



## **Review article: Understanding adherence to medication in ulcerative colitis: innovative thinking and evolving concepts**

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**Review article: Understanding adherence to medication in ulcerative colitis: innovative thinking and evolving concepts**

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**Review article: Understanding adherence to medication in ulcerative colitis: innovative thinking and evolving concepts**

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**Keywords**

Inflammatory bowel disease, ulcerative colitis, adherence, necessity—concerns framework.

## SUMMARY

### Background

Non-adherence to medication is an important challenge in the treatment of ulcerative colitis (UC). Epidemiological studies have demonstrated that non-adherence affects 40-60% of UC patients, and has a substantial impact on the course of the disease. In one study, non-adherence was associated with a five-fold increase in the risk of relapse.

### Aims

We review factors contributing to non-adherence to UC therapy, and emerging concepts in addressing the problem.

### Results

Adherence is a complex, multifactorial issue, with factors varying between patients and changing over time. Identifying patients at risk of non-adherence is a key first step in targeting interventions to improve adherence. However, investigations of single factors that affect adherence have provided conflicting evidence. Evaluating physical and perceptual barriers to adherence, and acknowledging the role of patients' beliefs and concerns regarding treatment, provides valuable insights into the causes of non-adherence. This allows development of targeted interventions to improve adherence to UC therapy. Clinical tools to identify patients at risk of non-adherence are being developed to facilitate this approach.

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**Conclusions**

To help patients adhere better to maintenance therapy for UC, it is vital to consider patients’ beliefs and concerns, and to evaluate and address both physical and perceptual barriers to adherence.

For Peer Review

## Background

Non-adherence to medication is highly prevalent and is a particular challenge in the treatment of long-term conditions. Recent reports from the World Health Organization (WHO) and the National Institute for Health and Clinical Excellence (NICE) indicate that, in patients with chronic, long-term illnesses, as many as 30–50% are non-adherent.<sup>1;2</sup> Asymptomatic conditions, such as hypertension, have particularly low rates of adherence.<sup>1;2</sup>

Ulcerative colitis (UC) is an idiopathic, chronic inflammatory disease of the colon,<sup>3</sup> characterised by periods of acute, active disease interspersed with phases of asymptomatic remission. The onset of relapses is both unpredictable and associated with a marked reduction in quality of life.<sup>4</sup> For both the induction and maintenance of remission in mild to moderate UC, 5-aminosalicylic acid (5-ASA) is a key first line treatment.<sup>5</sup> Studies of adherence in UC patients demonstrate that 40–60% of patients are not fully adherent (defined in these studies as taking less than 80% of their medication) to their prescribed 5-ASA regimens.<sup>6;7</sup>

A number of terms have been used to describe the concept of non-adherence. Compliance, adherence, concordance and persistence have all been commonly used to define instances in which a patient is not strictly following the prescribed regimen, yet each has a distinct meaning. Horne *et al.* clearly defined the

differences between these terms in their 2006 report for the National Institute for Health Research (NIHR), and the definitions are summarised in Table 1.<sup>8</sup>

The definition of compliance implies that the patient is not involved in the decision making process, whereas adherence implies the need for agreement between patient and physician. Persistence is largely used when discussing long-term aspects of adherence in chronic illnesses, as adherence will often change over time. Consequently, and in line with the recommendations of the NICE and WHO reports, adherence is used as the term of choice in this article.

With non-adherence to medication being so prevalent, considerable efforts are being invested to elucidate the causative factors, and to develop successful interventions to promote adherence. However, adherence is a complicated issue for healthcare providers to successfully address. The term ‘non-adherence’ encompasses a very broad spectrum of behaviour, from a patient who misses an occasional dose, to a patient who does not take any of their medication. In addition, these patients may have very different reasons for not taking their medication, and will respond differently to measures to improve adherence. In this review, we outline the successes and shortcomings of traditional approaches to adherence in UC therapy, discuss the newly emerging concepts for dealing with this important issue, and elucidate how these may be translated into clinical practice.

### **Clinical impact of non-adherence to ulcerative colitis therapy**

The reported levels of non-adherence in UC therapy indicate that as many as 40–60% of patients are not fully adherent to their medication.<sup>6,7</sup> This has a significant impact on the course of the disease. In a non-interventional study, Kane *et al.* followed a cohort of 99 UC patients who were in remission, and demonstrated that there was a strong correlation between non-adherence (defined as taking less than 80% of the prescribed medication) and disease flares. In total, 89% of adherent patients maintained remission over the 2-year period compared to only 39% of the non-adherent patients.<sup>3</sup> In addition, the authors calculated that patients in remission who are non-adherent are five times more likely to relapse than adherent patients (hazard ratio 5.5 [95% CI 2.3–13],  $p < 0.001$ ).<sup>3</sup> Furthermore, there is evidence to suggest that 5-ASA may have a chemoprotective effect against colorectal cancer.<sup>9</sup> It could, therefore, be postulated that adherence to UC therapy may also reduce the risk of patients developing this disease.<sup>9</sup>

Studies investigating the healthcare costs of UC patients suggest that non-adherence not only has a substantial impact on a patient's health, but also confers a significantly higher cost to the healthcare provider. A study of over 4000 UC patients receiving 5-ASA maintenance therapy demonstrated that non-adherence (defined as failure to refill a prescription) is strongly correlated with higher healthcare costs, with non-adherence being associated with a two-fold increase in inpatient costs, compared to adherent patients ( $p < 0.01$ ).<sup>10</sup> In addition,



the same study found that adherence to 5-ASA therapy for UC resulted in 12.5% lower total annual healthcare costs, compared to non-adherent patients, despite increased medication expenditure.<sup>10</sup> These findings indicate that increased adherence not only provides benefits to patients, in terms of health and quality of life, but may also result in significant savings for healthcare providers.

**Conventional approaches to identifying non-adherence**

In order to effectively target interventions and initiatives to improve adherence, it is important to identify patients who are non-adherent. This is often difficult in routine clinical practice, and there is currently no widely accepted standard method for measuring adherence. In clinical trials, adherence can be measured based on assessments such as pill count, patient self-reporting or prescription refills. One commonly used measure is the Medication Possession Ratio (MPR), which is the ratio of the number of days' supply of medication obtained by a patient to the number of days in the study period.<sup>11</sup> However, in real-world situations, the use of such detailed measures of adherence is not feasible in everyday practice.

Therefore, the identification of factors that are predictive of non-adherence would be useful. However, adherence is a complex and multifactorial issue, in which a wide variety of factors play a role yet no single factor predominates (Figure 1A).<sup>12</sup> Identifying demographic characteristics that are predictive of non-adherence represents an attractive possibility; however, demographic studies have provided

contradictory evidence.<sup>3;7;10;13;14</sup> Conversely, disease-related factors do have a significant effect on adherence, with those patients who experience more frequent and more severe flares being more likely to have higher rates of adherence.<sup>3;7;15</sup> Indeed, adherence rates not only vary between patients, but also over time. Anecdotal observations have suggested that patients who adhere to therapy during acute exacerbations of UC may become less adherent during periods of quiescent disease. This is analogous to the very well known situation of patients who are prescribed antibiotics: while symptoms are present there is ample motivation to take the medication, yet when the symptoms subside many patients will not complete the prescribed course.

One factor that has commanded much attention in recent years, particularly relating to 5-ASA therapy, is the therapeutic regimen. A factor that stands out for many patients is that 5-ASA therapy may be delivered rectally, and in this case the discomfort and potential inconvenience of the therapy may affect adherence. However, the true impact of rectal 5-ASA therapies on adherence remains poorly established, and the published literature provides conflicting evidence on the levels of adherence when comparing rectal and oral 5-ASA therapy.<sup>13;14</sup>

More recently, there has been considerable debate regarding the complexity of oral 5-ASA regimens. Historically, 5-ASA was prescribed in divided doses, three- or four-times daily, but modern 5-ASA formulations have enabled the simplification of regimens to once- or twice-daily (OD or BD). A meta-analysis by

Claxton *et al.*, drawing data from several disease areas, has suggested that less frequent dosing is related to higher adherence.<sup>16</sup> However, significant differences were only demonstrated between once-daily and three-times daily ( $p=0.008$ ), or four-times daily ( $p<0.001$ ) dosing.<sup>16</sup> No significant difference was found between OD and BD regimens.<sup>16</sup> Similarly, studies specific to UC have failed to demonstrate a consistent significant relationship between dosing frequency and adherence.<sup>7;17</sup> Although one study reported higher adherence to once-daily than twice- or three-times daily regimens after 3 months, by 6 months there was no significant difference between the regimens.<sup>17</sup> In a recent systematic review, Jackson *et al.* noted that the number of daily doses is not consistently related to non-adherence, and none of the significant relationships that have been observed relate to OD dosing compared to BD.<sup>18</sup> Additionally, no significant differences in adherence have been found between the various oral 5-ASA formulations or different daily dosages.<sup>7;10</sup> Although there remains much discussion regarding the optimum dosage of 5-ASA, a fact that places additional context on patients' adherence decisions, the impact of such controversy on adherence has not been evaluated and so remains unclear.

Taken together, these data suggest that, while individual patients may be more adherent to certain regimens, or have preferences for different oral 5-ASA formulations, these factors are unable to provide a universal solution to non-adherence in UC patients.<sup>7;10;13;16;17</sup>

### Emerging concepts: anticipating non-adherence in ulcerative colitis

Traditional approaches to identifying and addressing non-adherence in UC, based on generalised strategies focussing on risk factors (such as demographics, regimen or formulation), have given disappointing results.<sup>19</sup> Consequently, leading experts on medicines adherence have proposed alternative approaches, whereby non-adherence is explained based on key patient-specific issues.<sup>20-22</sup> In this way, it adherence is approached not by investigating risk factors contributing to non-adherence across large populations, but rather, by switching the emphasis towards addressing the specific reasons behind non-adherence in individual patients.

The newly emerging approaches to non-adherence are summarised in Figure 1B. These approaches combine a number of models, in particular the practicalities and perceptions approach and the necessity–concerns framework.<sup>20,21</sup>

Non-adherent patients can be divided into two classifications: unintentional and intentional (Figure 1B).<sup>23</sup> In the former case, patients are unable to take their medication for reasons beyond their control. Conversely, intentionally non-adherent patients make a conscious decision not to take their medication.

According to the perceptions and practicalities approach, for both the intentional and unintentional groups, there may be a combination of practical and perceptual

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3 barriers that affect adherence. Practical barriers may include the size of the pills,  
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5 the cost of prescriptions, the route of delivery (e.g. rectal or oral), or side effects.  
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7 In contrast, perceptual barriers are more complex, and are based on an internal  
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9 negotiation between the perceived necessity of the treatment and any concerns  
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11 relating to it (Figure 1B).  
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18 To illustrate, an intentionally non-adherent patient may choose not to take their  
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20 medication for a variety of perceptual reasons, such as a fear of side effects or a  
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22 belief that it isn't necessary, but may also be influenced by practical factors such  
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24 as cost. Equally, one of the most common reasons cited by patients for non-  
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26 adherence is forgetfulness, which represents an important element of  
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28 unintentional non-adherence, influenced by both practical (e.g. complex dosing  
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30 regimens) and perceptual factors (e.g. lack of belief in the necessity of the  
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32 medication). One confounding factor in this case is that forgetfulness may be  
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34 misreported by patients; for example, a patient may believe that their doctor has  
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36 certain expectations of them, and feel obliged to live up to them.  
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43 The necessity–concerns framework aims to further understand perceptual  
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45 barriers to adherence. Although practical barriers to adherence can be relatively  
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47 simple to evaluate, whereas perceptual barriers, based on patients' beliefs and  
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49 concerns, are often far more complex. The concept of a balance between beliefs  
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51 and concerns affecting health decisions was first espoused by researchers at the  
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53 US Public Health Service in the 1960s, in an attempt to understand the reasons  
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for low uptake of free tuberculosis check-ups.<sup>24</sup> Horne *et al.* took this concept, applied it to the study of non-adherence in chronic illness, and developed the necessity–concerns framework,<sup>25</sup> which describes how adherence is affected by the interplay between a patient’s belief in the necessity of their medication and their concerns relating to it. To develop the necessity–concerns framework, Horne *et al.* developed standardised questionnaires (the Beliefs about Medicines Questionnaire [BMQ]<sup>26</sup> and the Medication Adherence Report Scale [MARS]<sup>27</sup>) to allow quantitative analyses of patients’ perceptions and levels of adherence to be performed. The necessity–concerns framework allows a detailed insight to be gained into the root causes of non-adherence, thus providing possible factors to be targeted to encourage adherence.

A further development to the necessity–concerns framework is the addition of attitudinal analysis.<sup>22</sup> Quantitative assessment of patients’ beliefs and concerns, using the BMQ, allows patients to be categorised into four “attitudinal groups” – accepting, ambivalent, indifferent and sceptical (Figure 2).<sup>22</sup> Patients who report that they believe in the necessity of their medication, for example those that agree with the statement in the BMQ “My life would be impossible without this medication”, would gain high scores for necessity. They would, therefore, be categorised as accepting or ambivalent (Figure 2). Similarly, patients with strong concerns about their medication (e.g. those who agree with the BMQ statement “Having to take this medicine worries me”), would be classed as sceptical or ambivalent. It would seem logical that these attitudinal groups might have a

relationship to adherence. Indeed, this hypothesis has been borne out by experimental observations. A large survey was conducted, collecting data from 1871 patients suffering from inflammatory bowel disease. Analysis of these data demonstrates that significant relationships exist between adherence rates and attitudinal grouping.<sup>22</sup> Patients categorised into the accepting group, who believe their medication is necessary and have few concerns about their medication, have the highest levels of adherence. In contrast, those in the sceptical group, who are more concerned and less convinced of the necessity of their medication, have the lowest levels of adherence (Figure 3).<sup>22</sup>

The necessity–concerns framework and attitudinal analysis provide methods of quantifying the complex balance of factors that affect adherence as a whole. This allows non-adherence to be anticipated, and patients at risk of non-adherence can be identified.

**Addressing non-adherence: new clinical approaches**

Evaluation of patients’ attitudes and beliefs enables the identification of the root causes of non-adherence, and, therefore, provides potential targets to assist in improving adherence. This approach makes it possible to establish a framework that allows specific interventions to be developed for individual patients, thereby maximising the chance of successfully improving adherence.

To facilitate such approaches, it would be beneficial to develop tools to identify patients' beliefs and concerns. These tools could be used in a clinical setting to screen patients and identify those at risk of non-adherence, while simultaneously identifying the probable causes of non-adherence, should it manifest. To date, no standardised approach has been adopted. However, several clinics have piloted short questionnaires, based on the more detailed BMQ and MARS tools, to be completed by patients in the clinic – while waiting to see their doctor, for example. These can be quickly evaluated to identify potentially non-adherent patients and rapidly identify their reasons, allowing specific issues to be addressed.

Given that patients' beliefs and concerns play a key role in adherence,<sup>22</sup> they should, therefore, be taken into account during consultations. In line with the guidelines from NICE, treatment decisions should be reached following an informed dialogue between patient and physician.<sup>2</sup> To illustrate with a previous example, a patient who is involved in their treatment decisions, and believes that the treatment is appropriate and effective, may be more motivated to take their medication. Such a patient may also be less likely to forget to take their medication. In this way, informed discussion may positively influence both intentional and unintentional non-adherence.

Closely linked to this is the concept of health literacy. Patients may not fully understand their condition or the purpose of their medication, so an element of



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3 patient education could be included in consultations. There are a number of  
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5 sources of information and support available throughout the wider healthcare  
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7 system. In particular, it may be beneficial to direct patients to relevant patient  
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9 groups, which can provide valuable information and support. A well-informed  
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11 patient may be better equipped to make reasoned, logical decisions regarding  
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13 their treatment. Additionally, patient education could help to reinforce the  
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15 necessity of maintenance therapy. For example, patients should be reminded of  
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17 the evidence that there is a far higher risk of relapse if they do not adhere to their  
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19 medication.<sup>3</sup> In addition, it may be beneficial to discuss the potential  
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21 chemoprotective effects of 5-ASA.<sup>9</sup>  
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29 Evidence suggests that adherence varies with time, with patients often becoming  
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31 less adherent with increasing duration of treatment.<sup>13</sup> Maintaining adherence for  
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33 extended periods of time is defined as persistence. A study investigating the  
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35 prescription refill data from more than 3500 UC patients over a 2-year period  
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37 demonstrated that there is a marked decrease in adherence over time, with 57%  
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39 of patients adherent at 3 months, but only 55% of those patients were still  
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41 adherent after 12 months.<sup>13</sup> This suggests that patients may need some  
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43 reinforcement of the importance of their medication at certain time points. This is  
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45 the premise behind a concept which could be termed “interval empathy”,  
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47 whereby patients are contacted at certain times when the risk of non-adherence  
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49 is judged to be greater. For example, after 3 months, a patient is likely to be in  
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51 remission but may be at increased risk of non-adherence. The patient could be  
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3 contacted to reinforce the message that continuing with their treatment is  
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5 beneficial to their health. This could also give patients an opportunity to voice any  
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7 new concerns that may have arisen since their last consultation. Various  
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9 approaches are being piloted, with doctors or specialist nurses contacting  
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11 patients by means such as telephone, text message or email.  
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18 Whilst predictive tools to identify patients at risk of non-adherence are likely to be  
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20 very useful, it is still important to monitor adherence between consultations and  
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22 identify, at the earliest opportunity, those patients who slip through the net and do  
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24 still become non-adherent. One approach that could be developed in the future  
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26 might be the adoption of a more integrated approach, whereby pharmacies and  
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28 primary care could coordinate with secondary care clinicians to identify signs that  
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30 a patient is not adhering to their medication. This may assist clinicians who, when  
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32 encountering relapsing patients, may wish to take steps to ensure that the  
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34 prescribed regimen is being adhered to before starting a new course of therapy.  
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## 43 **Conclusions**

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45 Non-adherence to medication is a significant issue in the treatment of chronic  
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47 conditions. Indeed, it has even been suggested that, due to the broad  
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49 applicability of any interventional measures, a successful strategy to improve  
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51 medication adherence may have a greater benefit to the health of the general  
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53 population than improvements in medical therapies.<sup>19</sup> In the treatment of UC,  
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there are significant clinical and financial impacts correlated with low adherence to maintenance therapy, resulting from a substantially increased risk of relapse.<sup>3;10</sup> Therefore, addressing non-adherence represents a priority issue for UC therapy.

However, adherence is a complex issue, with multiple factors all contributing to overall levels. This has made it difficult to target effective interventions based on the traditional approach of employing generalised strategies based on specific risk factors. For example, no clear evidence has demonstrated that once-daily dosing is superior to twice-daily, in terms of adherence. Evaluating the complex combination of barriers to adherence is an essential step towards improving adherence rates in UC.

Levels of adherence are determined by a mixture of both physical and perceptual factors, based on a subtle balance of an individual patient's beliefs and concerns. The necessity–concerns framework and attitudinal analysis provide a clear insight into patients' reasons for non-adherence. Furthermore, they also allow the balance between beliefs and concerns to be evaluated and related to the likelihood of non-adherence. Using this framework as a basis, clinical tools can be developed to facilitate the rapid identification of patients at increased risk of non-adherence and enable specific interventions to be targeted to individual patients.

Identifying non-adherent patients is also important in addressing the issue. Assessment of adherence could form a key element of consultations with relapsing patients, to ensure that the prescribed regimen is being adhered to. There is also a need for improved health literacy and patient education, permitting an informed dialogue between patient and physician. This could facilitate a better agreement on the proposed treatment regimen, and potentially lead to increased adherence.

Further studies are needed to optimise the application of the necessity–concerns framework in the clinic, but the potential benefits of such an approach could provide significant improvements, for both patients and healthcare providers, in the management of UC.

**Authors' declaration of personal interests:**

Dr Kane has served as a consultant to Warner Chilcott UK Ltd, Ferring Pharmaceuticals and Shire Pharmaceuticals Group plc, and has received research funding from Shire Pharmaceuticals Group plc.

Dr Robinson has served as a speaker, a consultant or an advisory board member for Procter & Gamble Pharmaceuticals Ltd, Warner Chilcott UK Ltd, Ferring Pharmaceuticals Ltd, Dr Falk Pharma GmbH, Abbott Laboratories Ltd, and Chiesi Ltd.

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**FIGURE LEGENDS**

**Figure 1.** Traditional approaches and emerging concepts in the identification and prediction of non-adherence. (A) Traditional approach: adherence is dependant on a wide variety of factors, of which no one predominates.<sup>12</sup> Adapted and reprinted with permission from the *Journal of Managed Care Pharmacy*. Copyright © 2008, Academy of Managed Care Pharmacy (B) Emerging concept: non-adherence can be divided into intentional and unintentional, both of which are influenced by practical and perceptual barriers

**Figure 2.** Attitudinal analysis. Based on their beliefs and concerns, patients can be classified into four distinct attitudinal groups.<sup>22</sup> Repinted with permission of John Wiley & Sons, Inc. Copyright © 2009, The Crohn's and Colitis Foundation of America, Inc

**Figure 3.** Adherence in patients with inflammatory bowel disease is correlated with attitudinal group. Analysis of survey results from 1871 patients with inflammatory bowel disease demonstrated the relationship between attitudinal group and adherence.<sup>22</sup> MARS-4, medication adherence report scale; \*p<0.001 versus accepting patients. Reprinted with permission of John Wiley & Sons, Inc. Copyright © 2009, The Crohn's and Colitis Foundation of America, Inc

## FIGURES AND TABLES

**Table 1.** Definitions of the key terms commonly used to describe the concept of non-adherence<sup>8</sup>

**Compliance** is defined as “the extent to which the patient’s behaviour matches the prescriber’s recommendations”.

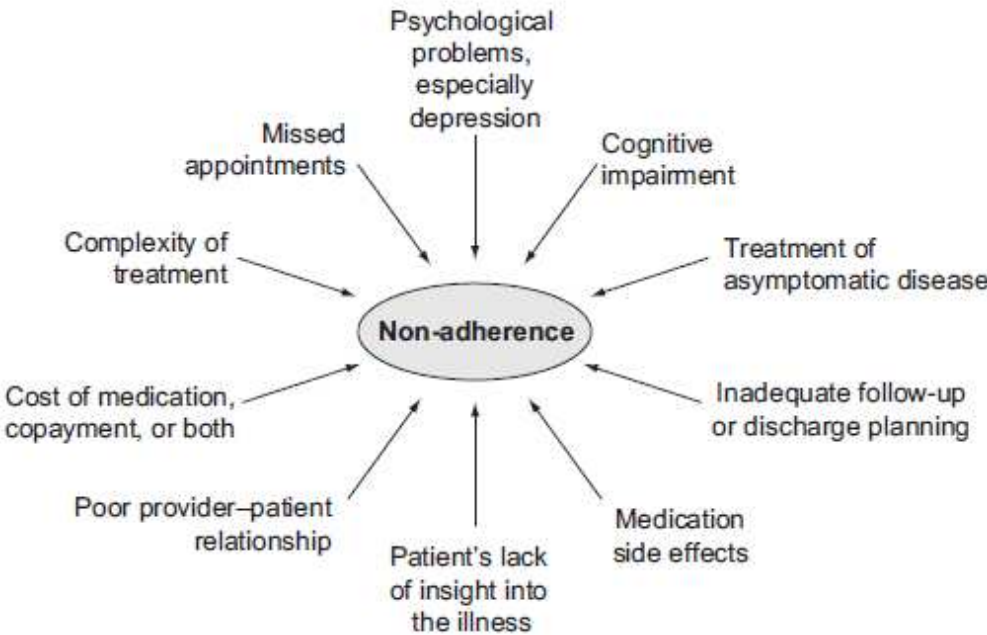
**Adherence** is defined as “the extent to which the patient’s behaviour matches agreed recommendations from the prescriber”.

**Concordance** is a relatively new concept, predominantly applied in the UK, defined as a two-way relationship between patient and physician, where treatment decisions are discussed and the treatment of choice is the one most acceptable to both parties.

**Persistence** is defined as the continued adherence over time to the prescribed medication.

Figure 1

A



B

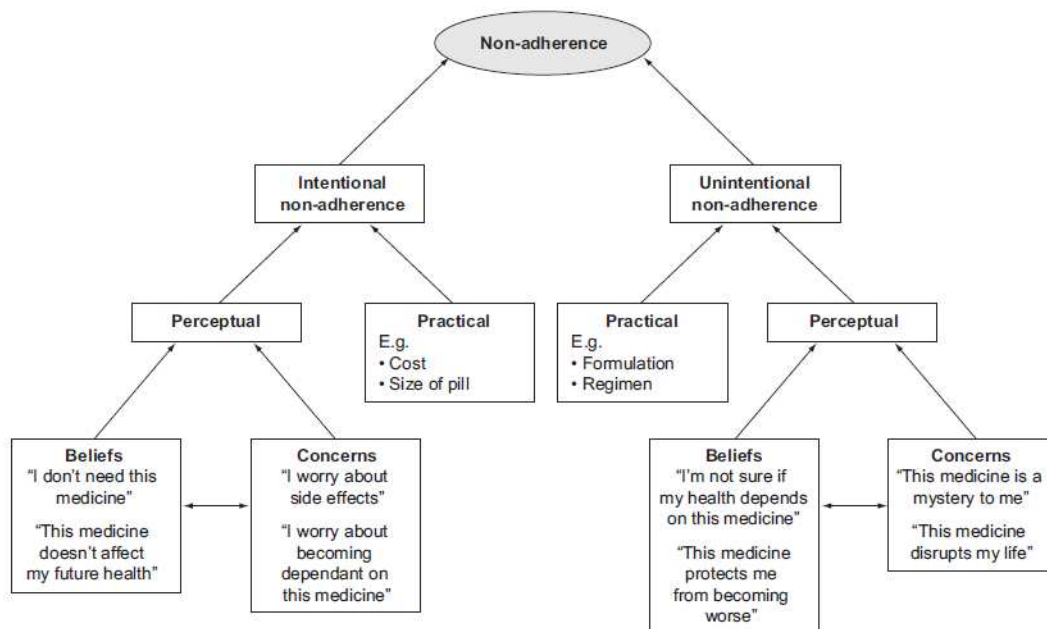


Figure 2

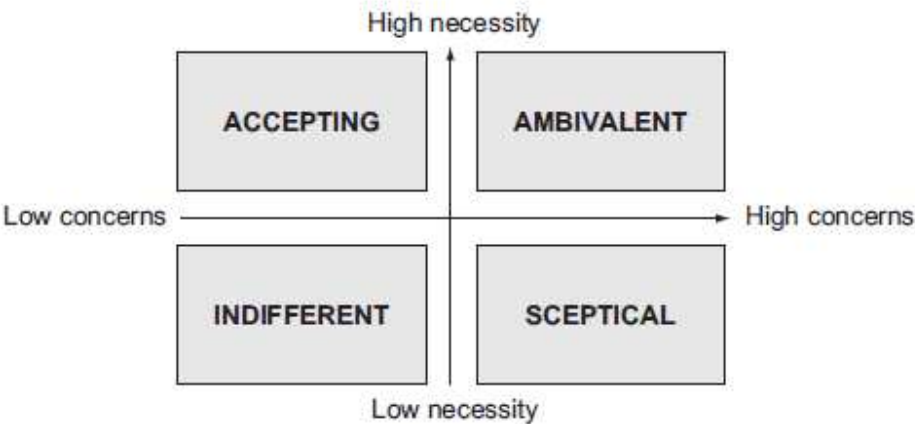
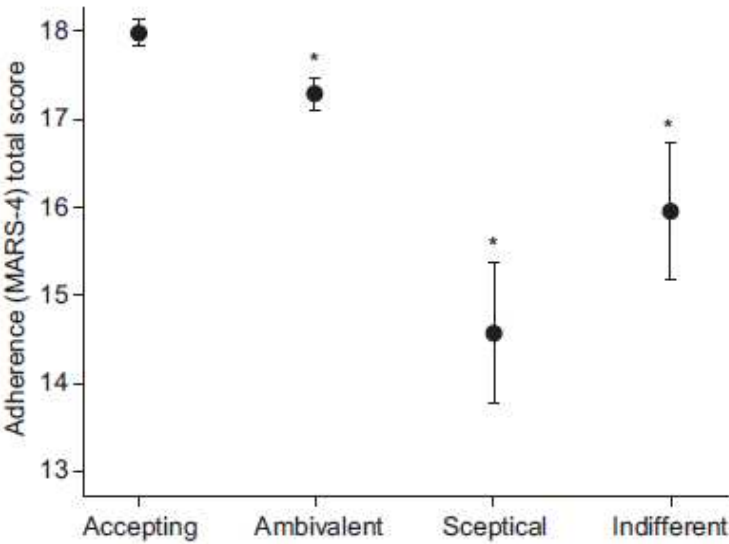


Figure 3



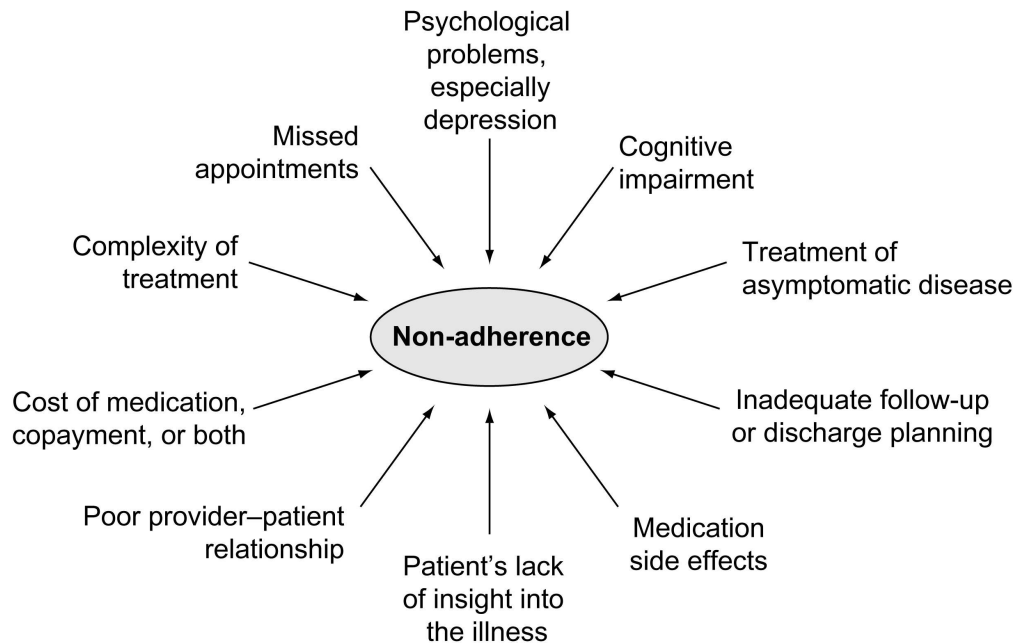


Figure 1. Traditional approaches and emerging concepts in the identification and prediction of non-adherence. (A) Traditional approach: adherence is dependant on a wide variety of factors, of which no one predominates.<sup>12</sup> Adapted and reprinted with permission from the Journal of Managed Care Pharmacy. Copyright © 2008, Academy of Managed Care Pharmacy (B) Emerging concept: non-adherence can be divided into intentional and unintentional, both of which are influenced by practical and perceptual barriers

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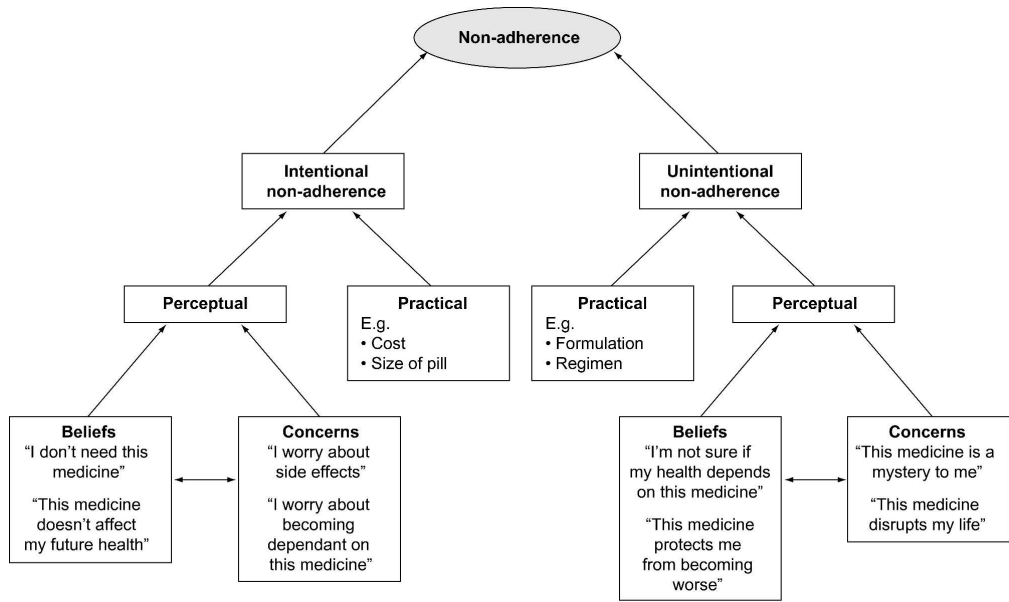


Figure 1. Traditional approaches and emerging concepts in the identification and prediction of non-adherence. (A) Traditional approach: adherence is dependant on a wide variety of factors, of which no one predominates.<sup>12</sup> Adapted and reprinted with permission from the Journal of Managed Care Pharmacy. Copyright © 2008, Academy of Managed Care Pharmacy (B) Emerging concept: non-adherence can be divided into intentional and unintentional, both of which are influenced by practical and perceptual barriers

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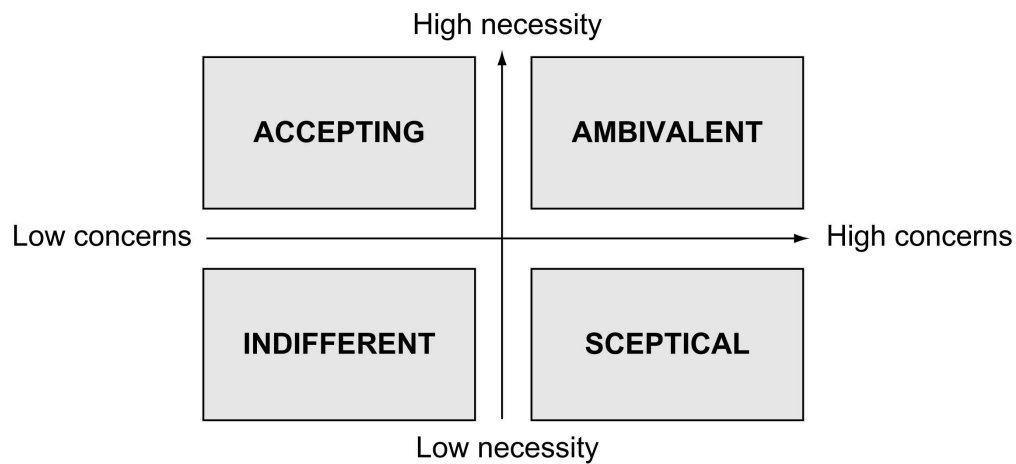


Figure 2. Attitudinal analysis. Based on their beliefs and concerns, patients can be classified into four distinct attitudinal groups.<sup>23</sup> Repinted with permission of John Wiley & Sons, Inc. Copyright © 2009, The Crohn's and Colitis Foundation of America, Inc  
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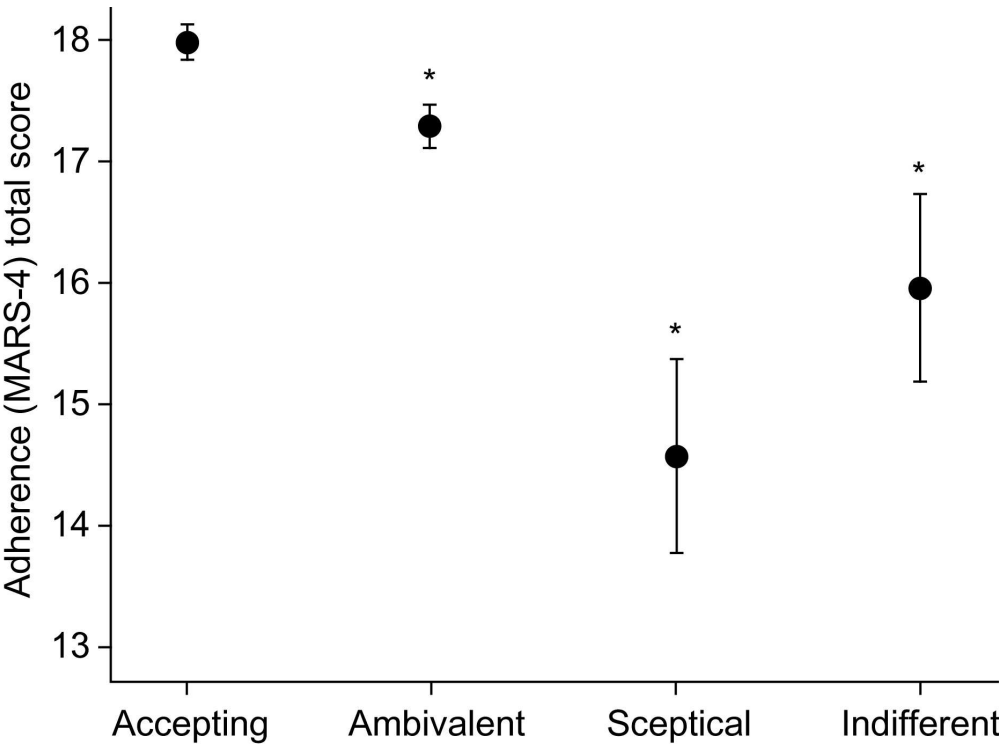


Figure 3. Adherence in patients with inflammatory bowel disease is correlated with attitudinal group. Analysis of survey results from 1871 patients with inflammatory bowel disease demonstrated the relationship between attitudinal group and adherence.<sup>23</sup> MARS-4, medication adherence report scale; \*p<0.001 versus accepting patients. Reprinted with permission of John Wiley & Sons, Inc. Copyright © 2009, The Crohn's and Colitis Foundation of America, Inc 78x58mm (600 x 600 DPI)