking behaviour. The outstanding research questions are:

1. What is the economic impact of nonadherence in diseases where nonadherence has been proven to have clinical consequences (such as, diabetes, asthma, HIV infection, cancer, cardiovascular disease, severe mental health problems, organ transplantation, etc)? This evidence needs to be supplemented by an assessment of the level of preventability of nonadherence in each group studied and associated economic impact. Patient groups within disease types likely to incur the greatest increases in morbidity due to nonadherence need to be identified (such as patients with multiple co-morbidities).
2. Are data routinely collected and readily available that can be used to allow assessment of impact of nonadherence, and if not, how can these minimum datasets be developed?
3. How does the prescription charge system in England, Wales and Scotland, affect prescription filling for essential and non-essential medicines, subsequent patient health, present and future health service and societal cost?
4. How effective, equitable, timely, patient-centred and efficient are national and regional adherence-enhancing policies and initiatives?
5. Does the use of medicines change because of deregulation and is this change in use appropriate or inappropriate? Does deregulation lead to financial barriers that reduce use in some groups?
6. Does the introduction of supplementary and independent prescribing rights for non-medical prescribers create a welcome or confusing plurality of service provision, and how might this impact on medicines-taking behaviour?
7. How are pharmacists carrying out medicines use reviews (MURs), do they affect patients' beliefs, medicines-taking behaviour or health, and how can pharmacists optimise the MUR process to support informed choice about medicines?

Theme 4: Interventions to facilitate adherence

The literature on adherence interventions has been the subject of three major systematic reviews over the past five years, culminating in a Cochrane systematic review in 2002. As part of our scoping exercise we extended the scope of the Cochrane review by including studies that met the stringent quality criteria, but were not eligible for inclusion in the Cochrane review because they had measured adherence but not clinical outcome. We do not dispute the Cochrane reviewers' rationale that improving adherence is only valuable if it brings clinical benefits to the patient. However, we wanted to examine whether including studies that had measured adherence (but not clinical outcome) might provide

valuable information about how to change adherence behaviours. Our examination and updating of the systematic review data was consistent with the previous findings and can be summarised as:

1 Interventions to promote adherence are broadly efficacious. However, the effects were generally modest - we know that adherence can be increased, but there is considerable room for improvement.

2 Few interventions have been systematically developed using appropriate theoretical models, nor have they have been modelled and piloted with assessment of process variables as well as outcomes (as recommended in the MRC framework for complex interventions to effect behaviour change). Consequently, it is difficult to tell why some interventions work and others do not.

3 Comprehensive interventions that combined approaches were typically more effective than interventions focusing on single causes of nonadherence. However, few interventions could be described as 'patient-centred' as they did not individualise the approach to match patient's needs and preferences.

Our analysis of the literature on the causes of nonadherence and our assessment of the reasons for the limited success of interventions provide clear pointers to improving content, development and testing of interventions. The main lessons are:

Content Interventions should be tailored to meet the needs of patients, taking account of the particular perpetual (eg, beliefs and preferences) and practical (eg, capacity and resources) factors influencing intentional and unintentional nonadherence for that individual.

Development and testing Interventions should be developed using an appropriate theoretical framework with a phased approach to testing that includes assessment of process (ie, the things that are targeted for change) as well as outcomes. The MRC framework for complex interventions to effect behaviour change may be useful in this respect[21].

The fundamental questions that need to be addressed in order to develop such interventions are:

1 What are the most effective methods for addressing the cognitive (eg, beliefs and attitudes), emotional and capacity factors (eg, memory limitations; changes in routines/habits, etc), which result in reduced adherence to appropriate medication?'

2 How can we enable prescribers and other members of the NHS workforce to support patients by facilitating informed choice and optimal adherence to appropriate prescriptions?

3 How can we incorporate an awareness of patient needs in relation to medicines and adherence support into the organisation and delivery of everyday healthcare to meet the requirements of NSFs,

[21] Campbell, M, Fitzpatrick, R, Haines, A, Kinmonth, AL, Sandercock, P, Spiegelhalter, D et al. 2000. Framework for design and evaluation of complex interventions to improve health. *BMJ, 321:* 694-6.

a patient-led NHS and the drive for greater efficiency in healthcare delivery?

The overriding priority for the empirical research agenda is the development of effective, realisable, efficient and equitable interventions to facilitate informed choice and optimal adherence to appropriately prescribed medicines[22]. Interventions will need to address three stages:

1 Initiating treatment - for newly prescribed medication.

2 Maintenance of appropriate adherence patterns, preventing sub-optimal adherence - how do we keep people doing the right thing?

3 Changing sub-optimal adherence, once patterns have developed.

These interventions can be developed at several levels:

- Interventions targeted at the individual patient level, such as cognitive behavioural approaches. The available evidence suggests that these are likely to be more effective if they address both motivational factors and capacity limitations (the perceptions and practicalities approach).
- Interventions focusing on others. For example, changing the behaviour of healthcare practitioners (eg, providing adherence support training for clinicians), facilitating support from non-professional helpers (eg, the Expert Patient Programme; http://www.expertpatients.nhs.uk/), or targeting the household unit.
- Organisational or service modification, such as introducing an additional 'medicines-management' consultation with a pharmacist as part of programme of care for elderly patients.
- Population level interventions such as media-delivered information or behaviour change campaigns, often known as social marketing.

Developing technologies for behaviour change

We need to develop interventions of varying complexity, from simple minimal interventions targeted to all patients, through to more comprehensive interventions targeted to patients most at risk of nonadherence.

We need to develop and evaluate 'technologies' for behaviour change and adherence support. These might include apparently 'non-technical' solutions. such as cognitive-behavioural approaches, education and social support, as well as innovative applications of existing and new technologies, such as computers and mobile phones.

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[22] How we define an 'appropriate' prescription may vary according to individual circumstances, and this needs to be addressed within a normative research agenda. However, the essence of appropriate prescribing is the application of the scientific evidence base to the unique needs and preferences of the individual, taking account of their desires and capacity for involvement in the decision.

This is likely to require collaborations across the range of disciplines that have contributed to adherence research, but might also draw on other disciplines that have yet to become extensively involved, such as ergonomics. Specific initiatives may be required to promote interactions between the NHS and the UK science, engineering and technology base and industry, to develop technologies to facilitate informed adherence to appropriate prescriptions. The Faraday Partnerships may offer a model for consideration (http://www.faradaypartnerships.org.uk/).

The systematic development and evaluation of interventions: applying the Medical Research Council (MRC) framework for complex interventions to adherence

It is important that interventions are developed in a systematic way with staged studies accumulating increasing evidence for what might work and why. This is necessary to ensure that not only the interventions, but also the way they are evaluated, is efficient and represents 'value for money.'

The randomised controlled trial remains the definitive evaluation method for a fully-developed intervention. However, full-scale RCTs are expensive and time-consuming. Before committing to this, preliminary development work is necessary to identify the components of the intervention, the mechanism by which they will influence adherence, and to evaluate the feasibility of the protocol.

The MRC Framework for the evaluation of complex interventions to effect behaviour change sets out five stages in this process, from preclinical development of a theoretical model, through to long-term implementation.

This framework might prove to be helpful in developing adherence interventions. Our scoping exercise suggested that many of the key questions relating to the development of interventions to facilitate adherence in NHS priority areas and other conditions where adherence matters most, are located at the early stages of development. These studies would entail the modelling at Phase 1 and feasibility studies at Phase 2 of the MRC framework.

Once developmental work is complete and development moves to full scale randomised controlled trials and implementation research (Phases three and 4

four of the MRC framework), then it is important to evaluate the cost-effectiveness (efficiency) as well as the efficacy of the intervention.

The normative agenda

The ethical agenda of balancing respect for patient autonomy with paternalistic and public good considerations, and the fundamental questions about the nature of good prescribing and medicines taking, give rise to crucial normative research questions that overlap with, and must be fed into, the agenda setting for scientific research. Similarly, the normative agenda needs to be informed by some of the empirical research questions. For example, ideals of patient-prescriber interaction need to be deliverable in the real world. For each of the four research questions (sometimes more research agendas) below, we would expect

answers to vary according to circumstances and cases; they all need analysing both generically and also through an empirically informed consideration of contrasting cases.

1 What joint decision-making processes are ethically acceptable?

2 How far, and in what ways and instances, should medicines taking policies and strategies be framed around choice rather than 'compliance'? (For example, what forms of encouragement or 'pressure' can be acceptable, in which circumstances, to get people to take medicines?)

3 How should patients' reasons and/or motivations for taking medicines influence the way we judge the success of compliance/adherence policies and strategies? Does it matter why people adhere to recommended regimes (informed choice? exaggerated fear?) or only that they adhere – and where these diverge, how should they be balanced together?

4 How should differences in forms and levels of accountability for professionals and patients determine the degrees and kinds of patient influence in medicines decision-making? This, we would argue, is a critical issue.

Overarching issues: adherence in vulnerable groups

Consideration of vulnerable groups cuts across the explanatory themes and is relevant for most research questions, regardless of whether research is targeted at explaining individual behaviour, investigating communication in healthcare, societal policy and practice or evaluating interventions. The issue is also relevant for the normative questions. Work in this area requires systematic reviews of the available literature followed by empirical studies. Specific questions are:

1 What are the effects of social disadvantage and ethnicity on accessing prescriptions and adherence to prescribed medication?

2 How do the perceptions and life circumstances of different age groups (children, young adults, elderly people) influence adherence and what are the implications for interventions?

3 What are the particular barriers to medicines use for people with multiple pathologies (and their informal carers) and what interventions are required?

Mapping research questions onto the SDO research priorities

Key research questions mapped onto SDO research priority areas

Patient choice[23]

1 In what ways can and should patients' initial choices and preferences be modified?

2 In what ways and in what circumstances should patient choice form the basis for decision making in prescribing and medicine-taking?

3 What are most effective ways of representing evidence for the likely benefits and risks of medication?

4 How can we tailor medicines information to match the requirements of individual patients and their carers?

5 Where patients' decisions are based on misplaced beliefs or misconceptions about the illness and treatment, how and when should this be addressed?

6 How can we help people make 'informed choices' about adherence to prescribed medication?

7 How should we communicate and deal with uncertainty within prescribing-relating consultations?

8 How can professional and lay accountability be best aligned to support patient choice?

9 How do patient preferences for involvement in medication-related decisions vary and how should prescribers responds to this?

10 How do patients' perceptions, preferences, choices and medication-taking behaviour change over time in conditions where adherence to medication matters most?

Access and continuity of care

11 How can we help patients to overcome the capacity and resource limitations preventing access to effective healthcare?

12 How can we address and identify misconceptions about illness and treatment that prevent access to appropriate medication?

Workforce

13 How can we equip prescribers (and their patients) to deal with the cognitive and emotional challenges of working in partnership to achieve informed choice and optimal adherence to appropriately prescribed medicines, where adherence matters most?

14 How can adherence review and adherence support be incorporated into medication-usage review in a way that promotes informed

[23] CARERS -Many of the questions that are relevant to patient choice and support will also apply to their carers and there is scope for synergy and continuity with the SDO programme on carers.

choice and supports adherence to agreed, appropriate prescriptions?

15 What are patients' perceptions and behavioural reactions to new prescribers (eg, nurses and pharmacists)?

16 What are the barriers to effective and efficient multi disciplinary approaches to appropriate prescribing and adherence support? How can these be overcome?

17 How can we enable new and existing prescribers to identify patients who are priority for medication-review and adherence support?

18 How can we support prescribers to meet the challenges of quality frameworks relating to medication-usage as a component of self-management?

19 In what ways is it possible to supplement the activities of the NHS workforce in facilitating optimal mediation usage through other, complimentary approaches (eg, the use of 'expert patients', family support, etc).

e-Health

20 How can technology developments (eg, computers, mobile telephones, etc) be utilised to provide ongoing support for informed choice and adherence to agreed prescriptions?

21 How can we develop and apply effective 'technologies' to facilitate behaviour-change to achieve optimal adherence to appropriate and agreed prescriptions. Here technologies may be 'talk treatments' such as cognitive behaviour approaches?

Methodologies

22 How can we facilitate the honest disclosure of medication-taking behaviours within prescribing-related consultations and medication use reviews? How can we equip health practitioners to respond appropriately and effectively?

23 What are the alternatives to full-scale RCTs that can be used to conduct preliminary evaluations of the components of interventions to support informed choice and adherence (corresponding to MRC Phases 1 and 2)?

24 How can existing validated methods for assessing adherence-related perceptions and adherence behaviours be adapted for routine use in the NHS?

25 How can we enable new and existing prescribers to identify patients at risk of nonadherence or who are a priority for medication-review and adherence support and how can we provide it – new methods, new practitioners (eg, health trainers)?

26 How should we operationalise 'informed choice' in relation to medications taking?

Governance

27 How do differences in the arrangements existing in England, Wales and Scotland, such as the role of prescription charges, affect prescription filling for essential and non-essential medicines, subsequent patient health, present and future health service and societal cost?

Issues about adherence in vulnerable groups, discussed earlier in this chapter, will also be applicable to the research questions identified here as relevant to the SDO.

Conclusions

Nonadherence to appropriate medication may be the rate limiting step in translating scientific advances in pharmacological treatments into improved outcomes for patients. This is especially relevant in chronic medical conditions, including NHS priority areas, where current levels of nonadherence are of concern to patients and healthcare providers alike.

Helping patients to get the best from medicines is a priority for research, practice and policy in healthcare. However, effective interventions remain elusive, partly because of limitations in the way that interventions have been designed and tested.

The key research agenda is therefore one of behaviour-change. However, medicines carry the potential for harm as well as benefit and there are also questions about what is good-prescribing and good medicine-taking. We have therefore identified two agendas: an *empirical* agenda to address the question of how adherence might be improved and a *normative* agenda to tell us what is the right thing to do.

In an ideal world the normative agenda would come first and inform the empirical agenda. However, there is an imperative to move ahead with the empirical agenda in conditions where there is strong supporting evidence for the benefits of medication and importance of adherence. These include current NHS priority areas but also other conditions such as highly active anti-retroviral therapy for HIV, immunosuppressant medication following transplantation and preventer medication in asthma.

The priority for empirical research is therefore to develop effective, efficient and equitable interventions to facilitate informed choice and optimal adherence to appropriate prescriptions where adherence matters most. The key research question is: *What are the most effective methods for changing the cognitive (i.e. beliefs; attitudes), emotional and capacity (i.e. memory limitations; changes in routines/habits etc) factors, which result in reduced adherence to appropriate medication?*

In this scoping exercise we grouped the literature on adherence into core themes: explaining patient behaviour, patient-provider interactions and societal policy and practice, all of which are relevant to our forth theme, the development of interventions. Our review of the literature identified existing knowledge and outstanding research questions within each of the themes that can inform the development of innovative interventions to facilitate optimal adherence to appropriate medicines.

We believe that the time is right to move forward. Several contextual factors are in place. Major research funding bodies such as the Medical Research Council (MRC) have identified behaviour change as a priority. The challenges for a research agenda in medication adherence are similar to those for other health-related behaviours such as smoking cessation, exercise and diet: how to influence and change behaviour. The MRC has produced a framework for the development of complex interventions to effect behaviour change and this might be operationalised in relation to adherence interventions.

Many of these questions are relevant to the SDO research priorities and the NCCSDO could make an important contribution by commissioning research that might inform the content of subsequent interventions. Moreover, several new policy and service delivery initiatives within the NHS have implications for medication-taking (e.g. new prescribers, increasing patient choice) and SDO commissioned research could provide ongoing evaluation of their effects on medication-taking.

Several core policy initiatives within the NHS place patient self-management and involvement in decisions at the forefront of healthcare delivery. Examples include the Expert Patient programme as developed by the Modernisation Agency, the National Service Frameworks and the increasing interest of regulatory bodies such as National Institute for Health and Clinical Excellence (NICE), in the issue of patient acceptability of treatments. These offer strong incentives and provide an excellent context for the development of interventions to help patients get the best from medicines.

Appendices

Appendix 1: Information provided for service-users

A) Information sent to the service-user volunteers prior to the consultation group meeting

NHS SERVICE DELIVERY AND ORGANISATION R&D PROGRAMME

Programme of research on patient and carer centred services

CONCORDANCE, ADHERENCE AND COMPLIANCE IN MEDICINE TAKING: SCOPING EXERCISE

Project Leader - Professor Rob Horne, University of Brighton

What the project is about:

This project is designed to help the NHS to understand patients' perspectives of medicines and what needs to be done to help people get the best from medicines. This is an important issue for several reasons.

Medicines can have a real benefit for many people, especially those with long-term illnesses and we need to find the best ways to bring these benefits to as many people as possible.

The prescription of a medicine is the common way of treating illness. Medicines are so widely used that the NHS spends more on them than any other form of treatment (about £6 billion a year).

Many of these medicines are not used as prescribed. If the prescription was right and a good choice, then this represents a loss for patients and the NHS. The patient loses because they don't get the benefit of the treatment and their illness may get worse. The NHS loses because resources may be wasted and there may be 'knock-on' costs if the patient gets worse and needs more intensive treatment later.

Perhaps not surprisingly, a lot of research has been done to try to understand what influences the way patients use (or don't use) medicines and what should be done to help patients get the best from their medicines.

The purpose of this project is to pull all this together and to summarise what we currently know about the topic and to identify what we don't know.

Why it is important to patients and the NHS

The project is important to patients and the NHS because it will also identify what research now needs to be done to improve patient care and their experiences with medicines.

WHY WE NEED YOUR HELP

This project will involve a detailed examination of research that has examined patients' views about medicines. At the same time, we would also like to hear from people with experience of medicines and get their views about the matter and about this project. We are particularly interested in your views about three issues:

1 What affects whether patients take or don't take medicines?

2 What could health care professionals and patients do to help get the best from medicines?

3 What research should be done to improve the way medicines are prescribed and used?

Getting the views of patients is vital to make sure that our work is anchored in the real world!

DISCUSSION POINTS

To help us get your views and focus, our discussion would like you to consider the following questions:

1 Is there anything you would like to tell us from your own experience of medicines and how they are prescribed that you think might help us to understand the following issues:
   - What affects whether patients take or don't take medicines?
   - What could health care professionals and patients do to help get the best from medicines?

2 Are there any changes you would like to see in the way in which medicines are prescribed by doctors (and other healthcare practitioners)?

3 Are there any changes you would like to see in the way in which medicines are used by patients?

4 There is a lot of discussion about patients taking more control over their illness and being more involved in decisions about the medicines prescribed for them. What do you think about this?

5 What research should be done to improve the way medicines are prescribed and used?

Once you have read the project protocol:

Once you have read the project protocol and the background to the project, please could you answer the following questions?

1 Is there anything we have missed out that you think is important to yourself or others?

2 Are there any other comments you would like to make about this project?

B) Summary protocol posted on Medicines Partnership website/ sent to participants prior to the service-user consultation group

NHS SERVICE DELIVERY AND ORGANISATION R&D PROGRAMME

Programme of research on patient and carer centred services

CONCORDANCE, ADHERENCE AND COMPLIANCE IN MEDICINE TAKING: SCOPING EXERCISE

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Concordance, adherence and compliance in medicine taking scoping exercise

Background for patients and service users and explanation of terms

Why this project is needed

This project is designed to help the NHS to understand patients' perspectives of medicines and what needs to be done to help people get the best from medicines. This is important for several reasons.

1 The prescription of a medicine is the common way of treating illness. Medicines are so widely used that the NHS spends more on them than any other form of treatment (about £6 billion a year).

2 Many of these medicines are not used as prescribed. If the prescription was right and a good choice then this represents a loss for patients and the NHS. The patient loses because they don't get the benefit of the treatment and their illness may get worse. The NHS loses because resources may be wasted and there may be 'knock-on' costs if the patient gets worse and needs more intensive treatment later.

3 Medicines can have a real benefit for many people, especially those with long-term illnesses and we need to find the best ways to bring these benefits to as many people as possible.

Perhaps not surprisingly, a lot of research has been done to try to understand what influences the way patients use (or don't use) medicines and what should be done to help patients get the best from their medicines.

Thousands of academic papers have been published on the subject. However, it is very difficult to get a clear, simple picture of this complex topic. One of the first problems is that are at least three different terms used in relation to the topic: compliance, adherence and concordance.

Explaining the terms

Compliance this can be simply defined as '*the degree to which the patient's behaviour matches the prescriber's recommendations'*. At first sight this seems to be a useful term to describe what patients do with the treatment. However, many people object to this term because they think it implies that it is the patient's *duty* to take the medicine as directed. They argue that it seems to portray a doctor-patient relationship in which the role of the doctor is to prescribe and the role of the patient is to follow the doctor's orders! The problem occurs if people make a value judgement in which compliance (taking the medicine as advised) is good and nonadherence (not taking the medicine or taking in a way that differs from the recommendations) is bad. For this reason, others have suggested that *adherence* be used instead of *compliance.*

Adherence This really means the same thing as compliance (the degree to which the patient's behaviour matches the prescriber's

recommendations) but was suggested as an alternative term to recognise the importance of free choice and to emphasise that nonadherence is no reason to blame the patient. Rather the emphasis should be on understanding the patient's perspectives of their treatment and helping them to get the best from treatment.

Concordance This term is really quite different. It refers to the relationship between the patient and the prescriber and the degree to which they agree about the treatment. Concordance has become more frequently used over the last few years. This is mainly due to a review by the Royal Pharmaceutical Society of Great Britain (RPSGB) and MSD (a large pharmaceutical company) which looked at the reasons why patients don't take medicines. Although this is quite complex, there are two basic reasons: people can't or don't want to.

Nonadherence (not taking the medicine or taking in a way that differs from the recommendations) may be unintentional when the patient decides to take the medication as prescribed but are prevented from doing so by barriers that are beyond their control. For example, they may not have understood the instructions or may experience practical problems in using administering the medicine (e.g. finding it difficult to pour liquids or use an inhaler), or simply forget to take it. Nonadherence may also be intentional when the patient decides not to take the medicine or takes it a way that differs from the recommendations.

Until about 10 years ago we knew very little about intentional nonadherence. Most of the research had focussed on unintentional nonadherence. Surprisingly little work had been done to try to understand why someone might go to the trouble of seeing the doctor and then chose not to follow the treatment advice. This changed when researchers began to look more closely at patients' beliefs about their illness and treatment. They found that doctors[24] and patients often have very different views about the illness and treatment. When viewed from the doctor's perspective, deciding not to follow treatment recommendation might seem an odd thing to do. However, when we step inside the patients' shoes (by finding out their personal beliefs about the illness and treatment) nonadherence often appears as a logical and understandable response to their perceptions of the treatment.

It follows that adherence will be more likely if the patient and doctor share similar views about the illness and the treatment. This is the essence of the *concordance* concept. It is based on the idea that doctors and patients should work towards a mutual understanding in relation to medicines and work in partnership to get the best from medicines. Concordance is a difficult concept to pin down and there a lot of unanswered questions and a few problems. One of these is that many people talk about concordance when they mean compliance/adherence.

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[24] We have used the term 'doctor' here because most of the prescribing of pharmaceutical medicines is done by medical doctors. However, other healthcare professionals such as pharmacists and nurses are becoming increasingly involved in prescribing and we mean to include these when we use the term 'doctor'.

However, the most important problem is that we still do not really know how best to help patients get the most from medicines. This project aims to help us progress on this path by summarising what we currently know, identifying what we need to know and from this, making recommendations for what research should now be done to show us how to improve patients' experience of prescribing and to help us get the best from medicines.

Concordance, adherence and compliance in medicine taking scoping exercise: technical proposal

This proposal outlines a plan of work to carry out a scoping exercise in concordance, adherence and compliance with medication for the NHS Service Delivery and Organisation (SDO) National Programme.

(A) Aims

1 Summarise current knowledge about the determinants of medication taking

2 Construct a conceptual map of the area of compliance, adherence and concordance

3 Identify priorities for future research of relevance to the NHS, with particular emphasis on identifying what new knowledge is needed to be able to develop effective, realisable, efficient and equitable interventions to promote the appropriate use of medicines for the benefit of patients and the NHS.

(B) Background

The prescription of a medicine is one of the most frequent and costly interventions in health care and the appropriate use of medicines is key to the self-management of most chronic illnesses. However, it is estimated that over a third of all prescriptions for chronic illness are not taken as advised and this is thought to represent a significant loss to both the patients and health care system. Due to variations in the definition and measurement of medication taking behaviour across studies, it is difficult to gain a definitive picture scale of the problem and so far we know very little about its economic consequences. A plethora of research studies have identified many of the reasons for nonadherence (noncompliance) yet effective methods for improving medicines usage have proved elusive (Haynes, McDonald, Garg and Montague, 2003) and the issue remains complex and fraught with controversy. The proposed scoping exercise will focus on issues at four levels – 1) patients' behaviours; 2) interactions between patients and providers; 3) societal policies and practices; 4) interventions.

B1) Patients' medication behaviours - intentional and unintentional nonadherence

At the root of the problem is the fact that nonadherence results from two quite different types of behaviour: *unintentional* and *intentional* (Horne, 1998). Unintentional nonadherence occurs when patients' intentions to take prescribed medication are thwarted by barriers such as forgetting,

poor comprehension, or difficulties in opening the packaging. Intentional nonadherence is the result of a decision by the patient not to take the medication or to take less or more than recommended. This distinction has profound implications for how the problem of sub-optimal use of medicines is conceptualised and dealt with, as these different causes would demand different solutions. There is little literature on the extent to which each of these types of nonadherence contributes to the overall picture. However, a recent study of 239 patients starting new medication for a chronic condition found that of the 67 non-adherent patients, 55 per cent were unintentionally nonadherent (Barber, Parsons, Clifford, Darracott and Horne, 2004).

Unintentional nonadherence can be addressed by a number of conceptual models. These include the provision, understanding and recall of instructions (Ley, 1982), approaches based on an understanding of the barriers between intention and action (Horne and Weinman, 1998) and the effects of local circumstances and system errors in health care organisations (Barber, 2002).

Intentional nonadherence is best understood in terms of patient and practitioner beliefs attitudes and expectations influencing the motivation to take (or not to take) medicines. Here, research conducted across a range of illness groups and between different cultural and institutional contexts confirms that patients beliefs about their illness often differ from the medical view, yet have their own internal logical and influence how information (e.g. recommendations to take medication) are interpreted and acted upon (Horne & Weinman, 2002; Horne and Weinman, 1999; Morgan, 1996). The question of how to manage intentional nonadherence raises issues of patient-provider relationships as well as broader questions, at a societal level, regarding the right of the patient to refuse treatment and the degree of uncertainty about the risks and benefits of the treatment for the individual.

Recent reviews (World Health Organisation, 2003; Myers and Midence, 1998) have summarised literature relating to intentional and unintentional nonadherence, and aimed to contrast patient and professional perspectives or to explain nonadherence with prescribed medication in relation to particular conditions. However, there is a need to identify what is known in relation to a) different groups in the population, particularly in terms of social disadvantage and ethnic minority groups, children and adults and b) different broad groups of conditions and related treatment strategies (eg, minor acute vs. severely disabling/life-threatening, preventive *vs* symptomatic treatment).

B2) Interactions between patients and providers

Concordance: limitations and outstanding questions

The concordance concept (Royal Pharmaceutical Society of Great Britain, 1997) attempts to knit together two issues relating to the use of medicines. First it responds to recent evidence for the importance of patients' beliefs (conceptual models) about illness and medication as determinant of medication taking behaviour. Second, it attempts to embody principles of individual rights and issues of the power differentials within prescribing-related consultations to describe the creation of an agreement that respects the wishes and beliefs of the patient (Horne, 2001). Few would disagree with the underlying principles of concordance: respect for patient autonomy and the need to take

account of the beliefs and preferences of individual patients in the provision of healthcare. However, the concept has not been fully defined and there is confusion about how it should be operationalised in research and practice (Dieppe & Horne, 2002; Heath, 2003).

Beyond the consultation

This scoping exercise will consider the prescribing-related consultation but also go beyond it to address *unintentional* nonadherence and other issues outlined in the SDO Briefing document, including access to and interpretation of information about medicines. It will also consider broader issues relating to societal policies and practice.

B3) Societal policies and practice

It may be too simplistic to consider the consultation in isolation. It is more than a meeting between patient and clinician. The core decision involves at least three parties: the patient, the prescriber and the payer. A philosophy of prescribing which ignores the latter may be noble but ultimately limited in its capacity to foster pragmatic solutions to questions of how best to use medicines. Within the UK NHS, the prescriber is responsible for allocating resources on behalf of 'society' and the needs of the individual must be viewed in the context of the needs of others. What happens when the patient's preferences conflict with the 'greater good' (Horne and Weinman, 2004)? A closer examination of the balance between individual wants and greater good is essential because of the high costs of medicines. The economic stakes are high. The NHS spent £6.8 billion on medicines in 2002 (National Statistics, 2003). Despite the high costs of medicines, we know little about the costs of nonadherence (Howard, Beasley, Hunt and Partridge, 2003). These will need to be considered beyond the cost of wasted (unused) medicines to include the knock-on costs including additional demands on services from under treated illness and failures of preventive strategies.

Concordance is both a philosophy of ends and a philosophy of means – it defines both the desired outcome and the means by which it will be reached. However, this concept is neither related to the other literature on the ends of health care and prescribing, nor the literature on the ways to achieve them. Important elements in the complex balancing act of prescribing are not recognised in the definition of concordance. For example, Cribb and Barber (1997) have argued that good prescribing needs to balance the technical, evidence based properties of the drug with the patient's wants, and with issues of the greater good. Buetow et al. (1997) carefully reviewed the literature on prescribing appropriateness and came to a similar conclusion. Concordance needs to be related to the wider literatures on ethics and philosophies of healthcare delivery that address these difficult issues. It needs to be examined to establish whether its statements about ends and means have either supporting arguments or supporting evidence.

Concordance, and other concepts for achieving better use of medicines, need to be examined under difficult prescribing decisions. What should be done if a fully informed patient chooses not to take her TB therapy? What if a patient rejects a potentially life-saving treatment (such as immunosuppresant therapy following renal transplantation) due to erroneous interpretations of the likely risks vs benefits or because of beliefs which are factually incorrect? How should a doctor with

prescribing targets and Evidence Based Medicine guidelines balance these against a patient's wishes?

B4) Focus on interventions to promote the optimum use of medicines in chronic illness

The conceptual map produced within this scoping exercise will summarise our current knowledge and outstanding questions at the patient, patient-provider interactions and societal policies and practice levels. In doing this, our priority will be the identification of effective equitable, realisable interventions to promote the optimum use of medicines. We will focus on chronic illness, as here there is the greatest potential to enhance the quantity and quality of life.

(C) Methods

C1) Strategy for the scoping exercise

The scoping exercise will not involve an exhaustive review of the primary literature – this has already been done to good effect and is beyond the scope and timescale of the project. Rather the scoping exercise will provide a conceptual map to guide policy makers and researchers through this complex field, enabling them to obtain a clear overview of current knowledge and outstanding questions and to identify priorities for research.

The task will draw on the expertise of three groups:

1) PROJECT TEAM

The Project Team consists of five academics with extensive personal involvement in research into medication prescribing and taking. The team is multidisciplinary, encompassing pharmacy, health, psychology, medical sociology and health economics. The Project Team will evaluate the literature, derive the conceptual map and write the scoping report.

All members of the Project Team have contributed to the literature on medication taking and their expertise spans many of the relevant disciplines and approaches. They have published primary and secondary research in the topic. Professors Horne and Weinman have published extensively on the causes of nonadherence and have developed psychological models and validated tools for assessing practitioner and patient perspectives and use of medication. Dr Morgan is a medical sociologist who has conducted qualitative studies of nonadherence, particularly among ethnic minorities and undertaken research on the medical consultation. She has also successfully undertaken an SDO scoping exercise on Access to Health. Professor Barber has published widely on the philosophy and ethics of prescribing and on the healthcare systems and policy relating to the use of medicines. Dr Elliott is one of the few health economists within the UK specialising on the economic aspects of adherence and adherence interventions. Gaps in expertise are addressed within the Expert Panel.

2) EXPERT PANEL

The Expert Panel consists of nine opinion-leaders representing a range of expertise augmenting the project team: health informatics, health policy, medical ethics, evidence based medicine, medical education, specialist medicine, mental health, nursing, industry and NHS management. The Expert Panel will be contracted to provide written feedback on the draft conceptual map and research priorities produced by the Project Team. The Expert Panel members and their expertise and affiliation are listed in Table 1.

3) CONSULTATION GROUP

This will comprise a wider group of researchers, opinion leaders and stakeholders. It will include some of the unsuccessful applicants to the SDO scoping exercise who will be invited by Medicines Partnership. Involvement of the Consultation Group is a listening exercise. The Consultation Group will be involved in two ways:

a) A workshop held in London in which a maximum of 30 people representing academia, healthcare professionals, NHS policy and management, and patient groups will present their views. This process will inform the conceptual map and research priorities drafted by the PT and sent to the EP for comment.

b) Written comment on the draft conceptual map and research priorities sent out at the same time as it goes to the expert panel.

Key Stages

The project will run from 1 July 2004 to 31 May 2005. Key milestones are:-

1. Drafting summary of current knowledge and outstanding questions in 4 topic areas:-
   a) patient perspectives and behaviour
   b) patient provider interactions
   c) societal policies and practice
   d) intervention
2. A two-day meeting of the Project Team to discuss initial drafts of the four topic areas (above) and develop conceptual map and research agenda.
3. A seminar with the Consultation Group (including unsuccessful applicants). This will occur after the two-day meeting of the Project Team and will help us to refine our thoughts and take action of input. The emphasis will be on eliciting the ideas of the group rather than presenting out thoughts at this stage.
4. Compilation of the draft conceptual map by the Project Team.
5. Circulation of draft conceptual map and research agenda to Expert Panel (and the Consultation Group) for comment.
6. Synthesis of comments and preparation of final report.

(D) Outputs and deliverables

The following outputs will be provided for each of the levels of investigation:

Patient behaviour

1 An evaluation and comparison of theories, philosophies and evidence for the underlying reasons for nonadherence, including both intentional and unintentional reasons. We will also identify the degree to which explanations for nonadherence and interventions to facilitate adherences are generalisible or need to be situation specific (eg, across illness and treatment types, across socio-economic groups and ages, including children and adolescents).

2 A review of methods for assessing medication-taking behaviour and identify priorities for further developments, as well as methods for eliciting and assessing patients' beliefs, attitudes, preferences and experiences relative to medication taking. Here we will consider the application of measures in clinical practice as well as research.

Patient-provider interactions

3 A summary of the evidence for the effects of patient-provider interactions on the use of medicines that identifies key studies that have assessed gaps between patient and provider inputs (e.g. beliefs, attitudes, knowledge, preferences) and methods for addressing gaps within the prescribing-related consultation. This will consider the role of different health professionals (eg, doctors, nurses and pharmacists) and issues relating to inter-professional communication and the consistency of advice to patients.

4 A list of outstanding questions about how to equip healthcare practitioners with the knowledge, skills and attitudes to elicit and take account of patients' beliefs and preferences and to tailor approaches to the needs of the individual in order to promote the optimal use of medication.

Societal policies and practice

5 A critical appraisal of the concept of concordance and related concepts such as partnership in medicine taking and patient-centred care; a mapping of these onto ethical theory and consideration of application to practice settings.

6 A summary of outstanding questions relating to the economics of nonadherence and the implications for adherence interventions.

7 A summary of outstanding questions about concordance, adherence and compliance and how they relate to healthcare policy.

Interventions

8 An explanation of why adherence interventions have, in systematic reviews, been shown to be relatively ineffective. This will lead to a critical appraisal of theories and approaches that could improve medicines taking, including concordance, and other related concepts, such as shared decision-making and patient-centred care.

Synthesis across levels

9 A summary of current knowledge and outstanding questions relating to patients' access to and interpretation of information about medicines.

10 A clarification of terminology. We will explore the terms used to explain medicines-taking behaviour, primarily but not exclusively 'compliance', 'adherence' and 'concordance' and, if possible, propose standardisation of the terminology.

D1) Summary of deliverables

1 A summary of current knowledge about the process of medication taking that identifies outstanding questions at three levels: patient, patient-provider interactions and societal policies and practice.

2 A conceptual map for understanding concordance, adherence and compliance. This map will focus on the identification of effective, equitable and realisable interventions to promote the optimum use of medicines, particularly in chronic illness, as here there is the greatest potential to enhance the quantity and quality of life.

3 A research agenda that focuses on the key areas of theory and evidence that are essential to inform future policies and practice around optimising medicines taking. This will include recommendations for the primary research, secondary research and methodology that is necessary to clarify our understanding of the process of medication taking and of developing and evaluating interventions to facilitate the appropriate use of medication.

(E) References

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Table 1: Composition of the Advisory Panel

Name and Title	Affiliation	Expertise
Justin Keen **Professor of Health Politics and Information Management**	Nuffield Institute for Health, University of Leeds	Health informatics, health policy, access and utilisation of medicines information.
Richard Meakin **General Practitioner and Senior Lecturer in Primary Care**	Royal Free and University College School of Medicine	Studies of doctor-patient negotiation in primary care consultations. Assessment of patient expectations and satisfaction.
Alan Cribb **Professor of Bioethics and Education** **Director, Centre for Public Policy Research**	Department of Education and Professional Studies, King's College London	Links between empirical research on social/policy analysis and perspectives in applied ethics. Changing models of healthcare.
John Geddes **Professor of Epidemiological Psychiatry**	Centre for Evidence Based Mental Health Department of Psychiatry, University of Oxford	Randomised controlled trial and systematic reviews. Evidence-based practice.
Richard Vincent **Professor of Medical Science Consultant Cardiologist**	Associate Dean, Brighton and Sussex Medical School	Secondary medical care (cardiology). Medical education, multi-professional working.
Martin Anderson **Director of Patient Affairs**	Association of the British Pharmaceutical Industries (ABPI)	Pharmaceutical industry perspectives.
Paul Seddon **Consultant Paediatrician**	Brighton and Sussex University Hospitals	Will consider issues relating to children and adolescents.
Bob Sang **Consultant in Patient Perspectives**	Former Director of Patients Association	Understanding patient perspectives of healthcare. Applications to health policy.
Stephen Firn **Chief Executive**	Oxleas NHS Trust and Registered Mental Nurse	NHS Policy, NHS Management, Nursing policy and practice.

Appendix 2: Summary of the Consultation Groups

The project team was keen to consult widely with opinion leaders, stakeholders and researchers in the development of the conceptual map and research priorities. Two consultation groups were convened. To facilitate user group involvement, the project team liaised with Medicines Partnership (http://www.medicines-partnership.org/- an initiative supported by the Department of Health aimed at enabling patients to get the most out of medicines by involving them as partners in decisions about treatment and supporting them in medicine taking) regarding suitable patient representatives. Additionally, following discussion with INVOLVE (a national advisory group, funded by the Department of Health, which aims to promote and support active public involvement in NHS, public health and social care research), an invitation to apply to attend the patient representative consultation group meeting was advertised on the INVOLVE website (http://www.invo.org.uk/). This panel then convened on 22nd February 2005 at the Holborn Grange Hotel, London. A second meeting was held at the same venue on 14th March 2005, and involved representatives from academia, health care professions and NHS policy and management, recruited following recommendations from both project team and expert panel members. Both meetings generated broad and interesting discussions. A brief summary of each meeting is provided below.

Patient Representative Consultation Group (22nd February 2005)

Patient Representatives

- Ashley Green (British Lung Foundation)
- Katherine Darton (Mind)
- Carrie Britton (Choices for Families of Children with Arthritis)
- Nicola Russell (MS Trust)
- Paul Clift (HIV/AIDS, Lawson Unit, Brighton)
- Jassna Russo (Service User Research Enterprise)
- Diane Denton (Mindlink)

Project Team

- Nick Barber
- Rob Horne
- Ian Kellar

Rob Horne began by detailing the purpose and objectives of the SDO project, and giving definitions of compliance, adherence and concordance. This included a history of the development of the terms, and a discussion of the connotations. It was noted that adherence is only desirable if a prescription is appropriate, that not all prescribing was appropriate, and that nonadherence can be a sensible and appropriate

response to an unsuitable prescription, but that this response can be especially problematic where the nonadherence is undeclared.

Following this initial overview of the purpose and objectives of the project, the following themes emerged during the day:

Concerns about concordance

Concerns were raised over the practical implications and connotations of concordance. Representatives felt that patients would need more support and accurate information in order to share in decision making. Questions were raised regarding the intelligibility of risk information, and whether patients could be sufficiently supported to engage fully in the prescribing process:

`Concordance is a romantic ideal, not a practical likelihood'

`I am concerned that concordance places intellectual demands on patients that may be inappropriate'

`Concordance is only useful in long-term chronic illness'

`Concordance is a dishonest term, unimaginable in the mental health domain'

`Medical and risk information is often unintelligible. Patients are often caught between extreme or incorrect advice on web sites and impenetrable medical information'

Clinician–patient relations

Representatives discussed whether it is right to expect a doctor-patient relationship to be equal with respect to knowledge. Personal preference, time considerations and the nature of the doctor-patient relationship were all felt to be relevant factors. It was noted that religious or community figures may be more central in decisions regarding adherence, and that the doctor may be less influential in such circumstances. Debate took place regarding the nature of the relationship between doctor and patient, particularly with regard to the expert role of the doctor. It was put forward that doctors' expertise should be in listening as well as diagnosis and prescribing, and that patients would always have the final authority regarding adherence.

`Not all patients want equality in the doctor-patient relationship [with respect to knowledge],

`The doctor is not necessarily the central figure when it comes to important influences of medication taking'

`Non-expert patients may have little desire to participate in decisions around prescribing – is it the job of a doctor to educate them regarding the options available to them?'

`Clinicians are under pressure; repeated questioning could cause the relationship to deteriorate'

Acceptability of the term 'patient'

All but one representative disliked the term 'patient' and felt that this should be avoided or explained in the report. Representatives put forward the view that it was value-laden, and was problematic in terms

of implied status, especially in the mental health domain. That the issue was one of status rather than semantics was underlined by the positive appraisal of the term `expert patient.' However, the term 'service user' was preferred.

`The doctors see symptoms rather than the patient'

`The issue is about status change not semantics'

Informed adherence

The concept of informed adherence was discussed, focussing on the need for doctors to elicit patients' beliefs, preferences and expectations of treatment and to provide appropriate information accordingly. The question of how patients' perspectives of prescriptions and adherence may change practitioner perspectives was also discussed.

`Informing' should be a two way process'

`Clinicians should attempt to unpack beliefs about patients' illness'

Research questions

At the end of the discussion, free discussion was initiated, during which time the group members were encouraged to put forth research questions they felt needed answering:

- Why do some patients not want to participate in prescribing decisions?
- What are the barriers to decision making involvement? Are doctors' attitudes to shared decision making related to this?
- Could service user feedback be used to train clinicians?
- How do patients' perspectives on prescriptions and adherence change practitioner perspectives?

Academic/NHS Consultation Group (14th March 2005)

Academic/NHS Representatives

- Tina Brock (University of North Carolina)
- Michael Calnan (Professor of Medical Sociology, University of Bristol)
- Graham Davies (Senior Lecturer, University of Brighton)
- Lynn Myers (Senior Lecturer in Health Psychology, University College London)
- Sue Oakley (NHS Trust)
- Jane Ogden (Professor of Health Psychology, University of Surrey)
- Theo Raynor (Professor of Pharmacy Practice, Medicines and their Users, University of Leeds)
- Mike Schachter (Clinical Pharmacology, Imperial College)
- Joanne Shaw (Director, Medicines Partnership)

Project Team

- Nick Barber
- Rob Horne
- Ian Kellar
- Myfanwy Morgan
- John Weinman

Professor Horne began by detailing the purpose and objectives of the Academic/NHS Consultation Group meeting, explaining that much work had been undertaken, thus allowing for assessment of the initial strategy, but that sufficient time was left such that useful advice could be heeded. Details of the scoping exercise protocol were presented. This included an overview of the scoping exercise rationale, detailing the overall aims, the four key topic areas, the general methodology, the outputs and deliverables, and the key project dates. The meeting was then structured around the four themes of the scoping exercise. A detailed discussion ensued. Some of the main insights from this are represented below.

1. Patients' perceptions and behaviours

Following an outline of explanatory models of perceptions of illness/treatment and behaviour, concerns were raised regarding the validity of addressing intentional nonadherence, and the validity of this response in certain circumstances was noted. The focus then shifted from adherence/compliance to concordance. It was commented that concordance should not be thought of as another term for compliance, and stated that concordance was analogous to negotiation.

`How is it possible to respect patients' beliefs whilst aiming to intervene?'

`Concordance should not be thought of as another term for compliance – concordance is analogous to negotiation'

2. Patient-provider interactions

The literature relating to patient provider interaction was reviewed. There was a discussion of appropriate methodologies and outcome measures in this area, and it was noted that there is a dearth of process evaluation in this literature.

`Quality of life outcome measures may be more relevant than clinical outcome measures'

3. Societal policy and practice: conceptual and philosophical issues

Distinctions between compliance, adherence and concordance were presented, particularly noting the respective scientific and normative values implicit in each term, as well as the ethical issues involved.

Definitions of good and bad prescribing were also considered. There was a discussion surrounding the presentation of drug waste data, and the differing aims of patients and doctors.

`In my PCT much of the data on waste relies on information from unfilled prescriptions and this does not relate to compliance'

`I believe patients are looking for quality of life outcomes whereas doctors are looking for biomedical results – they have differing aims'

`Doctors seek quality of life outcomes for patients but they also have responsibility to wider society when it comes to appropriate resource use'

4. Interventions

The project group's approach to evaluating the efficacy of adherence interventions was generally approved. There was discussion about the methodological flaws in the present literature and general approval for a staged development of interventions as suggested in the MRC framework for developing and evaluating complex interventions to improve health. However, it was noted that this framework has yet to be operationalised in terms of medication adherence and this would need to be done in the near future if the framework was to be used in this way.

Summary

Notwithstanding the helpful suggestions made, the academic/NHS group broadly endorsed the approach to the scoping exercise. Moreover, the panel generally acknowledged the value in the methods taken thus far by the project team members in the topic areas detailed. The clear distinction between prescriptive and descriptive contribution made by the terms concordance, adherence and compliance received particular support. It was clear throughout the consultation that commentary on what distinguishes good from bad prescribing was desired by the group, and this was accepted by the project team members. It was also recommended that the report make clear statements about the need for high adherence to appropriate prescriptions - there is a 'right and wrong way to take medicines' and it is imperative that medicines are taken in the right way to optimise safety and efficacy and reduce wastage.

Appendix 3: Search strategy used to identify papers relating to adherence in children

Medline was searched for papers relating to adherence in children. The search strategy adopted was based on existing Cochrane reviews; the Haynes et al (2002) terminology was used to identify papers relating to nonadherence and terminology relating to children, adolescents, and family/carers was obtained from three additional Cochrane reviews (Larun et al., 2003; Shields et al., 2003; Thomas et al., 2003).

The search resulted in the identification of 3003 articles.

#	Search History	Results
1	patient compliance/ or patient dropouts/ or psychotherapy.mp. or treatment refusal/ or patient education/ or regimen:tw.mp.	112403
2	medicat:.tw. or drug therapy.mp.	189078
3	(patient compliance or patient adjacent to compliance).mp.	28782
4	Adolescen/ or exp child/	1597636
5	exp Students/	41225
6	(child$ or adolescen$ or pediatric$ or paediatric$).tw,jw.	781382
7	(boy$ or girl$ or kid$ or school$ or preschool$ or juvenile$ or under?age$ or teen$ or minor$ or pubescen$ or young people or young person$ or youth$ or student$).tw.	599972
8	or/4-7	2197830
9	exp parents/	38121
10	parent$.tw.	154567

11	family member$.tw.	27432
12	father$.tw.	15838
13	mother$.tw.	81140
14	classroom$.tw.	4658
15	elementary school$.tw.	2889
16	high school$.tw.	8752
17	community.tw.	120240
18	communities.tw.	22098
19	school$.tw.	94531
20	home.tw.	72713
21	home based.tw.	1452
22	family.tw.	272903
23	families.tw.	83166
24	community based.tw.	13401
25	family based.tw.	1327
26	exp family/	142436
27	exp family therapy/	5791
28	exp family health/	11077
29	exp schools/	45779
30	exp caregivers/	8345
31	or/9-30	861357
32	1 and 2	9833
33	32 or 3	33294
34	33 and 8 and 31	3003

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Larun, L, Nordheim, LV, Ekeland, E, Hagen, KB., Heian, F. 2003. Exercise in prevention and treatment of anxiety and depression among children and young people. *The Cochrane Database of Systematic Reviews:* Issue 4

Shields, L, Pratt, J, Flenady, VJ, Davis, LM, Hunter, J.2003. Family-centred care for children in hospital. (Protocol) *The Cochrane Database of Systematic Reviews*: Issue 4

Thomas, RE, Baker, P, Lorenzetti, D. 2003. Family-based programmes for preventing smoking by children and adolescents. (Protocol) *The Cochrane Database of Systematic Reviews*: Issue 4

Appendix 4: Psychological models of treatment adherence: a brief overview

John Weinman & Rob Horne

Since it is now strongly recommended that interventions to change health behaviours, including treatment adherence, are based on a theoretical model which provides an explanation of that behaviour (Campbell et al, 2000), this appendix provides a brief overview of a selection of currently used models.

A number of theoretical models have been developed to explain the variation in adherence to medical recommendations, including medication. Most of these have been developed within health psychology but it is important to note that other implicit models are used in the extensive sociological literature on adherence.

The Health Belief Model (HBM)

The HBM was developed to explain why people failed to take up disease prevention measures or screening tests before the onset of symptoms (Rosenstock, 1974). The original model proposed that the likelihood of someone carrying out a particular health behaviour (eg, attending for screening) was a function of their personal beliefs about the perceived *threat* of the disease and an assessment of the *risk/benefits* of the recommended course of action. Perceived threat, or vulnerability, is derived from beliefs about the perceived *seriousness* of the threat and the individual's perceived *susceptibility* to it. The individual then weighs up the perceived *benefits* of an action (eg, taking medication might ease symptoms) against the perceived *barriers* to the action (eg, fear of side-effects or costs of the treatment). A *cue* to action or stimulus must occur to trigger the behaviour. Thus, the HBM predicts that the likelihood of action is increased if the perceived threat of the disease is high and if the benefits of behaviour are thought to outweigh the barriers and if certain cues are in place.

The HBM or its components have been utilised in a large number of research studies investigating health-related behaviours (see Sheeran and Abraham, 1996, for an extensive review). Studies have included adherence to dietary recommendations (Urban et al, 1992; Caggiula and Watson, 1992), breast self-examination (Calnan, 1984), and dental behaviour (Chen and Land, 1986).

The HBM has also been used in studies investigating medication adherence across a range of treatments and illnesses including HIV/AIDS (Fourney and Williams, 2003; Muma et al, 1995; Malcolm et al, 2003), hypertension (Nelson et al, 1978; Taylor, 1979), diabetes (Alogna, 1980; Bloom-Cerkoney and Hart, 1980; Brownlee-Duffeck et al, 1987), kidney disease (Cummings et al, 1981), malaria prophylaxis (Abraham, Clift & Grabowski, 1999; Farquharson et al, 2004) and psychiatric disorders (Hogan, Awad and Eastwood, 1983; Kelly, Mamon and Scott, 1987; Pan and Tantam, 1989; Adams and Scott, 2000; Scott, 2002).

Studies applying the HBM to predict adherence to recommendations for treatment of chronic illnesses, have produced a mixed pattern of

findings. Adherence was typically predicted by various combinations of individual HBM components, rather than by the precise interaction of variables specified by the model. Although several studies have demonstrated the value of interventions based on the HBM in facilitating health-related behaviours such as attending for medical check-ups (Haefner and Kirscht, 1970) or using emergency care facilities in an acute asthma attack (Jones et al. 1987), few studies have applied this model to interventions to enhance medication adherence.

Theory of Planned Behaviour (TPB)

The Theory of Planned Behaviour (TPB) (Ajzen, 1991) was developed from research investigating relationships between attitudes and behaviour. It is not specific to health but has been widely used in this context (Stroebe and Stroebe, 1995). The central tenets of the TPB are that the formation of *intentions* precedes and predicts behaviour and that intentions are determined by *attitudes* towards the behaviour, *subjective norms* concerning the behaviour, and *perceived behavioural control.* Attitudes towards the behaviour are defined as the product of beliefs about the likely outcome (eg, `Following the doctor's recommendations for using insulin will keep my diabetes under control') and the perceived value of the outcome (eg, `Keeping my diabetes under control is important to me.'). The person's subjective norm comprises beliefs regarding others views about the behaviour (eg, `My partner wants me to follow the recommendations') and the motivation to support these views (eg, `I wish to please my partner by following the recommendations'). Perceived Behavioural Control describes the extent to which a person feels that behaving in a certain way is something that is within their control. This is dependent on control beliefs such as perception of both internal resources such as skills or information and external resources such as perceived barriers (Conner and Sparks, 1996). The concept is generally considered similar to Bandura's (1977) concept of self-efficacy (Ajzen, 1991; Schwarzer and Fuchs, 1996).

In the TPB, attitudes and subjective norms exert their influence on behaviour indirectly via their effect on intention. PBC has both an effect on intention and a direct effect on behaviour. For example, given equal intentions, the person who is confident of their ability and perceives few obstacles is more likely to actually perform the behaviour. However, Ajzen (1991) suggests that the importance of these three variables is likely to vary across behaviours and situations.

The TPB has been applied in studies investigating a range of health-related behaviours including giving up smoking (Godin et al, 1992), engaging in an exercise programme (Godin, Vezina, and LeClerc, 1989; Godin et al, 1991; Norman and Smith, 1995), and using a condom during sexual intercourse (Chan and Fishbein, 1993). Some of the components of the TRA and TPB have also proved to be useful in predicting adherence to medication prescribed for malaria prophylaxis (Abraham et al, 1999) and for the treatment of urinary tract infections (Ried and Christensen, 1988), psychiatric disorders (Cochran and Gitlin, 1988; Sultan and Bungener, 2002) and hypertension (Ried et al, 1985; Miller et al, 1992). Studies have generally shown that behavioural intentions are influenced by attitudes and subjective norms although the strength of the relationship between intentions and behaviour varies across studies and between behaviours (see Conner and Sparks, 1996, for a more detailed review).

Attribution theory and beliefs about cause and control over illness

Causal beliefs

Attribution Theory (Turnquist et al, 1988) is concerned with the cognitive processes by which people explain the causes of events. Its application is based on the notion that a fundamental response to adverse events such as illness is the search for explanations about cause and outcomes. Causal explanations are related to past experiences and can influence future response and adjustment to the illness.

Early research was mainly concerned with the extent of beliefs in internal (ie, related to their own behaviour) or external causes (ie, blaming fate or others). Recent work on attributional style and content has added further dimensions such as stability (ie, whether the cause of the illness is long lasting or temporary), globality (ie, global versus specific causes), universality (ie, universal versus personal causal influences) and controllability (ie, controllable *versus* uncontrollable influences).

A number of studies have investigated the specific application of attribution theory to health problems including end-stage renal disease ESRD (Wright et al, 1990) and adherence to recommendations for life-style changes among pre-operative coronary patients (Naea De Valle and Norman, 1992; Weinman et al, 2000). It is clear that causal attributions are related to beliefs about cure and can influence the patient's behavioural response and adaptation to illness. However, it has not been possible to identify one type of attribution which is universally adaptive. Certain attributions seem to adaptive in some situations but not others (Naea De Valle and Norman, 1992; Tennen et al, 1986).

Beliefs about control

The concept of perceived control was applied to health by Wallston and colleagues (1978) who developed a measure of *health specific locus of control* (HLOC). This categorised people according to whether they attributed control over their health to internal or external factors. Later this measure was revised and extended to form the *multidimensional health locus of control* (MHLOC) scale (Wallston et al, 1978), since research with patients indicated that control beliefs should be assigned to three separate unipolar scales called internal, chance and powerful others (Levenson, 1973a; Levenson, 1973b). There is some evidence that HLOC beliefs are predictive of certain health behaviours. For example, people with an internal HLOC were more likely to be successful in seeking out information on health issues or reducing smoking than those with an external locus of control (Wallston and Wallston, 1982). However, the relationship between measures of locus of control over health in general and *specific* health behaviours is fairly weak. For this reason there has recently been a move away from the idea that individuals have a general perception of control over all aspects of health. Instead, research has focused on the assessment of perceived control over specific aspects of health or illness such as control of diabetes (Bradley et al, 1990), giving up smoking (Georgiou and Bradley, 1992), aspects of dental health (Beck, 1980) and other measures (Furnham and Steele, 1993).

Empirical studies investigating the role of LOC beliefs in adherence are inconclusive. Some have found no association between control beliefs and adherence (Hazzard et al, 1990; Harvey and Peet, 1991; Harvey, 1992; West et al, 1993) and in studies where associations were found, there is little consistency in the type of control which is associated with adherence (Bruhn, 1983; Wilson, 1995). Situation specific control beliefs are likely to be more closely related to adherence than beliefs about control over health in general. For example, studies have failed to demonstrate significant interactions between peoples' beliefs about control over their health in general (MHLOC) and adherence to medication in several situations including affective disorders (Harvey and Peet, 1991; Harvey, 1992), renal transplantation (Frazier et al, 1994; Kiley, Lam and Pollack, 1993), HIV/AIDS (Altice et al, 2001), gastro-oesophageal reflux disease (Kamolz, 2002) and in predicting intended adherence to an imaginary regimen in a study involving college students (McCallum, Wieb and Keith, 1988). However, the use of disease specific measures for assessing LOC improves the utility of this construct in explaining medication related behaviour (Bradley et al, 1987, Kohlman et al, 1993; Johnson et al, 1989; Reynaert et al, 1995; Wallston et al, 1991).

Efficacy beliefs

Beliefs about one's ability to control or perform specific behaviours, and about their effectives have been proposed by Bandura (1986) to be central determinants of health related behaviours. Bandura has identified two types of efficacy beliefs as important: *outcome efficacy* which concerns beliefs about whether the behaviour will result in an effective outcome (eg, `Taking medication will reduce my blood pressure and so prevent renal complications') and *self-efficacy,* which covers the individual's beliefs as to whether they will be able to carry out the behaviour (eg, `I am confident that I will remember to take my medication every day'). Individuals may acquire their sense of self-efficacy from their assessment of the outcome of their own behaviour and the behaviour of others and feedback about their own behaviour which they receive from significant others. Several studies have demonstrated a relationship between perceived self-efficacy and adherence to medication (Kobau and Dilorio, 2003) and to recommended health-related behaviours such as giving up smoking (DiClemente et al, 1985) or carrying out an exercise program (Kaplan, Atkins and Reinsch, 1984).

In general, self-efficacy beliefs are likely to be more salient for complex or difficult behaviours, such as giving up smoking, than for behaviours such as adherence to a simple medication regimen (Flanders and McNamara, 1984). Beliefs about control over health and self-efficacy and outcome-efficacies may be influenced by previous experience and other cognitions.

Stage models

It has been suggested that health behaviour may proceed in stages and that different cognitions may be more important in particular stages than in others: for example, the thinking underlying *initiation* of a particular behaviours may be qualitative different from that involved in *maintenance* of the behaviour. For example, Weinstein (1988), suggests that some of the beliefs described in other models- such as beliefs about

personal susceptibility - are also best described in stages (eg, is aware of a potential health risk, believes that others are susceptible, believes that they are personally susceptible). He goes on to suggest that interventions to promote behaviour are likely to be more effective if they are targeted at the particular cognitions which characterise the particular stage that the individual has reached in their thinking about or implementation of the behaviour.

Several stage models of health behaviour have been proposed in which health behaviours occur as the result of several stages of cognition. The *Transtheoretical Model* (TTM) (Prochaska & DiClemente, 1983), which is often referred to as the `*Stages of Change*' model suggests that the maintenance of health behaviour occurs in five progressive stages of change: *pre-contemplation, contemplation, preparation, action and maintenance*.

This framework has been applied to a variety of situations, including contraceptive pill use (Johnson et al, 1998), smoking (DiClemente et al., 1991; Velicer et al, 1992), dietary modification and weight control (Suris-Rangel et al, 1988; Curry et al, 1992). McCann et al (1996) used this model to predict the participation of hyperlipidaemic individuals in a dietary intervention to lower cholesterol in a workplace setting, and found that those in preparation stage were significantly more likely to join than the contemplators or maintainers. Despite the intuitive appeal of stage models for developing tailored approaches to interventions to improve health-related behaviour, recent reviews of empirical studies have failed to provide convincing evidence in support of the model (Brindle et al, 2005).

A very different stage–type model has been proposed by Schwarzer (1992), known as the *Health Action Process Approach* (HAPA), and this incorporates concepts from the HBM and TPB, as well as efficacy beliefs. It does not envisage health behaviours as progressing through a number of discrete stages in a linear fashion, but proposes 2 broad phases: (i) a *motivational* phase, incorporating risk perceptions, self-efficacy beliefs and outcome expectancies, which act together to determine the strength of intention; and (ii) a *volitional* phase, in which intentions are transformed into action, through the use of action plans and control, also influenced by self efficacy beliefs. Thus in the HAPA, efficacy beliefs play a key role not only in the initial motivation of behaviour, but also in the level and type of action planning, monitoring and control necessary to carry out the required behaviours.

Leventhal's self-regulatory model of illness

Leventhal's self-regulatory model (SRM) was derived from early work investigating the impact of fear-arousing communications on preventive health behaviour (see Leventhal, Meyer and Nerenz, 1980). This showed that although a threat message was often necessary to motivate people towards preventative health behaviours such as taking a tetanus vaccination or giving up smoking, the threat alone was often insufficient. In order to achieve behavioural change, it was necessary to add an action plan to the threat message – eg, by giving clear instructions for successful action and helping the individual to incorporate this into their daily routine. This cognitive-behavioural approach generated actions which lasted longer than any fear aroused by the threat which had faded within a day or two. Leventhal surmised that the combination of fear and action plan had changed the 'cognitive representation' of the threat. This

stimulated interest in how people represented health threats and the interaction between representations and behaviour which led to the development of the self-regulatory model (SRM).

The fundamental premise of the SRM is a view of the patient as an active problem solver, whose health-related behaviour is an attempt to close the perceived gap between current health status and a future goal state. Threats to health and illness are regarded as a problem and the patient's behaviour is seen as an attempt to solve the problem. Patients respond to illness in a dynamic way based on their interpretation and evaluation of the illness. The choice of a particular coping response (eg, to take or not to take medication) is influenced by whether it makes sense in the light of their own ideas about the illness and personal experience of symptoms. Thus adherence/nonadherence can be thought of as one of a number of behaviour patterns adopted to cope with the illness as it is perceived. Responses to illness follow three broad stages:

a The cognitive representation of the health threat by which the patient identifies the meaning of the health threat. This can be stimulated by internal (eg, symptoms) and or external (eg, information) cues.

b The development and implementation of an action plan or coping procedure to deal with the threat.

c The appraisal of the outcome of the action plan.

In common with many other models, the SRM attempts to focuses on the individual's cognitive representation of the health threat as the key factor determining variations in behaviour. However, in the SRM, the interaction between cognition and behaviour is envisaged as a dynamic process, rather than the result of a single or staged decision. The selection of a coping procedure (taking aspirin) is determined by beliefs about the nature of the illness threat ('My headache is stress-related and should respond quickly to aspirin'). This is followed by an appraisal stage in which the patient evaluates the efficacy of their coping strategy (The pain is still there three hours after the aspirin). If the patient appraises a particular coping strategy as being ineffective, then this might result in the selection of an alternative coping strategy ('I will try a stronger pain killer') or even a change in the representation of the illness ('Aspirin hasn't worked, this might be something more serious than a headache').

Leventhal and colleagues have devoted much attention to the nature of the cognitive representation of illness threats and have identified two important aspects: content (an individual's ideas about the illness) and structure (how these ideas are cognitively organised). They suggest that people form 'common-sense' models of disease and illness organised around five components: *identity, cause, consequences, time-line* and *cure*. Identity consists of concrete symptoms and signs and an abstract label associated with them. Cause relates to perceived ideas about how one gets the disease. Time-line relates to perceptions about the likely course of the condition and how long it will last. Consequences are the expected outcomes in physical, psychological and social terms and cure deals with the person's beliefs about the potential for cure and control. (See Leventhal, Diefenbach and Leventhal [1992], Leventhal et al. [1997] and Cameron and Leventhal [2003] for a fuller description of self-regulatory theory).

There is some empirical support for the utility of self-regulatory theory in explaining adherence decisions. Illness representations were related to medication adherence in hypertension (Meyer et al, 1985), and regimen

adherence in diabetes (Gonder-Frederick and Cox, 1991). In a prospective study, adherence to recommendations to attend rehabilitation classes following a first myocardial infarction was predicted by illness beliefs (identity, consequences, control/cure) elicited during hospital convalescence (Petrie et al, 1996).

Whereas the SRM emphasises the role of patients' own beliefs about illness, it has recently been suggested that patients' ideas about *treatment* also play a key role in guiding adherence decisions (Horne, 1997). Horne and colleagues (1999) have shown that the strength of patients' beliefs about the necessity of their treatment together with their level of concerns play a stronger, more proximal role in determining treatment adherence than illness beliefs. A number of recent studies indicate that illness beliefs play a significant role in influencing these medication beliefs in a range of conditions, including hypertension (Ross et al, 2004), asthma (Horne and Weinman, 2002) and CHD (Byrne et al, 2005).

Medical error theory

Barber (2002) has sought to gain new insights into patient nonadherence with medicines through application of Reason's (1990) human error theory in organisations. Based on Reason's description of the causes of unsafe acts, he identifies the causes of nonadherence in terms of: Unintentional actions, that consist of slips due to lack of attention (ie, inadvertently taking the wrong tablet) and lapses (due to a failure of memory such as forgetting to take a dose) and intended actions that comprise mistakes and violations.

Mistakes form intended actions that depart from expectations/rules. They comprise rule-based mistakes, such as becoming concerned about a potential side-effect and therefore stopping the drug even though it does not cause the side-effect, and knowledge based failures such as running out of an important medicine for some reason that is not their fault and deciding to wait several days to see the doctor rather than getting an emergency supply from a pharmacist. Violations describe deliberate deviations from safe practice that may be either harmful (taking several medicines together to make life easier), or positive for the patient (eg, not taking a diuretic before a long bus journey).

Barber (2005) acknowledges that that the notion of error is difficult to apply to patients taking medicine where several conflicting concepts of 'good' might be at work. However, he argues that using the organisational model, people who make the error are viewed as inheritors rather than instigators of an accident. Barber argues that there is the need for a similar shift in terms of nonadherence from a focus on patient behaviour to their local environment and the organisation of care supporting them. For example, he notes that nonadherence may result from poor communication by the doctor or the system of information transfer on discharge of patients from secondary to primary care. An emphasis on identifying the underlying causes of nonadherence would shift blame away from the patient and focus attention on aspects of their environment. This may be of particular value in relation to rule-based mistakes and knowledge based failures.

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Appendix 5 Search strategy for the augmented review of adherence interventions

The search strategy undertaken by Haynes et al (2002) was used for the augmented review. This is outlined on page three of the Cochrane Review as follows:

The search strategy of the MEDLINE, CINAHL and HEALTHSTAR database at each time was as follows: ((patient compliance (mh) OR patient adjacent to compliance (title and abstract) AND (clinical trials (pt) OR clinical trial (mh) OR all random: (textword)).

The PSYCHLIT search strategy was as follows: ((random or clinical or control or trial) AND (adherence or compliance or noncompliance or dropouts or patient education) AND (drug therapy or drug or medicat or treatment or regimen) AND (intervention or outcomes or treatment outcomes)).

The SOCIOFILE search strategy was as follows: ((patient or treatment or dropouts) AND (clinical trials or control) AND (drugs or medicine)).

The IPA search strategy was as follows: ((random? or clinical? or control?) AND (patient or adherence or treatment adherence or noncompliance or dropouts or medication compliance) AND (drug therapy or drug or medicat? or treatment or drug regimen or medical regimen) AND (intervention or outcomes)). An additional strategy incorporated into this IPA search involved the joining of all pairs of words with a (w). For example, treatment (w) adherence, drug (w) regimen.

The Cochrane Library search strategy was as follows: ((random*) AND (complian* or adheren* or pharmacotherapy or regimen* or educat*) AND (medicat*)); patient compliance; patient adherence; medication compliance.

An additional search, of the EMBASE database, was conducted for citations in any language, during the publication years 1997 through 1998, with the words appearing anywhere, using the following strategy: ((random* or control*) AND (patient compliance or patient dropouts or illness behavior or psychotherapy or treatment refusal or patient education or regimen*) AND (intervention* or outcome* or treatment outcome) AND (medicat* or drug therapy) AND (clinical trial or controlled study or randomized controlled trial)).

References

Haynes, R, McDonald, H, Garg, A and Montague, P. 2002. `Interventions for helping patients to follow prescriptions for medications', *The Cochrane Database of Systematic Reviews:* Issue 2

Appendix 6: Details of the studies identified in the augmented reviews of adherence interventions

Study	Bailey, W. C., Richards, J. M., Brooks, M., Soong, S., Windsor, R., & Manzella, B. A. (1990). A randomized trial to improve self-management practices of adults with asthma. *Archives of Internal Medicine, 150*, 1664-1668.
Haynes review	Included
Method	RCT
Participants	225 patients meeting the following diagnostic criteria: recurrent episodes of wheezing or dyspnea, objective evidence of significantly increased resistance during episodes, objective evidence of improvement in airflow when symptom free. Patients excluded from the study were those less than 18 years of age and those with another pulmonary or severely debilitating disease that may have confused result interpretation.
Intervention(s)	Patients randomised to the control or usual care group were provided with a standardised set of asthma pamphlets which contained comprehensive information about asthma. No special steps were taken to ensure that patients actually read the pamphlets, and no special counselling, support groups, or systematic encouragement beyond routine physician encouragement were provided. Patients in the interventional self-management group were also provided with the standardised asthma pamphlets, in addition to a skill-oriented self-help workbook, a one-to-one counselling session, and several adherence-enhancing strategies, such as attending an asthma support group and receiving telephone calls from a health educator. Physicians emphasised these skills at regular clinic visits. A standard protocol for classifying patients in terms of level of severity and for relating their treatment

	regimen to their level of severity was employed.
Motivational component	Support group encouraged asthma concerns
Volitional component	Treatment skills
Outcome measures	Adherence checklist, relating to inhaler skills and s/r compliance, project staff rating
Mediational analysis	No
Theoretical model	D
Summary	Significant difference between groups on checklist and observed rating outcome measures.

Theoretical model key	
A	No theoretical basis
B	Theory mentioned but not operationalised
C	Theory partly operationalised
D	Theory fully operationalised

Study	Becker, L. A., Glanz, K., Sobel, E., Mossey, J., Zinn, S. L., & Knott, K. A. (1986). A randomized trial of special packaging of antihypertensive medications. *Journal of Family Practice, 22*(4), 357-361.
Haynes review	Included
Method	RCT
Participants	Patients between the ages of 20 and 80 years who were already taking medication for previously diagnosed hypertension, and who had already demonstrated poor blood pressure control (diastolic blood pressure 90mm Hg) on at least one visit during the preceding two years were included in the study. Patients who had significant visual, auditory, or mental problems that could interfere with their adherence were excluded.
Intervention(s)	Patients in the control group received all of their antihypertensive medications in the traditional pill vials (separate vials for each pill that were labelled with the drug name, dosage, medication instructions, and physician's name), whereas patients assigned to the experimental group received all their medications in the special packaging format (all pills taken together were packaged in a single plastic blister sealed with a foil backing on which was printed the day of the week and the time of day at which each medication was to be taken). All medications for both groups were provided free of charge to ensure that all patients would receive their medications.
Motivational component	N/A
Volitional component	Medications received either in visual vials or in special unit dose-reminder packs
Outcome measures	Adherence measured by self-report (patients who admitted less than perfect adherence

	were considered non-adherent) and pill count (patients were considered adherent if they had taken 80% or more of their prescribed medication). Blood pressure was taken three times during each visit. The first measure was discarded and an average of the second and third measures was used as the blood pressure measurement for that visit. Blood pressure control was defined as diastolic blood pressure less than 90 mm Hg.
Mediational analysis	No
Theoretical model	D
Summary	No significant differences between the experimental and control group on any of the compliance measures.

Study	Brown, C. S., Wright, R. G., & Christensen, D. B. (1987). Association between type of medication instruction and patients' knowledge, side effects, and compliance. *Hospital and Community Psychiatry, 38*, 55-60.
Haynes review	Excluded
Method	RCT (not blind), 4 sessions over 4 months.
Participants	30 patients. Inclusion criteria: at least 18 years old, schizophrenic or schizoaffective disorder, according to DSM-III criteria, receiving neuroleptic for at least one month.
Intervention(s)	Group 1 (controls): received verbal instructions about medication, minimum information about side effects; Group 2: received written and verbal instruction about medication, minimum information about side effects; Group 3: received verbal instruction, plus maximum side effect information; Group 4 received written & verbal instructions, plus maximum side effect information. Verbal instructions were supplied by a psychiatrist, using protocol, on medication, its purpose, directions for use, side effects and interaction with alcohol. Minimum side effect info was a general description of adverse reactions. Maximum side effect disclosure provided more specific information, including the usual time of onset and management advice. Written information was delivered in pamphlet form, and was consistent with verbal information
Motivational component	Drug information, especially side effect information.
Volitional component	N/A
Outcome measures	Knowledge level (structured survey), side effects (impact) reports (open-ended questions on report of side effects), and compliance (verbal reports to

	psychiatrist/case managers & pill count) evaluated by psychiatrist and case manager.
Mediational analysis	No
Theoretical model	D
Summary	No effect of instructional style, no change in compliance from baseline to time 4; side effect impact dropped for all groups but only reached significance in the group that received verbal instruction only, and the minimum side effect information group. Knowledge of drug alcohol interaction and side effects increased.

Study	Brus, H. L., van de Laar, M. A., Taal, E., Rasker, J. J., & Wiegman, O. (1998). Effects of patient education on compliance with basic treatment regimens and health in recent onset active rheumatoid arthritis. *Annals of the Rheumatic Diseases, 57*(3), 146-151
Haynes review	Included
Method	Patients were allocated at random to experimental (n=29) or control group (n=31). The randomisation was carried out blockwise per rheumatologist. No statement concerning concealment of allocation. Outcome assessors were blinded for allocation.
Participants	Patients suffering from rheumatoid arthritis (RA) for less than three years. Active disease defined by an erythrocyte sedimentation rate (ESR) greater than 28 mm 1st hour, the presence of six or more painful joints, and the presence of three or more swollen joints. DMARD therapy with sulphasalazine had to be indicated by the attending rheumatologist and agreed to by the patients. Patients who had used any DMARD other than hydroxychloroquine were excluded.
Intervention(s)	The experimental group attended six patient education meetings. The education programme focused on compliance with sulphasalazine therapy, physical exercises, endurance activities (walking, swimming, bicycling), advice on energy conservation, and joint protection. Four (two hour) meetings were offered during the first months. Reinforcement meetings were given after four and eight months. The programme was implemented in groups and partners were invited to attend the meetings. One instructor (HB) provided information on RA, attendant problems, and basic treatment. The related beliefs of the patients were discussed and, when necessary, corrected. If patients anticipated problems with the applications of any of the treatments, these were discussed, including possible solutions. Training was given in proper execution of

	physical exercise. Patients were encouraged to plan their treatment regimens. Their intentions were discussed and help was given in recasting unrealistic ones. Patients made contracts with themselves regarding their intentions. Feedback on the eventual implementation for therapeutic advice was included in each meeting. The control group received a brochure on RA, as provided by the Dutch League against Rheumatism. This brochure gives comprehensive information on medication, physical and occupational therapy. Sulfasalazine in the form of 500mg enteric coated tablets was prescribed to all patients. The daily dose was increased in four weeks by steps of one tablet, until a daily dose of four tablets was reached. In individual cases, this could be increased to six tablets a day, reduced as deemed necessary, or stopped in case of inefficacy or toxicity, at the description of the attending rheumatologist. All patients obtained the sulphasalazine tablets from the pharmacists according to the local Health Care System.
Motivational component	Information on RA and basic treatment. Beliefs of the patients were discussed and, when necessary, corrected. Intentions discussed and evaluated – contracts made.
Volitional component	Planning of treatment regimens. Feedback on eventual implementation of therapeutic advice. Anticipated problems with treatment were discussed and solutions found.
Outcome measures	Compliance with sulfasalazine therapy was evaluated at 3, 6, and 12 months. Medical records and pharmacy records were the source of data on the number of tablets prescribed and the number of tablets obtained. At each evaluation, the number of remaining tablets were counted. Compliance was defined as the number of tablets that had been taken during the preceding period divided by the number of tablets prescribed. Disease activity was measured by the disease activity score (DAS). This is a function of ESR, Ritchie score (0-78) and number of swollen joints (0-52). The DAS ranges from 0-10, where 0 represents the lowest level of disease activity possible, and 10 the highest. Physical function was measured by a Dutch version of the M-HAQ. The Dutch-AIMS questionnaire was used to

	assess physical function, psychological function, pain and social activities. Compliance rates with prescriptions for physical exercise and with endurance activity regiments (walking, swimming, cycling) were measured by questionnaire. Compliance with prescriptions for energy conservation was measured by questioning whether patients spread their activities over the day to prevent fatigue. A test for joint protection performance was used as an indication for the level of compliance with the prescription of joint protection. Patients were asked to perform actions representing relevant ergonomic principles. The test score ranges from 0 to 10, where 0 represents a poor performance and a 10 good performance.
Mediational analysis	No
Theoretical model	B
Summary	Compliance with Sulphasalazine exceeded 80% with no differences between groups.

Study	Chaplin, R., & Kent, A. (1998). Informing patients about tardive dyskinesia. Controlled trial of patient education. *British Journal of Psychiatry, 172*, 78-81
Haynes review	Included
Method	Patients were randomly assigned to 2 groups of 28 patients each. No statement concerning concealment of randomization.
Participants	Patients were included if they had an ICD-10 diagnosis of functional psychosis, were clinically stable, living in the community, and receiving anti-psychotic medication for at least 6 months. Patients were excluded if they were prescribed clozipine or were hospital in-patients. Sixty patients were approached. Fifty-six agreed to participate.
Intervention(s)	The study group participated in a discussion about the risks and benefits of neuroleptic medications based on individual semi-structured educational sessions with reference to a standardised information sheet modified from Kleinman et al (1989). Patients were asked whether they had heard of tardive dyskinesia (TD). The common movements of TD were modelled and the patients were asked whether they thought they had the condition or had seen others with it. They were informed that they were receiving an antipsychotic drug and were given information about extrapyramidal symptoms and TD, its risk factors, prevalence, treatment, potential irreversibility and the 1% risk of TD in non-antipsychotic-treated patients. They were told that gradual discontinuation of antipsychotic medication was the best way to prevent the condition but if done abruptly carries a high risk of relapse and of precipitating TD. It was stated that the optimum maintenance treatment, taking into account its risks and benefits, was to use the lowest dose of antipsychotic drug that would keep them well. Most importantly, they were asked not to make any changes to their treatment without discussion with their psychiatrist. Finally, they were given the

	opportunity to ask questions in an informal interactive session lasting 30 minutes, and were given an information sheet for reference. The control group received usual care.
Motivational component	Risks (side effects) and benefits of medication discussed. Patients were told how they should take medication but no practical help was offered.
Volitional component	N/A
Outcome measures	1. Relapse, defined as a period of hospitalization, evidence of clear clinical deterioration in the case-notes or in discussion with the key worker, or evidence of deterioration at follow-up interview. 2. Increase in antipsychotic dose of .200 mg chlorpromazine equivalents. 3. If the patient missed more than 2 weeks of their antipsychotic meds they were considered non-compliant.
Mediational analysis	No
Theoretical model	D
Summary	In this study, the intent was not to increase compliance; but to test whether information about benefits and adverse effects of the treatment would decrease compliance. Educational intervention was associated with nonadherence in 2 patients in the intervention group, whereas all the control patients complied. There were no significant differences in clinical outcome between the groups.

Study	Colcher, I. S., & Bass, J. W. (1972). Penicillin treatment of streptococcal pharyngitis. A comparison of schedules and the role of specific counselling. *Journal of the American Medical Association, 222*(6), 657-659
Haynes review	Included
Method	Random allocation without an indication of concealment
Participants	All children (aged 1-15) presenting to a paediatric outpatient clinic with streptococcal pharyngitis were included except those known to have received previous antimicrobial therapy of any type during the previous month, or those known to be allergic to penicillin.
Intervention(s)	The parents of the 'normally informed' group were given instructions that the penicillin was to be taken three times per day for ten days, and any questions that they had were answered. Parents of the 'optimally informed' group received specific counselling stressing the necessity that the penicillin be taken for the full ten days in order to achieve the best cure/prevent relapse, and further, were given written instructions.
Motivational component	Specific counselling outlining the necessity of taking Penicillin for the full 10 days. Written instructions detailing the reasons were also given.
Volitional component	N/A
Outcome measures	There was a single measurement of adherence: Sarcina lutea growth inhibition by urine (a test for the presence of antimicrobial activity). Throat cultures were obtained at nine days, three and six weeks post-treatment. The incidence of relapse was also estimated in the various patient groups.

Mediational analysis	No
Theoretical model	D
Summary	Compliance was significantly greater in the counselling group compared to the group who were normally informed. However, there was no significant difference in compliance between the optimally informed group and group 1 who received a mixture of penicillin G procraine and penicillin G benzathine intramuscularly.

Study	Cote, J., Cartier, A., Robichaud, P., Boutin, H., Malo, J. L., Rouleau, M., et al. (1997). Influence on asthma morbidity of asthma education programs based on self-management plans following treatment optimization. *American Journal of Respiratory and Critical Care Medicine, 155*(5), 1509-1514
Haynes review	Included
Method	The method of random allocation was not described.
Participants	Patients were 16 years of age or older, with moderate to severe asthma and the need to take daily anti-inflammatory agent. The diagnosis of asthma was confirmed by either a documented reversibility greater than 15% in FEV1 or a PC20 methacholine less than or equal to 8 mg/ml when determined by the method described by Cockcroft and co-workers.
Intervention(s)	The intervention was an asthma education program with an action plan based on peak-flow monitoring (Group P) or an action plan based on asthma symptoms (Group S). The control group (Group C) received instructions from their pulmonologists regarding medication use and influence of allergenic and nonallergenic triggers. They were taught how to use their inhaler properly by the educator. A verbal action plan could be given by the physician. Groups P and S received the same education as the controls plus individual counselling with the specialized educator during a 1-hour session. All participants received a book entitled "Understand and Control Your Asthma" at no extra charge. Group P received a self-management plan based on peak expiratory flow (PEF). They were asked to continue measuring PEF twice a day and to keep a diary of the results. Each time, subjects only recorded the best of three measurements. Every attempt was made to ensure that patients knew how to interpret the measurement and how to respond to a change in PEF. At each follow-up visit, the

	patient's diary card was reviewed, and if the action plan had not been implemented when required, further explanations were given regarding when treatment should be modified. Group S received a self-management plan based on asthma symptom monitoring. These patients were asked to keep a daily diary of asthma symptom scores, using a scale of 0 (no symptoms) to 3 (night-time asthma symptoms, severe daily symptoms preventing usual activities), and adjust their medications according to the severity of respiratory symptoms using the guidelines of the action plan.
Motivational component	N/A
Volitional component	Self-management plans: one based on PEF and one based on asthma symptom monitoring.
Outcome measures	Adherence was assessed at each follow-up by weighing the used medication canisters. Patients were unaware of this. Treatment outcome was assessed, in terms of asthma morbidity, by a count of the days missed from work or school, the number of hospitalizations or visits to the emergency room for asthma, and the number of oral corticosteroids courses used since their last visit. These were self-reported in a diary and recorded at each of the 1, 3, 6, 9, and 12 month visits after randomization. Data regarding the number of visits to the emergency room, number of hospitalizations, and absenteeism at work or school during the 12 months prior to enrolment in the study were also collected for all patients by administering a questionnaire and reviewing the medical charts. Knowledge of asthma was also measured at randomization and at the final visit using a questionnaire.
Mediational analysis	No
Theoretical model	D
Summary	To reduce financial barriers to treatment adherence, the investigators supplied

	asthma medication at no charge throughout the trial. At the beginning of the study poor compliance with treatment (patients taking less than 60% of the prescribed dose over 1 month) was more commonly observed in the control group than in the educated groups (p=0.03). However, 3, 6, 9 and 12 months after, compliance was similar in all groups (p=0.06).

Study	Daley, B. (1992). Sponsorship for adolescents with diabetes. *Health and Social Work, 17*, 173-182
Haynes review	Excluded
Method	RCT
Participants	54 adolescents (21 males, 33 females) with Insulin dependent diabetes mellitus. Age range: 12-16. Representative of IDDM adolescents at recruitment hospital.
Intervention(s)	Selected IDDM adults received two training sessions from a social worker, and were supported over a 10-month period, during which they were paired with IDDM adolescents, matched for gender, mutual interests, and geographic area. The pairing met bi-monthly, taking part in a range of social activities, whereby the sponsor demonstrated their adherence.
Motivational component	N/A
Volitional component	Modelling adherent behaviour
Adherence outcome measures	Quality of glycemic control (glycosylated hemoglobins)
Theoretical model	Social Learning Theory / C
Summary	No significant difference between the intervention and control group.

Study	Friedman, R. H., Kazis, L. E., Jette, A., Smith, M. B., Stollerman, J., Torgerson, J., et al. (1996). A telecommunications system for monitoring and counseling patients with hypertension. Impact on medication adherence and blood pressure control. *American Journal of Hypertension, 9*(4 Pt 1), 285-292
Haynes review	Included
Method	Random allocation using a paired randomization protocol.
Participants	Patients were 60 years or older, under the care of a physician for hypertension and prescribed an antihypertensive medication. They needed to have systolic blood pressure greater than or equal to 160 mmHg or a diastolic blood pressure greater than or equal to 90 mmHg based on an average of two determinations taken 5 minutes apart. Individuals were excluded if they had a life-threatening illness, were not English-speaking, did not have a telephone or could not use one, or refused to consent to participate.
Intervention(s)	Telephone-Linked Computer (TLC) system that converses with patients in their homes between visits to their physicians. Patients called TLC weekly to report their self-measured blood pressures, knowledge and adherence to antihypertensive medication regimens and medication side-effects.
Motivational component	TLC provided education and motivational counselling to improve adherence.
Volitional component	N/A
Outcome measures	Antihypertensive medication adherence was assessed by home pill count conducted by the field technicians. Clinical outcome measures included change in systolic and

	diastolic blood pressure. Outcome measures were recorded by the field technicians, at the two home visits performed 6 months apart. The measures were also reported on a weekly basis by the participant.
Mediational analysis	No
Theoretical model	D
Summary	Mean antihypertensive medication adherence improved 17.7% for telephone system users and 11.7% for controls (P = .03).

Study	Gabriel, M., Gagnon, J. P., & Bryan, C. K. (1977). Improved patient compliance through use of a daily drug reminder chart. *American Journal of Public Health, 67*, 968-969
Haynes review	Excluded
Method	3 visits, one month apart. Random allocation to daily drug reminder chart or control group.
Participants	79 patients. Inclusion criteria included having been diagnosed with hypertension for at least one year, age 50 or above, taking at least two chronic prescription medications. Mean age = 65.
Intervention(s)	Patients randomly assigned to receive (Group A), or not to receive (Group B), a daily drug reminder chart. The chart contained information such as the name of the drug, dose, use, and time(s) of administration information. Patients marked the chart, which was assessed by a pharmacist. For those in Group A, the pharmacist spent an equal amount of time discussing the use and administration of each drug. Group A received a daily drug chart at their second monthly visit to examine the effect that it may have on their subsequent adherence.
Motivational component	N/A
Volitional component	Planning
Outcome measures	Tablet counts, objective interviews to assess knowledge and adherence
Mediational analysis	No

Theoretical model	D
Summary	No significant difference in compliance at baseline; significant at time 2, non-significant at time 3. Chart acted as reminder, although there was nonadherence to ticks.

Study	Gallefoss, F., & Bakke, P. S. (1999). How does patient education and self-management among asthmatics and patients with chronic obstructive pulmonary disease affect medication? *American Journal of Respiratory and Critical Care Medicine, 160*(6), 2000-2005
Haynes review	Included
Method	Random allocation. Concealment of allocation unclear. Outcome assessors were blinded to allocation group.
Participants	Eligible subjects were patients with bronchial asthma or COPD between 18 and 70 years of age, not suffering from any serious disease, such as unstable coronary heart disease, heart failure, serious hypertension, diabetes mellitus, kidney or liver failure. Participants with stable asthma were to have a prebronchodilator FEV1 equal to or higher than 80% of predicted value. Furthermore, either a positive reversibility test, a documented 20% spontaneous variability (PEF or FEV1) or a positive methacholine test (provocative dose causing a 20% decrease in FEV1 [PD20]) was required. A positive reversibility test required at least a 20% increase (FEV1 or PEF) after inhalation of 400ug salbutamol. Subjects with COPD were to have a prebronchodilator FEV1 equal to or higher than 40% and lower than 80% of predicted.
Intervention(s)	The intervention group received a 19-page booklet with essential information about asthma/COPD, medication, compliance, self-care, and self-management plan. Instructions about recoding of PEF and symptoms in a diary were given to both asthmatics and patients with COPD. The asthmatics and patients with COPD were educated in separate groups. The COPD group received more information about tobacco weaning, but otherwise the educational interventions were comparable. The education consisted of two 2-hour group sessions of five to eight persons on two separate days. The subjects then had one to

	two individual sessions by a nurse and one to two individual sessions by a physiotherapist.
Motivational component	Importance of self-care emphasised, the rationale for treatment use was discussed.
Volitional component	Nurse concentrated on self-care, inhalation technique checked.
Outcome measures	Compliance to regular medication was calculated as a percentage: (dispensed Defined Daily Dosage/ Prescribed Defined Daily Dosage) x 100 over the 1-yr. follow-up. Patients were defined as compliant when dispensed regular medication was greater than 75% of prescribed regular medication during the study period. Prebronchodilator spirometry was performed before randomization and at 12 month follow-up by standard methods.
Mediational analysis	No
Theoretical model	D
Summary	The median Steroid Inhaler Compliance (SIC) was higher in the intervention group than in the control group. This difference reached borderline statistical significance (p = 0.08). No differences were between the intervention and control group in terms of compliance to other medications (inhalations or tablets).

Study	Garnett, W. R., Davis, L. J., McKenney, J. M., & Steiner, K. C. (1981). Effect of telephone follow-up on medication compliance. *American Journal of Hospital Pharmacy, 38*(676-9)
Haynes review	Excluded
Method	RCT comparing the effectiveness of the following two strategies in increasing compliance: (1) a follow-up telephone call and (2) written instructions and oral consultation by a pharmacist.
Participants	82 patients. Inclusion criteria: Patients receiving a prescription, filled at the MCVH pharmacy, for an oral solid dose of 250mg or 500mg of ampicillin, penicillin, tertracyclin or erythromycin, four times a day for 10-14 days.
Intervention(s)	Group A received the prescription and had the standard instructions and accessory labels read to them by the pharmacist. Group B had their prescriptions filled and had the standard instructions and accessory labels reviewed and also received written and oral consultation from the pharmacist. A dosing calendar was included to tailor and record the dosing to suit the patient's daily habits. The two groups were then randomly divided into four subgroups, two of which (AS and B2) were to receive a follow-up telephone call on the fourth or fifth day of therapy. The purpose of this call was to reinforce the importance of taking medication as directed, to encourage patients to continue therapy until completion, to explain why this is important and to determine if the patients were having any problems with the prescribed regimen.
Motivational component	The importance of taking medication was reinforced in the follow-up telephone call. Patients were encouraged to continue therapy until completion and told why this is important. Whether patients were experiencing any problems with the treatment is also ascertained.

Volitional component	Treatment instructions written down. Dosing calendar given. Oral consultation from a pharmacist (content unclear).
Outcome measures	Compliance was assessed on the ninth or tenth day of therapy by a patient dosage unit count, and the patient's knowledge of the medication regimen was evaluated by a structured interview.
Mediational analysis	No
Theoretical model	D
Summary	The mean compliance was 76.6% for the control group, 86.6% for Group 2, 87.5% for Group 3, and 85.4% for Group 4. The compliance in the control group was significantly less than for each of the study groups (p = 0.0295), but the three study groups were not significantly different (p less than 0.05). Patients receiving written and oral consultation had significantly greater knowledge about side effects and what to do if they missed doses (p less than 0.002). After follow-up telephone call was equal to, but did not enhance, written and oral consultation in improving patient compliance.

Study	Gibbs, S., Waters, W. E., & George, C. F. (1989). The benefits of prescription information leaflets. *British Journal of Clinical Pharmacology, 27*, 723-739
Haynes review	Excluded
Method	Three towns received leaflets, 1 received no information (control)
Participants	719 (300 control / 419 intervention) NSAID, beta-adrenoceptor antagonist, and inhaled bronchodilators patients.
Intervention(s)	NSAID, beta-adrenoceptor antagonists, and inhaled bronchodilators patient information leaflets 2 towns received leaflets from doctors, 1 town received leaflets from pharmacists.
Motivational component	Treatment information
Volitional component	N/A
Outcome measures	Semi-structured interview and pill count 2 weeks after leaflet. Follow-up questionnaire at 1 year assessing medicine knowledge and adherence, and satisfaction with information. Interview about information and leaflets.
Mediational analysis	No
Theoretical model	D
Summary	Increased knowledge and side effect knowledge, reduction in beta androceptor side effects, increase in NSAID side effects, but no significant difference in compliance for either medication at two weeks.

Study	Haynes, R. B., Sackett, D. L., Gibson, E. S., Taylor, W. R., Hackett, B. C., Roberts, R. S., et al. (1976). Improvement of medication compliance in uncontrolled hypertension. *Lancet*, 1265-1268
Haynes review	Included
Method	Random allocation by 'minimisation', a method stated to be impervious to bias.
Participants	38 hypertensive Canadian steelworkers who were neither compliant with medication nor at goal diastolic blood-pressure six months after starting treatment.
Intervention(s)	Patients in the experimental group were all taught the correct method to measure their own blood pressures, were asked to chart their home blood pressures and pill taking, and taught how to tailor pill taking to their daily habits and rituals. These men were visited fortnightly at the worksite by a high-school graduate who reinforced the experimental manoeuvres and rewarded improvements in adherence and blood pressure. Rewards included allowing participants to earn credit for improvements in adherence and blood pressure that could be applied towards the eventual purchase of the blood pressure apparatus they had been loaned for the trial. Control patients received none of these interventions.
Motivational component	Patients taught to measure their own blood pressure and asked to chart their home blood pressures and pill taking. Fortnightly visits from a high-school graduate who rewarded improvements in adherence and blood pressure.
Volitional component	Patients taught how to tailor pill taking to their daily habits and rituals; the experimental manoeuvres were reinforced during fortnightly visits from a high-school graduate.

Outcome measures	An unobtrusive pill count done in the patient's home by a home visitor was the method of determining medication adherence. Adherence rates are reported as the proportion of pills prescribed for the twelfth month of therapy which were removed from their containers and, presumably, swallowed by the patients. In the twelfth month of treatment, patients were evaluated for adherence and blood pressure both at home and at the mill by examiners who were 'blind' to their experimental group allocation.
Mediational analysis	No
Theoretical model	D
Summary	Six months later, average compliance had risen by 21.3% in the intervention group and fallen by 1.5% in the control group.

Study	Henry, A., & Batey, R. G. (1999). Enhancing compliance not a prerequisite for effective eradication of Helicobacter pylori: the HelP Study. *American Journal of Gastroenterology, 94*(3), 811-815
Haynes review	Included
Method	119 patients were randomly allocated to intervention (n=60) and control (n=59) groups. The trial was single blinded in that, although patients were aware of the names of the study medication and the fact the study was a helicobacter pylori treatment trial, they were unaware of either the differences between the treatment groups or the compliance enhancing purpose of the trial.
Participants	All patients over the age of 18 years with helicobacter pylori infection were screened for eligibility. Patient exclusion criteria included inability or refusal to give informed consent, contraindication to the study medication, consultant's recommendation not to treat patient, consultant's wish to use an helicobacter pylori therapy other than the study medication and inpatient status.
Intervention(s)	All patients received 10 days of omeprazole 20 mg b.d., amoxycillin 500 mg t.d.s., and metronidazole 400 mg t.d.s., as well as verbal advice on medication use and possible side effects, in an initial 20 minute consultation. In addition, patients in the intervention group received medication in dose-dispensing units, an information sheet on helicobacter pylori treatment, and a medication chart. Compliance in intervention group patients was also encouraged by a phone call 2 days after the start of therapy.
Motivational component	Compliance encouraged by a phone call 2 days after the start of therapy.
Volitional component	Medication received in dose-dispensing units and a medication chart given to patients.

Outcome measures	Measurement of compliance: Compliance was assessed by telephone interview on day 10 of therapy, and by returned tablet count at the follow-up visit. Patients were defined as compliant if they were assessed by both pill count and interview as taking 80% of study medications. Total percentage of tablets taken in both groups was assessed by taking the lower of the two estimates of tablet consumption (pill count or interview data) for each patient. Measurement for health care outcomes: Patients were considered helicobacter pylori positive if the CLO-test, histopathology, or 13C-UBT was positive. 13C-UBT test using kits sent to a single central laboratory for analysis was performed for more than one month after cessation of helicobacter pylori treatment and any other antimicrobial therapy), 2 weeks after cessation of proton-pump inhibitor therapy and 1 week after cessation of histamine-receptor antagonists. An increase of 5 per million in the CO2 30 min after ingestion of C-urea compared with baseline measurements was considered positive for helicobacter pylori. Treatment was considered successful if 13C-UBT was negative. Side effects were assessed by telephone interview on day 10 of therapy and by returned side effects questionnaire. Patients were asked to rate specific side effects and give an overall rating where none = 0, mild = 1 (does not limit daily activities), moderate = 2 (interferes with daily activities), and severe = 3 (incapacitating, stops normal daily activities).
Mediational analysis	No
Theoretical model	D
Summary	In both the intervention and control groups, 97% of medications were taken. More control group patients than intervention patients had only verbal (interview) measures of compliance, and no pill count data was available – this may have overestimated adherence in the control group.

Study	Howland, J. S., Baker, M. G., & Poe, T. (1990). Does patient education cause side effects? A controlled trial. *Journal of Family Practice, 31*(1), 62-64.
Haynes review	Included
Method	Method of randomisation not stated. The physician educating the patients was not blinded, whereas the office nurse questioning patients in the follow-up period was blinded as to which patient was in which group.
Participants	98 adults aged over 18 years treated with erythromycin for an acute illness were included; patients with a history of allergy/intolerance to erythromycin were excluded.
Intervention(s)	Informed patients were told of six possible side-effects of treatment with erythromycin, while control (uninformed) patients were not made aware of potential side effects of treatment.
Motivational component	Informed patients made aware of side effects.
Volitional component	N/A
Outcome measures	The occurrence of side effects both before and after treatment. Adherence measured as the mean number of erythromycin pills taken per day, patients reporting that they missed at least one pill, and mean number of pills taken out of 40 pills.
Mediational analysis	No
Theoretical model	D

Summary	Compliance was similar for both groups.

Study	Johnson, A. L., Taylor, D. W., Sackett, D. L., Dunnett, C. W., & Shimizu, A. G. (1978). Self-recording of blood pressure in the management of hypertension. *Canadian Medical Association Journal, 119*(9), 1034-1039
Haynes review	Included
Method	Random allocation in a 2x2 factorial design. No statement concerning concealment of randomisation.
Participants	Volunteers from shopping centre blood pressure screening in Canada, with follow-up by usual family doctors. Men and women aged 35-65 who had been receiving antihypertensive medications for at least one year, but whose diastolic blood pressure had remained elevated.
Intervention(s)	The interventions consisted of (1) self-recording and monthly home visits, (2) self recording only, (3) monthly home visits, and the control group consisted of (4) neither self-recording nor home visits. Subjects in groups (1) and (2) received a blood pressure kit and instruction in self-recording. Patients in the self-recording groups were to keep charts of their daily blood pressure readings and were instructed to bring these charts to their physician at each appointment. Subjects in groups (1) and (3) had their blood pressure measured in their homes every four weeks, and the results were reported to both the patient and the physician.
Motivational component	Patients asked to self-record blood pressure. Patients received monthly home visits to measure blood pressure.
Volitional component	N/A

Outcome measures	Adherence with therapy was assessed by interview and pill counts (the percentage of prescribed pills that had been consumed was estimated by comparing pills on hand at a home visit with prescription records of pills dispensed and the regimen prescribed). Changes in mean diastolic blood pressure (mm Hg) were assessed. Since the initial blood pressure bears an important relation to the change in blood pressure over time, the change scores were adjusted for differences in entry values by covariance analysis. Outcome assessors were blinded to study group.
Mediational analysis	No
Theoretical model	D
Summary	No significant differences in compliance were apparent between the groups. However, both self-recording and monthly home visits produced a reduction in blood pressure among patients who admitted to difficulty in remembering to take this pills; a reduction was not seen among patient who said they had no such difficulty.

Study	Katon, W., Rutter, C., Ludman, E. J., Von Korff, M., Lin, E., Simon, G., et al. (2001). A randomized trial of relapse prevention of depression in primary care. *Archives of General Psychiatry, 58*(3), 241-247
Haynes review	Included
Method	Patients were randomized to the relapse prevention intervention vs. usual care in blocks of 8. Within each block, the randomization sequence was computer-generated. The telephone survey team conducting the follow-up assessments (at 3, 6, 9 and 12 months) were blinded to randomization status. Patients could not be blinded due to the nature of the intervention (i.e. patient education, visits with depression specialist, telephone monitoring and follow-up). The primary care physicians were not blinded.
Participants	386 patients with recurrent major depression or dysthymia who had largely recovered after 8 weeks of antidepressant treatment.
Intervention(s)	The intervention included patient education, 2 visits with a depression specialist, and telephone monitoring and follow-up. Before the first study visit, the intervention patients were provided with a book and videotape developed by the study team that was aimed at increasing patient education and enhancing self-treatment of their depression. They were also scheduled for 2 visits with a depression specialist (one 90-minute initial session and one 60-minute follow-up session) in the primary care clinic. Three additional telephone visits at 1, 4, and 8.5 months from session 2 with the depression specialist and 4 personalised mailings (2, 6, 10 and 12 months) were scheduled over the following year. The mailed personalised feedback contained a graph of patients' Beck Depression Inventory scores over the course of the intervention program and checklists for patients to send back to the depression specialist, including early warning signs of depression and whether they were still adhering to their medication plan. The

	depression specialist reviewed monthly automated pharmacy data on antidepressant refills and alerted the primary care physician and telephoned the patients when mailed feedback or automated data indicated they were symptomatic and/or had discontinued medication. The ultimate aim of the intervention was to have each patient complete and follow a 2-page written personal relapse prevention plan, which was also shared with his/her primary care provider. Follow-up telephone calls and mailings were geared toward monitoring progress and adherence to each patient's plan. Usual care for most patients was provided by the GHC family physicians in the 4 primary care clinics and involved prescription of an antidepressant medication, 2 to 4 visits over the first 6 months of treatment, and an option to refer to GHC mental health services. Both intervention and control patients could also self-refer to a GHC mental health provider.
Motivational component	Telephone visits and personalised mailings included checklists of whether patients were still adhering to their medication plan. The depression specialist telephoned the patients when mailed feedback or pharmacy data indicated that they had discontinued medication.
Volitional component	N/A
Outcome measures	Compliance: Patients' adherence to antidepressant medication was measured at 3, 6, 9 and 12 months after randomization by a telephone interviewer. Computerised automated data from prescription refills was also used to assess adherence at the 3, 6, 9 and 12-month follow-up periods as well as to assess whether patients had received adequate dosage of antidepressant medication for 90 days or more during the 1-year period. The lowest dosages in the ranges recommended in the Agency for Health Care Policy and Research guidelines developed for newer agents were used to define a minimum dosage standard. Measurement of Clinical Health Outcomes: Baseline and follow-up interviews assessing depressive symptoms (at 3, 6, 9 and 12-months) included the SCL-20 depression items (scored on a 0-4 scale), the dysthymia

	and current depression modules of the SCID, the NEO Personality Inventory Neuroticism Scale and the Longitudinal Interval Follow-up Evaluation to measure incidence and duration of episodes within each 3-month block of time.
Mediational analysis	No
Theoretical model	D
Summary	Those in the intervention group had significantly greater adherence to adequate dosage of antidepressant medication for 90 days or more within the first and second 6-month periods and were significantly more likely to refill medication prescriptions during the 12-month follow-up compared with the usual care controls.

Study	Kemp, R., Hayward, P., Applewhaite, G., Everitt, B., & David, A. (1996). Compliance therapy in psychotic patients: randomised controlled trial. *British Medical Journal, 312*(7027), 345-349
Haynes review	Included
Method	Random allocation by means of a table of random numbers.
Participants	Patients between the ages of 18 and 65 who were admitted to hospital with acute psychosis over eight months. DSM III-R diagnoses of subjects included schizophrenia, severe affective disorders, schizophreniform, schizoaffective disorder, delusional disorders, and psychotic disorder not otherwise classified. Non-English speakers and subjects with low IQ scores, deafness, or organic brain disease were excluded.
Intervention(s)	Control group treatment consisted of 4 to 6 supportive counselling sessions with the same therapist. Therapists listened to patient concerns but declined to discuss treatment. Experimental intervention treatment consisted of 4 to 6 sessions of "compliance therapy", a strategy that borrows from motivational interviewing. During sessions 1 and 2, patients reviewed their illness and conceptualised the problem. In the next 2 sessions, patients focused on symptoms and side effects of treatment. In the last 2 sessions, the stigma of drug treatment was addressed.
Motivational component	"Compliance therapy" sessions, during which the benefits of treatment were discussed.
Volitional component	N/A

Outcome measures	Initial compliance was rated blind to intervention by the patients' primary nurses on a seven-point rating scale. All ratings were repeated before discharge and after the intervention.
Mediational analysis	No
Theoretical model	D
Summary	A 23% improvement in compliance was found in the intervention group; improvement was maintained after discharge, during a 6-month follow-up period.

Study	Kemp, R., Kirov, G., Everitt, B., Hayward, P., & David, A. (1998). Randomised controlled trial of compliance therapy. 18-month follow-up. *British Journal of Psychiatry, 172*, 413-419.
Haynes review	Included
Method	Random allocation by means of a table of random numbers.
Participants	Patients between the ages of 18 and 65 who were admitted to hospital with acute psychosis over 14 months. DSM III-R diagnoses of subjects included schizophrenia, severe affective disorders, schizophreniform, schizoaffective disorder, delusional disorders, and psychotic disorder not otherwise classified. Non-English speakers and subjects with low IQ scores, deafness, or organic brain disease were excluded.
Intervention(s)	Control group treatment consisted of 4 to 6 supportive counselling sessions with the same therapist. Therapists listened to patients' concerns but when medication issues were broached, patients were directed to discuss such issues with their treatment teams. Experimental intervention treatment consisted of 4 to 6 sessions of "compliance therapy" - a strategy that borrows from motivational interviewing. During session 1 and session 2, patients reviewed their illness and conceptualised the problem. In the next 2 sessions, patients focused on symptoms and the side effects of treatment. In the last 2 sessions, the stigma of drug treatment was addressed.
Motivational component	Compliance therapy: All sessions.
Volitional component	N/A
Outcome measures	Adherence scores were measured using a 7-point scale (1 = complete refusal to 7=

	active participation and ready acceptance of regimen). The clinical outcome measures included ratings on a brief psychiatric rating scale, global functioning assessment, schedule for assessment of insight, drug attitudes inventory, attitude to medication questionnaire, Simpson-Angus Scale for extrapyramidal side-effects. Measures were obtained in-hospital pre-intervention and post-intervention. Following discharge, measurements were made at 3, 6, 12, and 18 months. Initial compliance was rated by the patient's primary nurse. Follow-up compliance ratings were obtained using the seven-point scale, based on corroboration from as many sources as possible (mean number of sources was approximately 2).
Mediational analysis	No
Theoretical model	D
Summary	There was a significant advantage for the compliance therapy group immediately post-treatment and this advantage was maintained at a constant level over all post-intervention assessments.

Study	Levy, M. L., Robb, M., Allen, J., Doherty, C., Bland, J. M., & Winter, R. J. (2000). A randomized controlled evaluation of specialist nurse education following accident and emergency department attendance for acute asthma. *Respiratory Medicine, 94*(9), 900-908.
Haynes review	Included
Method	Patients were randomized consecutively into intervention and control groups using equal blocks of four generated using the Clinstat program. This was done by the two nurses at their respective hospitals, by first producing two patient lists, by date order of receipt of their consent forms i) completed when attending or ii) returned by post. 108 patients were randomly allocated into the control group, and 103 patients were randomly allocated into the intervention group. Study nurses were not blinded with regard to allocation after randomization occurred.
Participants	211 patients over 18 years old attending emergency room department for asthma were included. Exclusion criteria not specified, except that patients with a previously recorded diagnosis of COPD were excluded.
Intervention(s)	The intervention group was invited to attend a 1h consultation with one of the nurses beginning 2 weeks after entry to the study, followed by two or more lasting half an hour, at 6-weekly intervals. The second and third could be substituted by a telephone call. Patients were phoned by the nurse before each appointment in order to improve attendance rates. Patients' asthma control and management were assessed followed by education on recognition and self-treatment of episodes of asthma. The patients were taught to step-up medication when they recognized uncontrolled asthma using PEF or symptoms. The advice was in accordance with national guidelines. Prescriptions were obtained from one of the doctors in the clinic

	or by providing the patient with a letter to their general practitioner. Patients presenting with severe asthma (severe symptoms of PEF below 60% of their best/normal) were referred immediately to the consultant. Patients in the control group continued with their usual medical treatment and were not offered any intervention during the study period.
Motivational component	Patients' knowledge expanded to include a basic understanding of asthma and their medication.
Volitional component	Education about how to recognise and self-treat episodes of asthma.
Outcome measures	Compliance: The primary outcome was patients' reported adherence to self-management of mild attacks within the previous 2 weeks or severe attacks in the previous 6 weeks Clinical Health Outcomes: Home peak flow and symptom diaries. Patients recorded the best of 3 PEF readings in the morning and evening, and also recorded symptom scores daily for 7 days. QOL was also assessed using the SGRQ, and patients' use of medical services was assessed.
Mediational analysis	No
Theoretical model	D
Summary	The intervention group increased their use of inhaled topical steroids in 31/61 (51%) attacks vs. 15/70 (21%) attacks in controls.

Study	Linkewich, J. A., Catalano, R. B., & Flack, H. S. (1974). The effect of packaging and instruction on outpatient compliance with medication regimens. *Drug Intelligence and Clinical Pharmacy, 1974*(8), 10-15.
Haynes review	Excluded
Method	RCT
Participants	Patients at hospital pharmacy with prescription for potassium phenoxymethyl penicillin tablets 250mg.
Intervention(s)	Patients in group 1 (control) received their penicillin in the standard vial with a standard label; the pharmacist read the physicians' directions with no further instruction. Group 2 patients received their penicillin in a standard vial but also received a calendar prepared with therapy dates and administration times. It was suggested that these patients keep this calendar with their medicine and that doses should be checked off as they were taken. Group 3 patients received 40 unit dose packaged penicillin tablets in 10 strips of four tablets (one day of therapy in one strip). Patients in group 4 received a 'Wyeth QID Strep-Pak' (tablets laid out in pre-packed 'diary chart' showing day of treatment and the time of day the tablet is to be taken). All 'intervention' patients received their medication with a standard label and an instruction card which emphasized the importance of completing treatment.
Motivational component	N/A
Volitional component	Calendar to act as a compliance aid; medication 'laid out' in pre-packed strips.
Outcome measures	Pill count, adherence questionnaire, reports of other meds being used, evaluation of daily

	dosing times, patients' impressions of packaging.
Mediational analysis	No
Theoretical model	D
Summary	Intervention groups significantly more compliant than control.

Study	Logan, A. G., Milne, B. J., Achber, C., Campbell, W. P., & Haynes, R. B. (1979). Work-site treatment of hypertension by specially trained nurses. A controlled trial. *Lancet, 2* (8153), 1175-1178.
Haynes review	Included
Method	Stratified random allocation. No indication of concealment.
Participants	Employees with an average diastolic blood pressure from two screens of 95 mm Hg or a diastolic blood pressure of 91-94 mm Hg and a systolic blood pressure 140 mm Hg were considered eligible for the study if they met the following criteria: (1) no expected termination of employment in the year after entry into the study, (2) no treatment for at least three months before screening, (3) not taking other daily medication, oral contraceptives, or oestrogen replacement therapy, (4) not pregnant or planning to become so during the year of the study, (5) no remediable form of secondary hypertension, and (6) no objections from their family physician.
Intervention(s)	Participants of the regular care/control group saw their own physicians. Each physician received the guidelines for hypertensive evaluation and management, and the goal blood pressure that was to be sought by the nurse. Subjects in the work-site care group were attended by two experienced nurses who were taught to manage hypertension according to a standard protocol. The nurses dealt with all aspects of hypertensive management but difficult problems were referred to the supervising physician, and unrelated medical problems were referred to the family physician. The standard protocol was as follows: patients were given a diuretic (step 1) to which, if hypertension was not controlled on

	maximum diuretic dosage, propranolol or methyldopa was added (step 2). Occasionally a third drug, hydralazine or prazosin, was required (step 3).
Motivational component	No
Volitional component	Patient's hypertension treated at their place of work.
Outcome measures	A questionnaire was administered to determine adherence with therapy. Participants who stated that they were taking their tablets were visited at home to assess exact adherence by an unobtrusive pill count (adherence was determined by noting the date, type and number of pills dispensed for the most recent prescriptions, assuming that missing pills represented consumption). Medication adherence was judged to be high if the patient claimed to be taking medications as instructed and if 80% or more of the prescribed drug was consumed, as determined by pill counts. At the six month evaluation, three blood pressure readings were taken. Goal blood pressure was defined as a reduction in diastolic blood pressure to less than 90 mm Hg in those with an entry diastolic blood pressure greater than 95 mm Hg, or a reduction in diastolic blood pressure of at least 6 mm Hg in those with an entry diastolic blood pressure of 95 mm Hg or less. Outcome assessors were blinded to study group.
Mediational analysis	N/A
Theoretical model	D
Summary	Work-site treatment resulted in significantly greater compliance with prescribed therapy ($p<0.005$).

Study	Logan, A. G., Milne, B. J., Achber, C., Campbell, W. P., & Haynes, R. B. (1981). Cost-effectiveness of a worksite hypertension treatment program. *Hypertension, 3*(2), 211-218.
Haynes review	Included
Method	Cost-effectiveness analysis based on original data, for Logan et al, 1979.
Participants	Employees with an average diastolic blood pressure from two screens of 95 mm Hg or a diastolic blood pressure of 91-94 mm Hg and a systolic blood pressure 140 mm Hg were considered eligible for the study if they met the following criteria: (1) no expected termination of employment in the year after entry into the study, (2) no treatment for at least three months before screening, (3) not taking other daily medication, oral contraceptives, or oestrogen replacement therapy, (4) not pregnant or planning to become so during the year of the study, (5) no remediable form of secondary hypertension, and (6) no objections from their family physician.
Intervention(s)	As with Logan et al (1979)
Motivational component	N/A
Volitional component	As with Logan et al (1979)
Outcome measures	As with Logan et al (1979)
Mediational analysis	No
Theoretical	D

model	
Summary	As with Logan et al (1979)

Study	Maiman, L. A., Becker, M. H., Liptak, G. S., Nazarian, L. F., & Rounds, K. A. (1978). Improving paediatricians' compliance-enhancing practices: A randomized trial. *American Journal of Diseases of Children, 142*, 773-779
Haynes review	Excluded
Method	RCT (Paediatricians randomly allocated)
Participants	Practicing community paediatricians (n=90) and mothers of children diagnosed with otitis media receiving a ten day oral penicillin based antibiotic regimen.
Intervention(s)	Paediatricians were given a tutorial with accompanying printed materials (TPM), or mailed printed material (MPM). This tutorial included a discussion of noncompliance as well as practical compliance
Motivational component	Paediatricians provided with compliance-enhancing strategies
Volitional component	N/A
Outcome measures	Pill/liquid count and self report. Researcher compliance assessment. Paediatrician assessments of mothers' compliance enhancing behaviour scale.
Mediational analysis	No
Theoretical model	Health Belief Model used in intervention for mothers / C
Summary	Paediatricians in the TPM group were more likely to have a greater proportion of patients who missed no doses and a lower proportion of patients who missed at least

four doses. (P<.05).

Study	Merinder, L. B., Viuff, A. G., Laugesen, H. D., Clemmensen, K., Misfelt, S., & Espensen, B. (1999). Patient and relative education in community psychiatry: a randomized controlled trial regarding its effectiveness. *Social Psychiatry and Psychiatric Epidemiology, 34*(6), 287-294
Haynes review	Included
Method	Patients were block-randomized, stratified for gender and for illness duration. The randomisation was carried out by an independent institution. Due to the nature of the intervention, patients could not be blinded. Ratings of psychopathology and psychosocial function were performed by researchers who were not informed of treatment allocation. Relapse and compliance outcomes were assessed by researchers blind to the allocation of the patients.
Participants	Patients aged 18-49 years with a clinical ICD-10 diagnosis of schizophrenia and in treatment at the time of recruitment were included.
Intervention(s)	The control group received usual treatment provided in community psychiatry. The experimental group received an 8-session intervention using a mainly didactic interactive method. The programme was standardized with a manual for group leaders, overhead presentations and a booklet for participants. Patient and relative interventions were the same, but conducted separately, in groups of 5 to 8 participants. Sessions were conducted weekly.
Motivational component	Psychoeducational programme including an examination of schizophrenia and its causes, medication effects and side effects, psychosocial treatment, creation of emergency plan in event of relapse, discussion of how family can assist as well as laws and regulations.

Volitional component	N/A
Outcome measures	Patient outcome measures were made at baseline and at 12-month follow-up (nonadherence episode defined non-receipt of medication for 14 days).
Mediational analysis	No
Theoretical model	D
Summary	No significant reduction in the number of nonadherence episodes were found at follow-up in the intervention group compared to the control group.

Study	Morisky, D. E., Malotte, C. K., Chol, P., Davidson, P., Rigler, S., & Sugland, B. (1990). A patient education program to improve adherence rates with anti-tuberculosis drug regimens. *Health Education Quarterly, 17*, 253-267.
Haynes review	Excluded
Method	RCT. Patients randomised either to a special intervention (SI) group, or a usual care (UC) group
Participants	205 active tuberculosis or preventative patients with no active disease
Intervention(s)	Control group received 'usual care' – contact and reschedule when appointment missed, up to two missed appointments. Intervention group received standardized 10 minute educational counselling which was behaviourally oriented and consisted of tailored educational messages based upon initial interview and subsequent assessment, written instructions about the regimen, educational reinforcement about TB, the enlistment of family and friend support, and positive verbal reinforcement for adherence to the regimen. The intervention group also received cash incentives for compliance and full compliance to appointment schedule. A booklet providing information about TB, the importance of treatment and possible side effects was given to all intervention patients at their initial session. The results of diagnostic tests, the patients' medications and ways to remember medications and future appointments were recorded in the booklet and discussed at each visit. The intervention lasted for length of prescription (6-9 months for active, 12 months for preventative patients).
Motivational component	Educational counselling included positive verbal reinforcement for adherence to the regimen. Cash incentives for compliance. Booklet with information about TB, the importance of treatment and possible side effects.

Volitional component	Educational counselling included written instructions about the regimen. Ways to remember medications were recorded in the booklet and discussed at each visit.
Outcome measures	Urine samples, kept appointments, & self-reported adherence.
Mediational analysis	N/A
Theoretical model	Precede / Health Belief Model
Summary	Increased appointment attendance was not significant for active SI patients, but was significant for preventative SI patients. SI patients had significantly higher levels of adherence to their medical regimen compared to UC patients (68% vs 38%; $p<0.001$).

Study	Ngoh, L. N., & Shepherd, M. D. (1997). Design, development, and evaluation of visual aids for communicating prescription drug instructions to nonliterate patients in rural Cameroon. *Patient Education Counseling, 31*(3), 245-261.
Haynes review	Excluded
Method	RCT. Patients randomly assigned to one of three study groups.
Participants	78 female ambulatory patients, aged 15-55, able to converse in Pidgin English, non-literate, recipients of prescription for oral dosage form antibiotics who have their prescription filled at study pharmacy.
Intervention(s)	Group 1 (control) patients received no information on their drug therapy. Group 2 patients received visual aids corresponding to the prescription instructions given orally by the pharmacy attendant or implied in writing when the medication was dispensed. Patients were told what each visual aid depicted and at the end of the session they were asked what they had learned. Group 3 patients received an 'Advanced Organiser' as the first intervention material; that is, introductory information given to learners intended to increase their ability to understand, learn and remember new material. The infectious disease process and the function of the study were explained. Each patient was then asked to explain the disease process and the role of the study drug in her own words. She received the same visual aids that were given to Group 2 and the same explanation of the messages depicted. All patients were given a post-comprehension test after their session.
Motivational component	Advanced Organiser explained why the drug is needed.
Volitional	Visual materials to explain how the drug is

component	taken.
Outcome measures	Pill count at 4 days
Mediational analysis	No
Theoretical model	Social learning theory / C
Summary	A significant difference in compliance was found between the experimental and control groups ($p<0.05$). No significant difference was found between the two experimental groups.

Study	Peterson, G. M., McLean, S., & Millingen, K. S. (1984). A randomised trial of strategies to improve patient compliance with anticonvulsant therapy. *Epilepsia, 25*(4), 412-417.
Haynes review	Included
Method	Coin toss randomisation.
Participants	Adult and teenage epileptic patients who were consecutive attenders at outpatient clinics during a four month period, who were responsible for their own medication, and who possessed a hospital pharmacy prescription book were included in the study.
Intervention(s)	Patients in the intervention group received several adherence-improving strategies: they were counselled on the goals of anticonvulsant therapy and the importance of good adherence in achieving these goals, provided with a schedule of medication taking that corresponded with their everyday habits, given an educational leaflet, provided with a 'dosette' medication container and counselled on its utility, instructed to use a medication/seizure diary, and reminded by mail of upcoming appointments and missed prescription refills. The control group received none of these interventions.
Motivational component	Educational leaflet: unclear of content. Mailed reminders to collect prescription refills and attend clinic appointments.
Volitional component	Patient counselling, special medication containers, self-recording of medication intake and seizures.
Outcome measures	Each patient had plasma anticonvulsant levels measured (provided that the patient's medication regimen had not been altered in the preceding two weeks), the patient's prescription record book was checked to

	assess prescription refill frequency (if the refill frequency was one or more weeks later than expected at least once during the previous six months, the patient was considered non-adherent), and patient appointment keeping frequency (patients who had attended all their scheduled appointments in the previous six months were considered compliant) were assessed. The median number of self-recorded seizures experienced by each patient was compared between the control and intervention groups.
Mediational analysis	No
Theoretical model	D
Summary	Compliance with anticonvulsant levels, as measured by plasma anticonvulsant levels and medication refill frequencies ($p<0.01$) was significantly improved.

Study	Peveler, R., George, C., Kinmonth, A. L., Campbell, M., & Thompson, C. (1999). Effect of antidepressant drug counselling and information leaflets on adherence to drug treatment in primary care: randomised controlled trial. *British Medical Journal, 319*(7210), 612-615
Haynes review	Included
Method	Immediately after referral patients were individually randomized in blocks of 8 to one of four treatment groups by prearranged random number sequence, stratified by drug type, in a factorial design. Patients were unaware of their allocation at first interview and were asked not to reveal drug-counselling sessions to the interviewer subsequently.
Participants	Patients were included if they were aged 18 or over and starting new courses of treatment with dothiepin or amitriptyline. Inclusion was based on clinical diagnosis of depressive illness. Patients were excluded if they had received either drug within 3 months, had a contraindication (allergy, heart disease, glaucoma, or pregnancy) or were receiving other incompatible drugs. Any patients at high risk of suicide were also excluded.
Intervention(s)	The four treatment groups were as follows: treatment as usual, leaflet, drug counselling, or both interventions. The information leaflet contained information about the drug, unwanted side effects, and what to do in the event of a missing dose. Patients were given drug counselling by a nurse at weeks 2 and 8, according to a written protocol. Sessions included assessment of daily routine and lifestyle, attitudes to treatment, and understanding of the reasons for treatment. Education was given about depressive illness and related problems, self-help and local resources. The importance of drug treatment was emphasized, and side effects and their management discussed. Advice was given about the use of reminders and cues, the need to continue treatment for up to 6

	months, and what to do in the event of forgetting a dose, and the feasibility of involving family or friends with medicine taking was explored.
Motivational component	Information leaflet. Drug counselling: assessment of daily routine and life-style, attitudes to treatment and understanding of the reasons for treatment. Education about depression. Importance of drug treatment was emphasised. Feasibility of involving family or friends was explored.
Volitional component	Drug counselling: Side effects and their management discussed. Advice given about the use of reminders and cues, the need to continue treatment for up to 6 months, and what to do in the event of forgetting a dose.
Outcome measures	At 6 weeks, self-reported compliance was assessed and was reassessed at the final visit.
Mediational analysis	No
Theoretical model	D
Summary	Leaflets had no effect on adherence, either on their own or in combination with counselling. Allocation to counselling had a significant effect on adherence compared with usual treatment (p=0.001) and in logistic regression, allocation to counselling was found to be a significant predictor of self-reported adherence.

Study	Piette, J. D., Weinberger, M., McPhee, S. J., Mah, C. A., Kraemer, F. B., & Crapo, L. M. (2000). Do automated calls with nurse follow-up improve self-care and glycemic control among vulnerable patients with diabetes? *American Journal of Medicine, 108*(1), 20-27
Haynes review	Included
Method	Randomization was based on a table of random numbers. Patients, care givers, and outcome assessors were not blinded to patient allocation.
Participants	Of the 588 patients identified as potentially eligible, 280 patients were enrolled and randomised to a treatment arm, 137 to intervention, 143 to control. Patients included had a diagnosis of diabetes mellitus or an active prescription for a hypoglycaemic agent. Patients were excluded if they were 75 years of age, had a diagnosed psychotic disorder, disabling sensory impairment, or life expectancy of less than 12 months, or whose primary language was neither English nor Spanish. Patients were also excluded if they controlled their blood glucose levels without hypoglycaemic medication, were newly diagnosed with diabetes (<6 months), planned to discontinue receiving services from the clinic within the 12-month follow-up period, or did not have a touch-tone telephone.
Intervention(s)	The intervention consisted of a series of automated telephone assessments designed to identify patients with health and self-care problems (TeleminderModel IV automated telephone messaging computer). Calls were made on a biweekly basis, up to 6 attempted calls, and involved a 5 to 8-minute assessment. During each assessment, patients used the touch-tone keypad to report information about self-monitored blood glucose readings, self-care, perceived glycaemic control, and symptoms of poor glycaemic control, foot problems, chest pain, and breathing problems, with automated prompts for out-of-range errors. The

	automated telephone calls were also used to deliver, at the patient's option, 1 of 30 targeted and tailored self-care education messages at the end of each telephone session. Patients only received a 1-page instruction sheet on the use of the phone. Each week, the automated assessment system generated reports organized according to the urgency of the reported problems, and a diabetes nurse educator used these reports to prioritize contacts for a telephone follow-up. During follow-up calls, the nurse addressed problems reported during the assessments and provided more general self-care information. After several months, intervention group patients were offered additional automated self-care calls that focused on glucose self-monitoring, foot care and medication adherence. In the medication adherence part of these sessions, patients were asked about their adherence to insulin, oral hypoglycaemic medications, antihypertensive medications, and antilipidemic medications. For each type of medication, patients without adherence problems received positive feedback and reinforcement. Patients reporting less than optimal adherence were asked about specific barriers and were given advice from the nurse about overcoming each barrier. The nurse was located outside the clinic and had no access to medical records other than the baseline info collected at enrolment and her own notes. She did not have any face-to-face contact with patients. The nurse addressed problems raised by patients in the automated calls and also gave general self-care education. The nurse also checked on patients who rarely responded to automated calls. A small no. of patients initiated calls to the nurse by toll free no. She referred these to the primary care physician as appropriate. During the course of the trial, patients in the intervention groups averaged 1.4 automated calls per month and had 6 minutes of nurse contact per month. Patients assigned to the usual care control group had no systematic monitoring between clinic visits or reminders of upcoming clinic appointments. Providers used their discretion to schedule follow-up visits. Additional visits were scheduled at the patient’s initiative.
Motivational component	Patients without adherence problems received positive feedback and reinforcement.

Volitional component	Patients offered self-care education messages at the end of each automated telephone session. Nurse follow-up included more self-care information. Patients offered additional automated self-care calls (with focus on glucose self-monitoring, foot care and medication adherence). Patients reporting less than optimal adherence were asked about specific barriers and given advice from the nurse about overcoming each barrier.
Outcome measures	Measurement of compliance: At baseline and 12 months, patients were surveyed by trained interviewers over the telephone. Patients were considered to have a problem with medication adherence if they reported that they "sometimes forget to take their medication", "sometimes stop taking their medication when they feel better", or "sometimes stop taking their medication when they feel worse".
Mediational analysis	No
Theoretical model	D
Summary	Intervention patients were substantially less likely to report problems with medication adherence (p=0.003). After adjustment for baseline differences, the intervention decreased the proportion of patients with medication adherence problems by 21% (from 69% to 48%; p= 0.003).

Study	Raynor, D. K., Booth, T. G., & Blenkinsopp, A. (1993). Effects of computer generated reminder charts on patients' compliance with drug regimens. *British Medical Journal, 306*(6886), 1158-1161
Haynes review	Excluded
Method	RCT. Patients were randomly allocated to one of four groups.
Participants	197 patients being discharged from hospital who were regularly taking 2-6 drugs, managing their own medications, and who did not have reading difficulties.
Intervention(s)	Those in group A (controls) received brief counselling from a nurse (a standard procedure for patients being discharged); patients in group B received the counselling and an individualised reminder chart (listing medication and times at which they should be taken); patients in group C received structured counselling from a pharmacist who described the name, purpose and timing of doses of each medicine and asked the patients if they had any questions. Patients in group D received structured counselling from a pharmacist and the reminder chart, which the pharmacist described in detail.
Motivational component	N/A
Volitional component	Patients received a reminder chart listing times to be taken and counselling by pharmacist who described the name, purpose and timing of dose of each medicine.
Outcome measures	Tablet count at 10 days, plus interview including discussion of patients drug regimen.
Mediational analysis	No

Theoretical model	D
Summary	Groups A and C (patients not given a reminder chart) both had an average mean compliance score of 86%, group B (patients given a reminder chart and counselled) had a score of 91%, and group D (patients given a reminder chart and counselled) had a score of 95%. The reminder chart had a significant effect on compliance ($p<0.001$).

Study	Razali, S., Hasanah, C., Khan, U., & Subramaniam, M. (2000). Psychosocial interventions for schizophrenia. *Journal of Mental Health, 9*(3), 283-289.
Haynes review	Included
Method	Patients were randomly assigned to the control group (n=86), or experimental group (n=80). Allocation was unblinded for treating psychiatrist and patient; outcome assessments were done by independent, blinded psychiatrists.
Participants	Recently discharged patients from the University Hospital with the diagnosis of schizophrenia (DSM-IV). Inclusion criteria included: at least 2 previous psychiatric admissions (including the latest admission), aged between 17-55 years, staying with a responsible relative who is willing to be involved in the study, stabilized for at least 4 weeks. Exclusion criteria not specified.
Intervention(s)	Control patients received standard Behaviour Family Therapy (BFT), consisting of family education, training in problem-solving skills and communication skills. Those in the experimental group received Culturally Modified Family Therapy (CMFT) consisting of a *sociocultural* approach of family education, drug intervention programme and problem-solving skills. The family education included explanations of the concept of schizophrenia from a cultural perspective and an attempt to correct negative attitudes toward modern treatment. The family education and drug intervention was delivered as a package. The drug intervention programme included information about drug counselling, clear instruction about dose and frequency, information about possible side effects, the role of carers in supervision of medication at home, and close monitoring of compliance by a drug intake check-list presented in every follow-up visit. Both groups of patients received routine prescription of medication. N.B. One psychiatrist treated the intervention group

	throughout the study, and a second psychiatrist treated the control group throughout the study. Patients in each group were followed-up on the same schedule; monthly for the first 3 months and then every 6 weeks in the next 9 months.
Motivational component	Counsellor had positive attitude towards drugs and modern treatment in an attempt to correct negative attitudes. Counselling included rationale for various treatments. Role of carer in supervision of medication at home emphasised.
Volitional component	Clear instruction about dose, frequency and side effects.
Outcome measures	Compliance was measured at the end of 6 months and 1 year after initiation of the intervention, by a semi-structured interview with the carer and examination of the amount of unused medication. A home visit was made to assess unused medication "in doubtful cases". Drug compliance was measured globally as a percentage of the total prescribed drug dosage actually taken during the previous 6 months. Compliance was reported on a 6-point ordinal scale, with 1 indicating non-compliant, 2 indicating 25% compliant, 3 indicating 50% compliant, 4 indicating 75% compliant, 5 indicating 90% compliant and 6 indicating 100% compliant.
Mediational analysis	No
Theoretical model	D
Summary	At 1 year follow-up, more patients in the intervention group reported 90% drug compliance than those in the control group; 85.1% and 55.1% respectively ($p < 0.001$). While this finding was also evident at the 6 month follow-up, it failed to reach significance; 73% and 59.4% respectively (NS).

Study	Sackett, D., Haynes, R., Gibson, E., Hackett, B., Taylor, D., Roberts, R., et al. (1975). Randomised clinical trial of strategies for improving medication compliance in primary hypertension. *Lancet, 1*, 1205-1207.
Haynes review	Included
Method	Random allocation, 2x2 factorial design, no indication of concealment.
Participants	Male steel company employees who exhibited persistently elevated diastolic blood pressure on repeated examination (at or above 95 mm Hg (fifth phase)), were free of secondary forms of hypertension, were taking no daily medication, and had not been prescribed antihypertensive medications for at least six months before the trial were eligible for the study.
Intervention(s)	Intervention 1 'augmented convenience:' Participants saw company physicians, rather than family physicians, for hypertensive and follow-up care during work hours. Intervention 2 'mastery learning:', participants were given facts about hypertension, its effects upon organ targets, health and life expectancy, benefits of hypertensive therapy, the need for adherence with medications and some simple reminders or taking pills (this information was provided in a slide-tape format, and reinforced by a secondary-school graduate "patient educator").
Motivational component	Mastery learning subjects were given instruction about hypertension and its treatment, including information about the benefits of treatment and the need for compliance.
Volitional component	Augmented convenience group saw their GP during working hours. Mastery learning group were educated about management of hypertension and provided with simple pill-taking reminders.

Outcome measures	Adherence was calculated by self-report, pill count, blood and urine analysis. Patients whose pill counts were consistent with adherence levels of 80% or more were considered 'compliant'. Blood pressure control was assessed by trained observers. Only patients whose diastolic blood pressure was below 90 mm Hg at six months were described as having 'goal blood pressure'. Outcome assessors were blinded to study group.
Mediational analysis	No
Theoretical model	D
Summary	Compliance was not improved by attempts to make care and follow-up more convenient (augmented convenience). Mastery learning was highly effective in teaching patients about hypertension and its management, but did not increase compliance.

Study	Sanmarti, L. S., Megias, J. A., Gomez, M. N., Soler, J. C., Alcala, E. N., Puigbo, M. R., et al. (1993). Evaluation of the efficacy of health education on the compliance with antituberculosis chemoprophylaxis in school children. A randomised clinical trial. *Tubercle and Lung Disease, 74*, 28-31.
Haynes review	Excluded
Method	RCT
Participants	392 tuberclin-positive school-children that had not been vaccinated.
Intervention(s)	All children enrolled in the study received a first examination to establish if tuberculosis was present. A preventative treatment (chemoprophylaxis) was then prescribed and parents were told how to take and given information leaflets on tuberculosis and its prevention. Control group patients received usual care whereby parents were told that unless they thought it appropriate, a return visit was not needed until they had followed the treatment for 12 months. In intervention group 1, the children's mothers were telephoned every 3 months by a specialist nurse who relayed the benefits of treatment and encouraged its continuation. In treatment group 2, another specialised nurse went to the patient's home every 3 months to provide health education to mother and child, as well as the information leaflets given at the initial visit, and mothers were encouraged the continuation of treatment. Also, the Eidus-Hamilton reaction was performed to objectively verify compliance. In treatment group 3 the child was seen by the physician every 3 months at a tuberculosis clinic; the doctor gave educational messages, the same information leaflets and the Eidus-Hamilton reaction. The final visit in all patients consisted of a medical examination and performance of the Eidus-Hamilton reaction.
Motivational	Treatment and disease information leaflets,

component	monitoring of compliance via Eidus-Hamilton test, nurses/doctors encouraged continuation of treatment
Volitional component	N/A
Outcome measures	Eidus-Hamilton test for acetyl-isoniazid in urine (test that medicine had been taken in the last 2-3 days) at 1 year.
Mediational analysis	No
Theoretical model	D
Summary	Intervention groups 1, 2 and 3 significantly more compliant than control ($p < .001$, .001, &, .0025, respectively), group 2 more compliant than group 3 ($p < .0025$).

Study	Sclar, D. A., Chin, A., Skaer, T. L., Okamoto, M. P., Nakahiro, R. K., & Gill, M. A. (1991). Effect of health education in promoting prescription refill compliance among patients with hypertension. *Clinical Therapeutics, 13*(4), 489-495.
Haynes review	Excluded
Method	RCT. Patients with either new or existing cases of mild-to-moderate hypertension randomly assigned to experimental or control group.
Participants	453 patients with mild-to-moderate hypertension prescribed a once daily regimen of atenolol.
Intervention(s)	Patients assigned to the intervention group received an enrolment kit when filling their initial prescription (new patients) or when requesting their next sequential refill (existing patients) during the study period. Each kit contained a 30-day supply of atenolol, an explanation of the intent and content of the educational program, a newsletter discussing the importance of compliance with antihypertensive therapy, and information regarding nutrition and life-style changes. Intervention patients also received a telephone reminder one week prior to their refill date and a compliance motivating message. They also received a reminder letter 10 days prior to subsequent script refills.
Motivational component	Motivational newsletter, reminder telephone call and motivational message, reminder letters.
Volitional component	N/A
Outcome measures	Number of requested pills compared to the ideal amount of requested pills.

Mediational analysis	No
Theoretical model	D
Summary	Enrolment of existing patients into the intervention group was associated with an increase of 27 days supply of medication obtained during the study period (P<0.001). Enrolment of new patients in the intervention was associated with an increase of 40 days supply of atenolol obtained during the study period (P<0.001).

Study	Sellors, J., Pickard, L., Mahony, J. B., Jackson, K., Nelligan, P., Zimic-Vincetic, M., et al. (1997). Understanding and enhancing compliance with the second dose of hepatitis B vaccine: a cohort analysis and a randomized controlled trial. *Canadian Medical Association Journal, 157*(2), 143-148.
Haynes review	Excluded
Method	RCT. Participants randomly assigned to an enhanced or regular intervention group.
Participants	256 adults attending an STD clinic, seronegative for hepatitis B virus, who consented to receive a hepatitis B vaccination, but failed to turn up for the second dose.
Intervention(s)	Participants who did not return for a second dose of the vaccine within 6 weeks after the first were randomly assigned to 1 of 2 groups; an 'enhanced' or 'regular' method of encouragement to return for the second dose. For those in the enhanced group, the clinic receptionist tried at least 3 times to contact them over the course of 2 weeks. If this was unsuccessful, a public health nurse then tried to call the patient at least 3 times over the following 2 weeks. With the regular method, no attempt was made to contact the subject by telephone. In both the regular and enhanced intervention group, those who did not return for their second dose after about 3 months received an appointment reminder letter.
Motivational Component	Regular intervention group received reminder letter. Enhanced intervention group received mail reminder and up to 6 reminder telephone calls
Volitional Component	N/A

Outcome measures	Receipt of second dose of vaccine.
Mediational analysis	No
Theoretical model	D
Summary	The enhanced intervention group had twice the compliance rates of the regular intervention group (48% v. 25%; p = 0.008).

Study	Sharpe, T. R., & Mikeal, R. L. (1974). Patient compliance with antibiotic regimens. *American Journal of Hospital Pharmacy, 31*(5), 479-484.
Haynes review	Excluded
Method	The level of information given to patients receiving antibiotics was randomly assigned for the first week of the study and alternated each week thereafter for a total of four weeks.
Participants	80 patients with a prescription for a ten day course of ampicillin, phenoxymethyl penicillin potassium or tetra cycline, not institutionalised, >14 years old.
Intervention(s)	Two levels of medication information were used. The control group patients received medication with the usual prescription label. Those in the intervention group received their medication with the usual label plus a supplementary label instructing the patient to consume the medication for the full course of therapy, plus an information sheet explaining the rationale for consuming the mediation at the proper times and for the full course.
Motivational Component	A 'compliance' label used on intervention group medication, as well as an information sheet explaining the rationale for consuming the mediation at the proper times and for the full course.
Volitional Component	N/A
Outcome measures	Pill count
Mediational analysis	No

Theoretical model	D
Summary	Those who received the higher level of information were significantly more compliant than controls ($p<0.05$).

Study	Simkins, C. V., & Wenzloff, N. J. (1986). Evaluation of a computerized reminder system in the enhancement of patient medication refill compliance. *Drug Intelligence and Clinical Pharmacy, 20*(10), 799-802
Haynes review	Excluded
Method	RCT
Participants	Patients due refills for chronic cardiovascular medications
Intervention(s)	Control group were monitored for refill compliance; intervention group 1 were sent reminder postcard a day before refill was due, intervention group 2 received a telephone call reminder
Motivational component	N/A
Volitional component	Prescription refill reminder cues
Outcome measures	Monthly prescription refill nonadherence over 3 months
Mediational analysis	No
Theoretical model	D

Summary	Significant difference between controls and intervention group 2 at 1 month, but not at 2 or 3 months

Study	Smith, N. A., Seale, J. P., Ley, P., Shaw, J., & Bracs, P. U. (1986). Effects of intervention on medication compliance in children with asthma. *Medical Journal of Australia, 144*(3), 119-122.
Haynes review	Excluded
Method	RCT
Participants	217 children with chronic asthma
Intervention(s)	Children were assigned at random to either control (received no intervention) or test (received the intervention) groups. Those in the intervention group received a treatment information leaflet, a consultation stressing the importance of compliance, tailored behaviour strategies from the physician, and supervision of compliance.
Motivational component	Disease and drug information, treatment necessity information.
Volitional component	Tailored behaviour strategies.
Outcome measures	Self-reported compliance, physician estimates of compliance, knowledge of disease and treatment, necessity and concern beliefs.
Mediational analysis	No, but specified antecedents were measured, and found to be associated with adherence.
Theoretical model	HBM / B
Summary	Significant 'good' (70% +) compliance difference ($p<.005$), significant mean compliance difference, .001; increased

	knowledge of disease (p<.001); increased knowledge of treatment elements (all p's <.005); increased knowledge of disease was associated with increased compliance in both intervention and control groups.

Study	Solomon, M. Z. and DeJong, W. (1988). The Impact of a Clinic-Based Educational Videotape on Knowledge and Treatment Behaviour of Men with Gonorrhea. *Sexually Transmitted Diseases, 15*: 127-132.
Haynes review	Excluded
Method	RCT. All male patients with a positive gram stain were referred by a clinician to the research assistant immediately after diagnosis; those who consented to participate where then assigned at random to intervention or control groups.
Participants	902 standard clinic visitors (treatment group, n=456; control group, n=446). Study 2 included 151 visitors (treatment group, n=121; control group n=130).
Intervention(s)	Study 1: The intervention group watched a 10 minute soap opera-style videotape which focused on knowledge and treatment of gonorrhoea. Both intervention and control patients saw a Disease Intervention Specialist (DIS) for a contact-tracing interview and then received medication from a nurse. For all patients both the DIS and nurse provided treatment instructions. Except for the showing of the videotape to patients in the intervention group, both groups of patients were treated identically. Study 2: A follow-up study was conducted to assess the impact of the video on patients' knowledge and beliefs, and on the percentage of patients returning for test of cure (TOC) examination.
Motivational Component	Patients shown videotape focusing on knowledge and treatment of gonorrhoea .
Volitional Component	N/A
Outcome	Return to clinic for test of cure examination

measures	14 days later. (Also ascertained whether patients notified their sex contacts to come to the clinic).
Mediational analysis	No
Theoretical model	HBM
Summary	In study 1, 53.5% of patients in the treatment group, but only 43.3% of those in the control group returned for the TOC (P <.003). In, study 2, of those seeing the videotape, 59% returned, but of those in the control group, only 39.1% returned (P <.0015).

Study	Solomon, M. Z., DeJong, W., & Jodrie, T. A. (1988). Improving drug regimen adherence among patients with sexually transmitted disease. *The Journal of Compliance in Health Care, 3*(1), 41-56.
Haynes review	Excluded
Method	RCT (2x2x2 factorial design)
Participants	321 STD clinical patients with a prescription for tetracycline.
Intervention(s)	Factor 1: 10 minute videotape targeting treatment planning, plus schedule card that identifies opportunities to take pills that gets reviewed by a doctor vs. no treatment. Factor 2: unit-dose packaging; vs. usual packaging. Factor 3: telephone interview at 2 days into treatment, vs. telephone interview on day 6.
Motivational component	Disease and drug information, treatment necessity information.
Volitional component	Tailored behaviour strategies.
Outcome measures	5 point, clinician rated compliance scale; test of patients' disease and treatment knowledge; patients' use of reminder cues; unsafe sexual health behaviour; treatment satisfaction, treatment efficacy, and disease severity.
Mediational analysis	No, but key specified antecedents were measured, and found to be associated with adherence.
Theoretical model	Health Belief Model / B

Summary	Video (p<.001), packaging (p<.001), and video by packaging interaction (p<.015) significant. Day of telephone call did not have a significant effect. Videotape had a significant effect on knowledge (p<.001); knowledge significantly predicted compliance (p<.05); significant videotape x packaging interaction on treatment satisfaction (p<.025), disease severity (p<.26), and treatment efficacy (p<.015).

Study	Strang, J., Falloon, I., Moss, H., Razani, J., & Boyd, J. (1981). The effects of family therapy on treatment compliance in schizophrenia. *Psychopharmacological Bulletin, 17*, 87-88
Haynes review	Included
Method	Random allocation, not otherwise specified.
Participants	Recently discharged patients with Present State Examination/CATEGO diagnoses of schizophrenia who were living with at least one parent who exhibited high 'expressed emotion' on the Camberwell Family Interview. All patients received oral neuroleptic medication (usually chlorpromazine).
Intervention(s)	All patients had scheduled therapy and monthly medication appointments. Patients were allocated to family therapy or individual support sessions.
Motivational component	N/A (unclear - no details of content of family therapy)
Volitional component	N/A (unclear)
Outcome measures	All patients were seen monthly by the prescribing psychiatrist, blinded to the group assignment, where medication status and adherence were assessed. Medication was adjusted based on mental status, side effects, and blood plasma levels. Patients with poor compliance for oral medications were given uphenazine decanoate injections. Adherence was defined in six ways: number of missed appointments with psychiatrist; number of patients change to intramuscular depot medication; tablet-taking compliance (pill counts, self-reports by patient or family, and blood plasma levels); variability in plasma levels; mean and modal doses

	prescribed for each treatment group; mean plasma level in each group. Relapse was the treatment outcome (no information on how measured).
Mediational analysis	No
Theoretical model	D
Summary	Patients receiving family therapy were more likely to attend 80% of their medication appointments and more likely to take 50% of their prescribed dose of treatment. More patients in the individual support sessions group were prescribed intramuscular neuroleptics; these patients were therefore more likely to have shown evidence of poor compliance with oral medication compared to those receiving family therapy.

Study	Tuldra, A., Fumaz, C. R., Ferrer, M. J., Bayes, R., Arno, A., Balague, M., et al. (2000). Prospective Randomized Two-Arm Controlled Study To Determine the Efficacy of a Specific Intervention to Improve Long-Term Adherence to Highly Active Antiretroviral Therapy. *Journal of Acquired Immunodeficiency Syndromes, 25*(3), 221-228
Haynes review	Included
Method	Patients receiving antiretroviral medicines for HIV were randomly allocated to intervention or control group. There is no statement in the report about blinding of physicians. Patients and psychologists were not blinded.
Participants	116 patients who initiated their first or second-line HAART at a general university hospital's HIV-outpatient unit were included. Exclusion criteria were not specified.
Intervention(s)	The experimental group received a psycho-educative assessment from a psychologist in addition to the regular clinical follow-up. Patients in this arm received explanations about the reasons for starting treatment and the relevance of appropriate adherence to prevent replication of viral mutations and the development of antiretroviral drug resistance. Patients' doubts about medication intake were addressed and a dosage schedule was developed with the patients' input. Study subjects were also taught to manage medication and tackle problems such as forgetting, delays, side effects and changes in the daily routine. A phone number was provided in case any questions arose before the next interview. During follow-up visits, adherence was verbally reinforced and strategies were developed to deal with problems that had appeared to that point, including rescheduling dose schedules to overcome adherence problems, providing skills to deal with minor adverse effects. Patients in the control group received a standard assessment consisting of an

	interview with a psychologist following the regular medical visit, in which only variables related to adherence were recorded. The control group received only normal clinical follow-up. Both groups were interviewed for data collection at 0, 4, 24, and 48 weeks of follow-up.
Motivational component	Intervention focused on improving patients' knowledge, and provided an explanation of the reasons for starting treatment and the relevance of appropriate adherence. During follow-up visits adherence was verbally reinforced.
Volitional component	A dosage schedule was developed with the patient's input. Subjects were taught to manage medication intake and overcome problems such as forgetting, delays, side effects and changes in the daily routine.
Outcome measures	Measurement of compliance: Self-reported adherence was registered at each visit. The proportion of compliance was calculated by dividing the number of pills taken during the month before by the number of pills prescribed during the same period. Patients who consumed 95% of medication prescribed were considered adherent. Randomized blood analyses were also performed without warning in 40% of the patients to measure plasma levels of protease inhibitors (PI). HIV-1 RNA levels (copies/ml) were used to determine clinical outcome.
Mediational analysis	No
Theoretical model	B
Summary	At 4 and 24 week follow-up, patients in the intervention group were more likely to have adherence levels of >95%, but this did not reach significance. At 48 week follow-up, 94% of patients in the intervention group had adherence levels of >95%, compared to 69% of those receiving standard care (p = .008).

Study	van Es, S. M., Nagelkerke, A. F., Colland, V. T., Scholten, R. J., & Bouter, L. M. (2001). An intervention programme using the ASE-model aimed at enhancing adherence in adolescents with asthma. *Patient Education and Counseling, 44*(3), 193-203.
Haynes review	Included
Method	RCT. Patients were recruited from six paediatric outpatient clinics and randomly allocated to usual care by a paediatrician or to the intervention programme. Randomisation was stratified according to hospital. Due to the nature of the intervention, blinding of the paediatricians and the patients was not feasible.
Participants	112 adolescents with asthma. Inclusion criteria were: asthma diagnosed by a physician; treatment prescribed by a paediatrician with daily inhalation of prophylactic asthma medication during a preceding period of at least 2 months; aged from 11 to 18 years; attending secondary school, ability to fill in a questionnaire in the Dutch language.
Intervention(s)	The programme, based on the ASE (attitude-social influence self-efficacy) model, aimed to enhance adherence by stimulating a positive attitude, increasing feelings of social support, and enhancing self-efficacy. During standard visits, a paediatrician discussed an asthma management zone system with the intervention participants. This system has been developed to instruct patients about disease characteristics, triggers for airway obstruction and treatment objectives. PEF measurements were also discussed. The visits to the paediatrician were each combined with a visit to an asthma nurse who discussed several aspects of the disease and instructed patients how to use their inhaler. The nurse also checked if patients remembered and understood the information given to them at the last visit. Participants were encouraged to ask questions during these visits. Intervention participants also

	attended three group sessions during which patients discussed how they coped with their asthma and role-played several difficult situations. To support these patients were shown videos and showed several situations in which having asthma can be difficult for adolescents. The various sessions of the intervention were spread out over 1 year; during the second year, all participants in both the control group and the experimental group received the same usual care from their paediatricians.
Motivational component	Asthma management zone system: instruction on disease characteristics, triggers for airway obstruction and treatment objectives. Discussion of peak expiratory flow measurements. Asthma nurses: discussion of asthma including info on medication and pulmonary conditions. Group discussions.
Volitional component	Asthma nurses: Instructed patients how to use their inhaler.
Outcome measures	The ASE-variables were operationalised in several questions, and for each variable a sum-score was calculated. Self-reported adherence was asked by participants to score their adherence on a 10-point scale. Intention to adhere was assessed on the basis of one statement on a 7-point scale (e.g. "I intend to take my asthma medicine every day"). Positive and negative attitude towards taking medication was also assessed. Social influences and self efficacy was also assessed based on a number of statements. Participants were also asked about feeling ashamed of having asthma and the quality of communication with the physician.
Mediational analysis	No
Theoretical model	A
Summary	At T1 (12m) follow-up there were no statistically significant differences found

	between the experimental and the control group on adherence. At T2 (24m) follow-up self-reported adherence was statistically significantly higher in the experimental group.

Study	Williams, R. L., Maiman, L. A., Broadbent, D. N., Kotok, D., Lawrence, R. A., Longfield, L. A., et al. (1986). Educational strategies to improve compliance with an antibiotic regimen. *American Journal of Diseases of Children, 140*(3), 216-220.
Haynes review	Excluded
Method	RCT
Participants	Parents of children (2-24 months old) with a first episode of acute suppurative otitis media, prescribed a ten day amoxicillin treatment course.
Intervention(s)	Parents of all patients were given 150mL of amoxicillin trihydrate, a 5 ml syringe, an information pamphlet and a self-monitoring reminder sticker. The information pamphlet described causes, treatment and complications of the condition and emphasized the importance of adherence to amoxicillin for the full ten day treatment course. The reminder sticker had boxes to be checked each time a dose was given. All patients were scheduled to return for a follow up examination where they were assigned to one of three groups: a baseline intervention group, a slide-tape group or a follow-up phone call group. The baseline intervention group received no further intervention. The slide-tape group observed a 4 minute slide-tape program where the content was similar to that of the pamphlet. Parents in the follow-up group received a phone call on the fourth day of therapy during which they were asked if they had any problems administering the amoxicillin and were encouraged to continue giving treatment for the whole treatment course.
Motivational Component	The slide-tape group viewed a slide-tape which emphasized the importance of adherence to treatment. The follow-up group received a phone call encouraging compliance to treatment.

Volitional Component	N/A
Outcome measures	Parental reports of missed doses, the number of boxes checked on the reminder record and the volume of amoxicillin that remained in the bottle were recorded. A urine assay for the presence of amoxicillin was also taken.
Mediational analysis	No
Theoretical model	D
Summary	Compliance was high in all three groups; there were no significant difference between the groups.

Study	Windsor, R. A., Bailey, W. C., Richards, J. M., Jr., Manzella, B., Soong, S. J., & Brooks, M. (1990). Evaluation of the efficacy and cost effectiveness of health education methods to increase medication adherence among adults with asthma. *American Journal of Public Health, 80*(12), 1519-1521
Haynes review	Excluded
Method	RCT
Participants	267 asthma patients; 135 adult asthma patients in control group, 132 patients in experimental group.
Intervention(s)	Experimental group received a health education intervention consisting of one individual and one group session.
Motivational Component	Health Education
Volitional Component	N/A (unclear)
Outcome measures	Four adherence measures were documented at baseline and 12-month follow-up: correct inhaler use, inhaler adherence, medication adherence, and total adherence rating.
Mediational analysis	No
Theoretical model	A
Summary	Experimental group patients exhibited a significantly higher level of improvement in adherence (44 percent) than control group patients (2 percent) after a 1-yr follow-up.

Study	Wysocki, T., Greco, P., Harris, M. A., Bubb, J., & White, N. H. (2001). Behavior therapy for families of adolescents with diabetes: Maintenance of treatment effects. *Diabetes Care, 24*(3), 441-446
Haynes review	Included
Method	Families were randomly assigned to one of the three groups. Randomisation was stratified by the adolescent's sex and by the treatment centre (no statement of concealment of allocation). Due to the nature of the intervention, patients could not be blinded.
Participants	Inclusion criteria included the following: 12-17 years of age, having Type I diabetes, no other major chronic diseases, no mental retardation, not incarcerated in foster care or in residential psychiatric treatment, no diagnoses of psychosis major depression or substance abuse disorder in adolescents or parents during the previous 6 months.
Intervention(s)	Families were randomized to three months of treatment with either Behavioural-Family Systems Therapy (BFST), an education and support (ES) group, or current therapy (CT). Patients in the CT group (along with those in the other groups) received standard diabetes therapy from paediatric endocrinologists, including an examination by a physician and a GHb assay at least quarterly; two or more daily injection of mixed intermediate- and short-acting insulins; self-monitoring of blood glucose and recording of test results; diabetes self-management training; a prescribed diet; physical exercise and an annual evaluation for diabetic complications. ES: In the first 3 months of the study, families attended 10 group meetings that provided diabetes education and social support. A social worker at one centre and a health educator at another centre served as group facilitators. Panels of 2-5 families began and completed 10 sessions together; the parents and the adolescent with the

	diabetes attended the sessions. Family communication and conflict resolution skills were specifically excluded from session content, because these are the primary targets of BFST. Each session included a 45-min educational presentation by a diabetes professional, followed by a 45-min interaction among the families about a topic led by the facilitator. BFST- Adolescents and caregivers in this group received 10 sessions of BFST. This consisted of four therapy components that were used in accordance with each family's treatment needs as identified by the project psychologists and was based on study data and family interaction during sessions. The four therapy components included problem-solving training, communication skills training, cognitive restructuring and functional and structural family therapy.
Motivational component	Patients in the education and support (ES) group received education presentations on diabetes.
Volitional component	Unclear: BFST group sessions consisted of family problem-solving discussions focusing on diabetes related conflicts.
Outcome measures	14-item, validated Self-Care inventory for 3 months, distributed at 3, 6 and 12 months after treatment.
Mediational analysis	No
Theoretical model	D
Summary	At post-treatment assessment there was no significant difference between groups. However, at 6- and 12- month follow-up, the BFST group showed improved treatment adherence whereas the CT and ES groups showed deteriorated adherence over time.

Study	Xiong, W., Phillips, M. R., Hu, X., & Wang, R. (1994). Family-based intervention for schizophrenic patients in China. A randomised controlled trial. *British Journal of Psychiatry, 165*(2), 239.
Haynes review	Included
Method	Random allocation not otherwise specified.
Participants	63 DSM-III-R Chinese schizophrenic patients living with family members.
Intervention(s)	Standard care (medication prescription at hospital discharge plus follow-up on patient's or family's initiative) vs. a family based intervention that included monthly 45 minute counselling sessions focussed on the management of social and occupational problems, medication management, family education, family group meetings, and crisis intervention.
Motivational component	Families in the intervention group were provided with information booklets and educated about schizophrenia.
Volitional component	Effective method of medication management developed. Common problems such as medication usage were discussed.
Outcome measures	Medication usage was assessed by family member reports. Time for which the patient took 50% of prescribed dosage was the measure for comparison of groups. Psychiatric outcomes were assessed at six, 12, and 18 months following hospital discharge by observers who were trained clinical researchers, blinded to study group allocation.
Mediational analysis	No

Theoretical model	D
Summary	The intervention group patients complied with psychiatrist's recommendations regarding medication for a greater proportion of the follow-up period than control patients, but these differences did not reach statistical significance. Overall, intervention patients used over 50% of the recommended dosage for 86.3% of the follow-up period compared with 73.8% for control group patients.

Study	Zhang, M., Wang, M., Li, J., & Phillips, M. R. (1994). Randomised control trial of family intervention for 78 first-episode male schizophrenic patients: an 18-month study in Suzhou, Jiangsu. *British Journal of Psychiatry*, 96, (24):96-102
Haynes review	Included
Method	Random allocation not otherwise specified.
Participants	78 men, discharged after their first admission to the hospital for schizophrenia. Schizophrenia was defined according to the Chinese Medical Association criteria. Inclusion criteria were no serious concurrent medical illnesses, living within commuting distance of the hospital, and willingness to attend regular family intervention sessions. Mean age was 24. Occupation was the only baseline characteristic that differed between groups.
Intervention(s)	Men in both groups came to the outpatient department by their own choice; no regular appointments were made and there was no routine follow-up. Medication was obtained at these visits. Family intervention: Families and patients were assigned to one of two counsellors for their ongoing care, were invited to come to a discharge session that focussed on education about the management of the patients treatment, asked to come to a family group counselling session with other families three months after discharge, and then attend three-monthly group sessions with other families with similar patient problems. Non-attendance triggered a visit from study staff. Each family was contacted at least once during the 18-month follow-up. Control group patients received no family interventions.
Motivational component	Importance of continuing the medication was discussed in sessions.
Volitional	Initial intervention session focused on

component	management of the patient's treatment.
Outcome measures	All patients were seen every three months by staff physicians, blinded to the group assignment, where medication status and adherence were assessed. Adherence was defined as taking at least 33% of dose prescribed at the time of the index discharge for at least six days/week. Treatment outcomes included re-admission to hospital and mean hospital-free period for those who were readmitted.
Mediational analysis	No
Theoretical model	D
Summary	The proportion of patients who used medication regularly was higher in the intervention group compared to the control group; 79.5% and 56.4% respectively ($p < 0.01$).

Appendix 7: Enhancing patients' adherence to medication through compliance therapy

Ian Kellar & Rob Horne

Developed from Cognitive Behavioural Therapy (CBT) and Motivational Interviewing, Compliance Therapy is a method of encouraging open discussion of beliefs about treatment, and fosters a therapeutic partnership between patient and clinician with respect to medicine taking. It aims to bring about insight into effects of beliefs on medicine taking, overcome reluctance that is the result of concerns or misconceptions regarding treatment or side-effects, and address denial of psychological problems. Compared with action planning or self-management interventions, Compliance Therapy is an intensive programme utilised among patients with psychotic disorders. Unlike more parsimonious approaches, this technique may be applied over an extended series of sessions, typically by psychotherapists trained in CBT (Kemp, David and Hayward, 1996).

Key studies utilising an intervention approach designed by Kemp et al. (1996) provide mixed evidence. The interventions studied involved four to six sessions lasting 20-60 minutes, roughly twice a week, and utilised guided problem solving and an educational component. Compliance was significantly improved over a six-month period among patients with psychotic disorders, and further, a study found adherence was maintained at an 18 month follow-up among patients with mood disorder and schizophrenia (Kemp, Kirov, Everitt, Hayward and David, 1998). However, O'Donnell et al (2003) used the same approach, exclusively with schizophrenic patients. In contrast to the previous studies, no significant difference in adherence, or any secondary outcomes were found.

Compliance Therapy shows promise as a means of enhancing adherence to medication among patients with psychotic disorders. Further research is needed to confirm its efficacy and mechanisms of action. The intervention programme uses cognitive behavioural approaches to address perceptual and practical barriers to adherence. Similar but abbreviated approaches may be helpful in non-psychiatric conditions.

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Appendix 8: Patient self-management of medication illness

Ian Kellar & Rob Horne

Self-management initiatives encompass a broad array of strategies that are characterised by a shift in responsibility for day-to-day health care from the clinician to the patient. These are typically operationalised in the form of interventions that seek to solve an identified health treatment problem by addressing beliefs related to illness and treatment, then identifying a problem solving strategy. Such strategies form part of government efforts to create a patient-centred NHS through the Expert Patient programme (Department of Health, 2001).

There is evidence for the efficacy of these approaches in terms of health status and health care utilisation for a range of chronic conditions, such as arthritis, asthma, cardiovascular disease, depression, diabetes, and chronic back pain (Bodenheimer, Lorig, Holman and Grumbach, 2002; Lorig and Holman, 2000; Newman, Mulligan and Steed, 2001; Bodenheimer, Lorig, Holman and Grumbach, 2002). Moreover, there is emerging evidence that self-management approaches can effect enhanced adherence to medication, with significant effects reported in relation to adherence to HAART (Smith, Rublein, Marcus, Brock and Chesney, 2003), steroid inhaler adherence among asthmatics (Gallefoss and Sigvald Bakke, 1999), and in terms of adherence related outcomes in type-2 diabetes (Norris, Engelgau and Narayan, 2001).

It has been suggested that the effects of this approach are mediated via changes in self-efficacy; enhancing the individual's sense of what they can cope with, and what they can achieve. Whilst there is evidence that self-management interventions do enhance self-efficacy (Barlow, Turner and Wright, 1998; Gifford, Laurent, Gonzales, Chesney and Lorig, 1998; Lorig et al, 2001; Lorig, Ritter, Laurent and Fries, 2004), key reviews do not provide evidence that changes in self-efficacy account for the effect of the intervention (Barlow, Wright, Sheasby, Turner and Hainsworth, 2002; Bodenheimer et al, 2002; Powell and Gibson, 2005).

Whilst further studies are required to confirm the efficacy of this approach in enhancing adherence to a range of medication regimens, self-management interventions show a good deal of promise as a means of enhancing adherence to medicines. Whilst there is evidence that self-efficacy is affected by such interventions, further work is required to demonstrate that this is the causal pathway. Thus far, studies have typically failed to adequately describe the intervention content, or properly evaluate the intervention elements, such that the effective elements may be identified (Barlow et al, 2002). Future research may seek to utilise the Self-Regulatory Model as a means of exploring problematic beliefs regarding both illness and treatment (Newman et al, 2001; Horne and Weinman, 2002). Additionally, the action planning component of self-management interventions may benefit from related research into implementation intention formation (Gollwitzer, 1999; Gollwitzer and Oettingen, 2000).

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Appendix 9: Assessing the economic impact of interventions to enhance adherence

Adherence-enhancing interventions, policies or initiatives use scarce resources, so should be informed by theory, based on causes of nonadherence and targeted at key patient groups. A cost-effective intervention to enhance adherence is one that is effective in reducing the burden of illness associated with nonadherence, at an optimal level of resource use.

We have reviewed the literature on efficiency of adherence-enhancing interventions and found 45 studies (Elliott, Barber and Horne, 2005). Existing evidence is poor. Studies are limited by one or more of: validity of adherence-enhancing intervention, quality of interventional study design, and quality of economic evaluation. Cost data are particularly badly prepared and analysed. Many interventions were very resource-intensive and, if implemented widely, would divert large amounts of resources from other aspects of health care. We have proposed pragmatic, minimum quality criteria for future evaluations, developed from economic evaluation quality criteria (Drummond and Jefferson, 1996), standard hierarchies of evidence (Concato, Shah and Horwitz, 2000) and key adherence-specific design issues (Nichol, Venturini and Sung, 1999):

- Randomized controlled trial design
- Power calculation prior to beginning study to determine sample size
- Report method of randomization or allocation
- Justify choice of AEI based on reasons for non-adherence
- Clearly describe usual care pathway
- Explicitly state adherence measure(s) used and report results
- Explicitly state outcome measure(s) used and report results
- Follow-up period of sufficient length for disease group
- Clearly incorporate direct cost of intervention and that of ensuing care
- Use patient-based resource use (not average costs), explain allocation of fixed costs and state source of unit costs
- Use appropriate statistical analysis of cost data
- Carry out discounting if appropriate
- Incremental economic analysis of outcome
- Carry out sensitivity analysis
- Investigate limitations of adherence measure used

These criteria must be followed before adherence-enhancing interventions can be shown to allow more efficient use of scarce resources.

Finally, the relevance and usefulness of economic information to policy-makers may be limited by the non-transferability of cost-savings across historically separated budget streams. If the increased use of a drug in primary care is going to reduce secondary care costs, then this cost-

saving will have no meaning to the drug budget holder. This is often a barrier in the transferral of theoretical cost savings into practice. Until incentives are aligned more constructively, the application of economic data will be limited.

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Addendum

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