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Medication adherence to 5-aminosalicylic acid therapy in patients with ulcerative colitis

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Tetyana Moshkovska MD

Department Health Sciences

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“To write prescriptions is easy, but to come to an understanding of people is hard”

Franz Kafka 1916

Medication adherence to 5-aminosalicylic acid therapy in patients with ulcerative colitis

Author: Tetyana Moshkovska

Abstract

5-aminosalycilic acid (5-ASA) therapy is effective for maintaining remission in patients with ulcerative colitis (UC) and may also reduce colorectal cancer risk. However, medication non-adherence is a known barrier to the effectiveness of prescribed regimes and there is a lack of evidence about methods of improving adherence to 5-ASA treatment. This research programme addressed the hypothesis that adherence can be improved by a multi-faceted intervention tailored to individual patient needs.

A qualitative study identified that important determinants of adherence to 5-ASA medication are: information provided, patient beliefs and the patient-clinician relationship. Adherence can change over time; the study highlighted the need for reinforcement and the fact that health care professionals have a crucial role to play in this dynamic.

A cross-sectional study confirmed the difficulty of accurately assessing medication adherence. The two measures used (self-report and urine analysis) were not correlated, phi correlation 0.029 ($p = 0.725$). Logistic regression identified a significant association between self-reported non-adherence and: younger age [OR for increased age 0.954, 95% CI 0.932–0.976] and also doubts about personal need for medication (OR for BMQ – Specific Necessity scores 0.578, 95%CI 0.366–0.913). For non-adherence based on urine analysis, only South Asian ethnicity was independently associated with non-adherence (OR 2.940, 95%CI 1.303–6.638).

A randomised controlled trial showed that a multi-faceted, tailored intervention (including an opportunity for patients to select reminder devices from a range offered) had a significant positive impact on maintaining adherence levels in the intervention group ($p=0.001$), with a 44% difference between adherence levels in the two groups at follow-up. Changes in questionnaire scores suggested a positive effect of the intervention on satisfaction with information ($p<0.001$). The intervention was feasible, and was acceptable to patients. The multi-faceted approach studied has potential for implementation in routine care for enhancing persistence with 5-ASA and thus improving patient outcomes.

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Publications

The following work relating to the content of this thesis has been published or has been accepted for publication and has been authored by me.

Original articles:

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Moshkovska T, Stone MA, Clatworthy J, Smith RM, Bankart J, Baker R, Wang J, Horne R, Mayberry JF. An investigation of medication adherence to 5-aminosalicylic acid therapy in patients with ulcerative colitis, using self-report and urinary drug excretion measurements*. Alimentary Pharmacology & Therapeutics.* 2009; 30 (11-12):1118-1127.

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Review article:

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Moshkovska T, Stone MA, Smith RM, Bankart J, Baker R, Mayberry JF. Impact of a tailored patient preference intervention in adherence to 5-aminosalycilic acid medication in ulcerative colitis: results from a randomised controlled trial. *Gut* 2010; 59 (Suppl III): A302. Presented at the 18th United European Gastroenterology Week (UEGW) 2010, Barcelona, October 23-27. Abstract: P0970.

Moshkovska T, Mayberry JF. Patient choice of pill box organisers in a randomised controlled trial (RCT) medication adherence in ulcerative colitis (UC). *Gut* 2010; 59 (Suppl III): A303. Presented at the 18th United European Gastroenterology Week (UEGW) 2010, Barcelona, October 23-27. Abstract: P0971.

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Abbreviations

5-ASA	5-Aminosalicylic acid
BAN	British Approved Name
BMQ	Beliefs about Medication Questionnaire
CRC	Colorectal cancer
$Fe(NO_3)_3$	Ferric nitrate
$FeCl_3$	Ferric chloride
GEEs	Generalised estimating equations
GH	General Harm
GO	General Overuse
HPLC	High-performance liquid chromatography
IMD	Indices of Multiple Deprivations scores for England
INN	International Nonproprietary Name
MMX	Multi Matrix System technology
MRC	Medical Research Council
NCPIE	National Council on Patient Information and Education
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
RCT	Randomised controlled trial
SA	Salicylic acid
SASP	Salicylazosulphapyridine
SC	Specific Concerns
SIMS	Satisfaction with Information about Medicines Scale
SN	Specific Necessity
SP	Sulphapyridin
UC	Ulcerative colitis
USAN	United States Adopted Name
WHO	World Health Organization
WIMD	Indices of Multiple Deprivations for Wales

Chapter 1

Introduction and guide to the thesis

1 Chapter 1: Introduction and guide to the thesis

Ulcerative colitis (UC) is a debilitating disease requiring lifelong treatment. Drugs containing 5-aminosalicylic acid (5-ASA) also known as Mesalazine (an International Nonproprietary Name (INN), a British Approved Name (BAN)) or Mesalamine (the United States Adopted Name (USAN)) have a well established role in the management of this condition. They provide some benefits in active disease, but are of particular value when taken regularly, as this reduces relapse rates. Adherence to 5-ASA medication should be viewed within the wider context of concordance between prescriber and patient. Its importance lies in better control of the disease in terms of reduced frequency of flare-ups, and also possible reduction of colorectal cancer (CRC) risk. However, the reasons for non-adherence to 5-ASA maintenance therapy are not entirely understood. Perceptual, practical and combined interventions have been suggested as methods which might influence adherence in general, but there is a lack of evidence about effective approaches relating to 5-ASA treatment in UC.

The research programme described in this thesis was designed with the overall aim of investigating barriers to 5-ASA medication adherence in UC and methods of overcoming these barriers. The hypothesis underlying the overall programme of work presented in this thesis can be summarised as follows:

- non-adherence is a known barrier to 5-ASA therapy effectiveness;
- factors responsible for poor adherence can be identified and addressed;
- a complex intervention addressing both practical and perceptual barriers, specifically tailored to the needs of individual patients, could lead to improved adherence to 5-ASA medication.

To address this hypothesis, the research programme described in the thesis comprised three main studies, representing the first two phases of the framework for the design and evaluation of complex interventions, as recommended by the Medical Research Council (MRC) guidelines (1), (2). A collaborative analytical chemistry research project with Department of Chemistry, Loughborough University was essential part of the preliminary work in terms of investigating methods of evaluating the intervention, and is also described in this thesis.

Figure 1.1 shows sequential phases of this research programme represented by reviews of the literature, including relevant theories (Preclinical phase), plus studies with different experimental designs and methods: a qualitative study and a cross-sectional quantitative survey, applied analytical chemistry research (Phase I), and an exploratory randomised controlled trial (RCT) (Phase II).

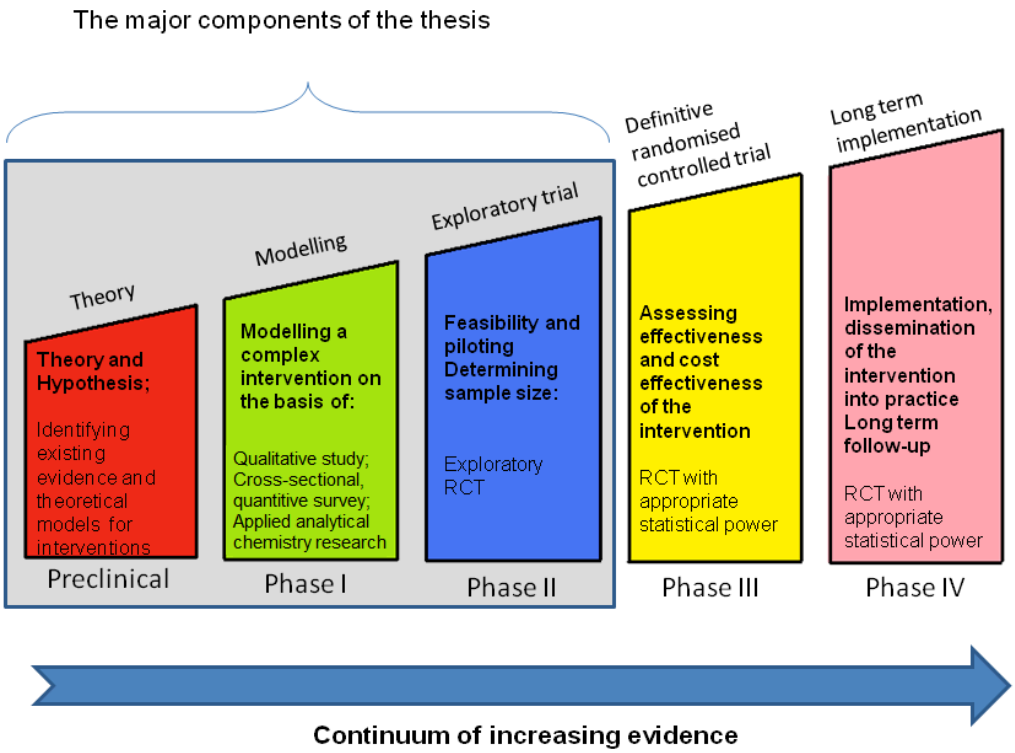


Figure 1.1: Sequential phases of the research programme illustrating the studies described in the thesis

Adapted from MRC guidelines: Campbell M, *et al. BMJ* 2000;321:694-696 & Craig P, *et al. BMJ* 2008;337:979-983.

The aims and justification for the empirical studies are described more fully in the course of the thesis but, briefly, the aims were:

- to identify and explore the reasons why patients fail to take prescribed 5-ASA medications;
- to determine levels of adherence to 5-ASA therapy in a range of communities, including the South Asian population in Leicester;

- to develop a package of interventions, which might increase adherence to 5-ASA therapy;
- to test the efficacy of such a package of interventions through an exploratory RCT;
- to inform the management of patients with UC, by disseminating the findings of the research through publication in peer review journals and by making available the details of effective interventions (if demonstrated);
- to inform the design and conduct of possible future studies, for example, studies meeting the criteria for Phases III and IV of the MRC framework as shown in Figure 1.1.

Chapter 2 of this thesis offers an overview of the broad topic of UC and is followed by the second background chapter (Chapter 3), where the use of 5-ASA medication is reviewed. The third background chapter (Chapter 4) discusses the benefits of 5-ASA medication adherence in UC. Chapter 5 introduces the programme of empirical study and presents the preliminary qualitative study that begins to identify factors that may increase adherence. Chapter 6 presents an observational study with a cross sectional design. The quantitative survey described was used to further investigate the issues explored in the qualitative study. This included assessing the prevalence of, and factors associated with, non-adherence to 5-ASA therapy in a range of communities, including the South Asian population in Leicester, and testing

the qualitative findings for generalisability using a larger sample. The work presented in Chapter 7 was carried out in collaboration with the Department of Chemistry at Loughborough University. This was essential in order to achieve the aim of the overall project. The practical work was undertaken by MSc and BSc students from this department. My personal contribution to this collaborative project included: literature review, overall project design, data collection and analysis, interpretation of results. I was also responsible for supervising MSc students during the analysis of urine samples within the clinical laboratory at Leicester General Hospital. This chapter describes the development of an analytical method for the determination of 5-ASA and its metabolites in urine. Chapter 7 also briefly describes a pilot pharmacokinetics study and the development and evaluation of a dipstick test for assessing adherence to 5-ASA medication. Chapter 8 presents existing evidence regarding adherence enhancing strategies, including theories underpinning these strategies; it also describes the development of the adherence enhancing intervention to be tested in the RCT. The final phase of the overall programme of work is described in Chapter 9. This chapter presents an exploratory RCT designed to test the effectiveness of the adherence-enhancing intervention. Finally, Chapter 10 summarises the main findings of the thesis, reflects on the programme of work and makes recommendations for the future use of complex adherence enhancing interventions.

Chapter 2

Background 1

An overview of ulcerative colitis

2 Chapter 2: Background 1 – an overview of ulcerative colitis

2.1 Introduction

In order to provide an overview and background information on the complex topic of 5-ASA medication adherence in UC, an exploratory literature review was conducted. PubMed, Medline, Cochrane Library, MEDLINE, EMBASE, International Pharmaceutical Abstracts (IPA), PsycINFO (all via OVID) databases were searched for studies published in English. Relevant articles and abstracts identified by Google searches and from my personal collection were also reviewed.

Articles were identified utilising multiple subject orientated search terms, such as: UC, IBD, colorectal cancer, 5-ASA, mesalazine (mesalamine), adherence, compliance, medication and UC, adherence enhancing interventions and health behaviour theories. Initial searches were not limited by publication date, in order to gain as many articles as possible. The citations identified were then filtered by relevance, including both historical interest and contemporary evidence.

The literature review has been divided into four background chapters. Chapter 2 is the first of four background chapters. This chapter provides an overview of the topic of UC. Specific areas covered include epidemiology and

aetiology, pathological and clinical features, medical management and prognosis. The second background chapter (Chapter 3) presents a history of 5-aminosalicilate development. The third background chapter (Chapter 4) discusses the benefits of 5-ASA maintenance therapy, together with the challenges in maintaining 5-ASA medication adherence. The fourth background chapter (Chapter 8) identifies existing concepts and theories relevant to adherence enhancing strategies.

2.2 Description of ulcerative colitis

UC is an inflammatory chronic relapsing and remitting disease primarily affecting the colonic mucosa; the extent and severity are variable. In its limited form UC may be restricted to the distal rectum, while in its most extended form the entire colon is involved (3). UC is a form of inflammatory bowel diseases (IBD), which is a general term for a group of chronic inflammatory disorders of unknown aetiology involving the gastrointestinal tract.

In 1859 Samuel Wilks was the first clinician who suggested that idiopathic colitis should be considered in a different category from specific epidemic dysentery when he described the “morbid appearance in the intestine of Miss Isabella Banes” (4). Wilks’s autopsy of this 42 year-old woman who died after several months of diarrhoea and fever demonstrated a transmural ulcerative inflammation of the colon and terminal ileum, originally designated as “simple

ulcerative colitis" (4). In1875 Wilks and Moxon (5) described ulceration and inflammation of the entire colon, which was anatomically indistinguishable from dysentery, in a young woman who had succumbed to severe bloody colitis. However, it was not caused by dysenteric pathogens. Later, Sir William Hale-White reported upon occasional patients with severe ulceration of the colon not due to tuberculosis, typhoid fever, or malignant disease. The origin remained obscure and he felt this condition should not be confused with bacillary dysentery (6). By 1909, 317 patients had been admitted to seven London hospitals with an inflammatory and ulcerative disease of the colon (7). Work on the recognition of UC was confirmed later (1921) by Sir Arthur Hurst (8). He suggested that a diagnosis of UC can only be made with the sigmoidoscope and gave the most complete description of the disease: "UC can be recognised at the first glance, but the appearance it presents is indistinguishable from that of bacillary dysentery. On the other hand, amoebic dysentery presents a quite distinctive picture. The disease seems always to originate in the most distal segment of the colon and to persist there longer than in any other part" (9). "The mucous membrane is bright red and thick, the swelling being particularly obvious. It bleeds very readily when touched. Superficial ulcers are invariably present, but in early cases they may be so small that they are difficult to recognise" (9).

2.2.1 Case definition

International diagnostic criteria have been agreed for ulcerative colitis (10), (11). They are based on symptomatology, histology and radiological findings.

The criteria for case definition outlined by Truelove and Witts in 1955 (12) allow valid comparisons of epidemiological data between countries and between studies. They include:

(i) an acceptable clinical history, namely passage of blood and mucus with or without diarrhoea

(ii) a history of remission or relapse or a chronic continuous course with or without symptom-free intervals for a period of 3-6 months and

(iii) at least one endoscopic examination showing features characteristic of inflammatory changes and histopathological feature of UC.

2.2.2 Epidemiology and aetiology

UC is traditionally considered to be common in the Western World with an incidence varying from 6 to 15 cases/ 100,000 population/ year (13), (14), (15), (16) and the prevalence of the disease in the community is approximately twelve times this figure (70 to 150 per 100,000). The incidence of UC has increased dramatically between World War II and 1980s (17). The incidence has remained steady between the 1950s and 1990s. However, during the past decades, the incidence pattern has change dramatically in geographic distribution (from 0.5 to 24.5 per 100,000/year), and particular changes in incidence over time within one area (18). The highest incidence rates are traditionally reported in Northern and Western Europe as well as North America (18), whereas lower rates are recorded in Asia, including Japan (19) and China (20). Data from the UK indicate a plateau with an UC incidence around 10-14 per 100,000/year (21). In contrast, recent data from

South Europe (22), East Europe (23) and Asia (24) in the mid-1990s report a rise in incidence in some areas already comparable to rates reported from Northern Europe and North America. Evidence demonstrates that the gap between areas with conventionally high and low incidence rates has diminished (25). There is still a lack of data from Latin America, Africa and Australia.

Colitis primarily affects young adults between 20 and 40 years old but it may present in any age group. Women tend to be affected more often than men but recent studies have failed to find a sex difference (26), (27). There is some evidence for ethnic variation in the disease. The disease is more common in Caucasian than in Black and Asian people (28). Several studies have shown an increased risk for ulcerative colitis in people of Jewish origin living in Western communities, with a prevalence of 37.1/ 100,000 (29), (30), (31). However, in Israel itself the prevalence is lower than in non-Jews in the United States or Western Europe. Moreover, in Israel, American and European-born Jews have double the incidence of those born in Africa, Asia or Israel (32). Migrant studies have shown that UC incidence is at least as high in subjects originating from South Asia living in the UK than in native British subjects (33), and has increased recently (34), thus suggesting that the British way of life increases the incidence of UC in migrants from Asia. This implies that environmental factors such as diet and smoking may be important.

While the exact aetiology of UC remains unknown, interplay of genetic, environmental, and immunologic factors are believed to play contributory roles in disease pathogenesis (35). The main suggestions as to its cause include infection, an allergic response to dietary components, immune reaction to bacteria or self antigens and an abnormality of the epithelial cells lining the gut. Environmental factors which also play a part include smoking and the oral contraceptive pill (36).

2.2.3 Genetics

A familial incidence of UC has been recognized for many years with approximately 10-20% of patients having at least one other family member affected (37). The general consensus is that most of the familial association is within first degree relatives. Other affected family members may have either Crohn's disease or UC, although the majority will have UC. A twins study by Tysk (38) demonstrated a much greater genetic influence in Crohn's disease compared to UC, with only one of sixteen pairs of monozygotic twins being concordant for UC and all twenty dizygotic pairs being discordant. Another study confirmed that disease concordance in monozygotic twins is only 19% in UC, as opposed to 50% in Crohn's disease (39).

2.3 Symptoms and signs

The leading initial symptom of UC is diarrhoea with blood and mucus, sometimes with abdominal pain (28) (Table 2.1). Other UC symptoms are less frequent.

Table 2.1: Frequency of initial symptoms in the course of UC

Symptoms	Frequency (%)
Diarrhoea	96.4%
Blood in stool	89.3%
Pain	81.3%
Generally unwell	40.2%
Weight loss	38.4%
Arthralgia	27.7%
Fever	20.5%
Skin changes	20.5%
Loss of appetite	15.2%
Ophthalmopathies	7.1%
Nausea	6.3%
Vomiting	4.5%
Abscesses	3.6%
Fistulae	3.6%
Lymph node swell	1.8%

Adapted from Ardizzone S. Ulcerative colitis. Orphanet encyclopaedia. September 2003: http://www.orpha.net/data/patho/GB/uk-UC.pdf1

Extraintestinal symptoms can be an initial manifestation or can occur later in the course of disease (28) (Table 2.2).

Table 2.2: Frequency of extraintestinal manifestations of the course of UC

Symptoms	Frequency %	Symptoms	Frequency %
All	**64-66%**		
Joints	**39.0%**	**Liver/Pancreas**	**16.8%**
Arthralgia	38.4%	Fatty liver	10.6%
Arthritis	11.3%	Hepatitis	1.8%
Ankylosing spondilitis	0.8%	Pericholangitis primary	3.5%
		Pancreatitis	2.7%
Skin	**15.9%**	**Eyes**	**9.7%**
Erythema nodosum	8.0%	Conjunctivitis	5.3%
Pyoderma Gangrenosum	7.1%	Iritis	4.4%
		Uveitis	0.9%

Adapted from Ardizzone S. Ulcerative colitis. Orphanet encyclopaedia. September 2003: http://www.orpha.net/data/patho/GB/uk-UC.pdf1

The prevalence of asymptomatic colitis may be as high as 34/100,000 (40), but when present the major symptoms include diarrhoea, rectal bleeding, the passage of mucus and abdominal pain. Generally their severity correlates with the severity of the disease. However, there is often a delay between the onset of inflammatory changes in the mucosa and the development of symptoms as active disease may be found at sigmoidoscopy in patients who are clinically asymptomatic. In addition, a delay in diagnosis may be compounded by late presentation as symptoms have usually been present for weeks or even months by the time a patient presents. The diagnosis can arise suddenly with no obvious cause or it may begin after a documented infection (e.g. salmonella) where the infection may have revealed pre-existing

silent disease or may have been the initiating factor. It may also present as intermittent episodes of diarrhoea and bleeding that were not of sufficient severity to cause the patient to seek medical attention. Disease of moderate or severe activity can lead to systemic symptoms including weight loss, fever, shortness of breath, ankle swelling and fatigue.

2.4 Assessment of disease severity

The severity of disease can be assessed by various techniques but the original scoring system was introduced by Truelove and Witts (12) and is considered to be a milestone on the road of evidence-based medicine. Truelove and Witts' index remains valuable and is simple and easy to use (Table 2.3).

Table 2.3: Truelove and Witts' disease severity index

Severity score	Mild	Moderate	Severe
Bloody stool/day	<4 streaks	4 or more	≥6 large
blood		obvious	amounts
Pulse	<90 bpm	≤90 bpm	>90 bpm
Temperature	<37.5 C	≤37.8 C	>37.8 C
Haemoglobin	>11.5 g/dL	>10.5 g/dL	<10.5 g/dL
ESR or	<20 mm/h	≤30 mm/h	>30 mm/h
CRP	normal	≤30 mg/L	>30 mg/L

Adapted from Truelove SC, Witts LJ. *B MJ* 1955; 2 (4947): 1041-1048.

2.5 Pathological and histological features

Initial pathological description of UC recognised the diffuse mucosal/ submucosal involvement, beginning in the rectum and rectosigmoid, and advancing proximally to involve the entire colon in a diffuse inflammation of the mucous membrane with chronic inflammatory cells, lymphocytes, plasma cells, and eosinophils, vascular congestion, goblet cell depletion, and crypt abscesses (41). The macroscopic features of UC are usually most severe in the rectum and extend proximally for variable distances along the colon. With mild inflammation the mucosa is hyperaemic, oedematous and granular (Figure 2.1).

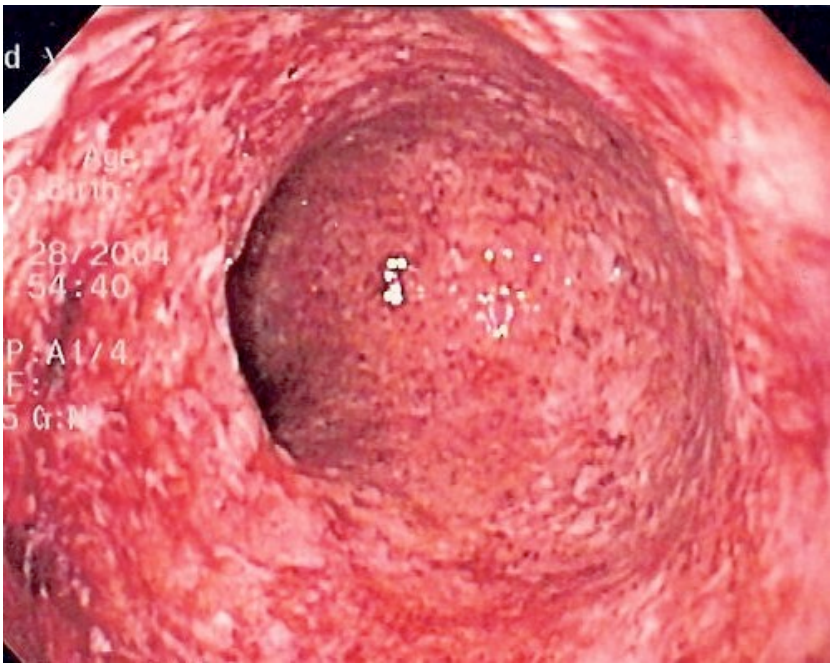


Figure 2.1: Abnormal colonic mucosa in ulcerative colitis

With severe disease, acute dilatation of the colon can develop where the bowel is thin and congested and this may lead to perforation. In most patients with severe disease punctate ulcers are seen which enlarge and extend to the lamina propria. In long-standing disease, pseudopolyps may occur as a result of exuberant epithelial regeneration. In remission the mucosa may look normal but over the years it becomes atrophic and featureless, which is accompanied by shortening and narrowing of the colon. Fibrosis is uncommon and strictures are rare.

Microscopically the changes are predominantly confined to the mucosa. The lamina propria is oedematous and capillaries are dilated and congested. There is an inflammatory infiltrate of neutrophils, lymphocytes, plasma cells, macrophages, eosinophils and mast cells. Neutrophils invade the epithelium leading to cryptitis and crypt abscesses with goblet cell depletion. Features suggesting chronicity include distorted crypt architecture, crypt atrophy, basal lymphoid aggregates and a chronic inflammatory infiltrate.

2.6 Complications

Patients with UC occasionally develop anal fissures, perianal abscesses or hemorrhoids, but the occurrence of extensive perianal lesions is more suggestive of Crohn’s disease. Significant haemorrhage is associated with severe attacks of the disease and if a patient requires six to eight units of

blood within 24 to 48 hours and is still bleeding, urgent colectomy must be considered.

An acute dilatation of the colon complicates about five percent of acute attacks and can be triggered by hypokalaemia or the administration of opiates. The most dangerous but rare local complication is perforation with a mortality rate in toxic megacolon as high as sixteen percent (42). About fifty percent of cases of acute dilatation recede with medical therapy alone but urgent colectomy is required for those who do not improve or deteriorate.

Colorectal cancer (CRC) has been recognized as the most serious long term complication of UC since the 1930s and cancer surveillance is one of the most difficult aspects of the management of colitis. Although the “true” cancer risk is unknown, patients with UC are estimated to have an approximately 11-fold increased risk for CRC compared with the general population (43) and there is a marked variation in the magnitude of the risk according to duration and extent of disease. There is a higher incidence of multiple cancers in UC compared with the general population and cancers in UC tend to be less well differentiated. Both duration and extent of UC are important risk factors for CRC, as is the presence of primary sclerosing cholangitis, family history of CRC, and early age at diagnosis of UC (44). Perhaps the most important risk factor is the duration of colitis. A review representing a meta-analysis of 116 studies revealed that the risk of CRC in UC is approximately 2% at 10 years, 8% at 20 years, and 18% at 30 years. This study also highlighted

geographical differences in the cancer incidence rate, for example, 5 per 1000 patient-years in the USA compared to 2 per 1000 patient-years in Scandinavia (45). However, the incidence of CRC in a Danish UC population study of 1161 patients was no higher than in the background population at 0.2% after 10 years, 1.4% after 20 years, and 3.1% by 30 years (46).

2.7 Medical management

Therapy for UC occurs in 2 steps. The first step is to induce remission and resolve all inflammatory symptoms, and the second is to maintain remission.

2.7.1 Induction

Aminosalicylates that contain 5-ASA [mesalazine] are the first agents for inducing remission in UC for patients with mild to moderate symptoms. The subject of 5-ASA therapy in UC will be reviewed in detail in Chapter 3. When 5-ASA therapy is inadequate or when symptoms of UC are moderate to severe, oral or topical administration of corticosteroids must be used to induce remission. Corticosteroids were introduced in the 1950s and they dramatically affected disease management along with improved supervision of fluids and electrolyte balance. The pioneer of controlled clinical trials was Sidney Truelove, who in 1955 published the first RCT on the effectiveness of corticosteroids in severe UC (12). Since then corticosteroids have proven beneficial orally as well as when used as topical treatments in the form of retention enemas, foams and suppositories. Prednisolone at a dose of 40 mg

or 60 mg daily is the usual initial corticosteroid prescription. When orally administered prednisolone is not effective, so patients must be hospitalised and treated with corticosteroids intravenously. If the flare-up has not responded after 5 to 7 days of intravenous therapy, two options remain: intravenously administered ciclosporin or colectomy (47).

2.7.2 Maintenance

Once a patient is in remission, the goal of continued therapy is to prevent recurrence. The level of therapy that induced remission dictates the selection of therapy for maintenance. If, for example, 5-ASA compounds successfully controlled symptoms, then 5-ASA compounds will likely be adequate for maintenance therapy (48). Patients with UC limited to the distal colon often require topical administration of 5-ASA to induce remission. Previous research has shown that to maintain remission in these patients, the combination of oral and intermittent rectal mesalazine treatments with enemas or suppositories is necessary on a long-term basis (49).

If corticosteroids are necessary to induce remission, large doses (up to 4.8g daily) of mesalazine may be required to prevent relapse as corticosteroids are tapered (50). Both oral cortisone and prednisolone have been shown to be ineffective in maintaining remission (51) and prolonged prescribing of this therapy is also contraindicated because of side effects which include weight gain, hair growth, hypertension and osteoporosis.

Clinical researchers have studied immunomodulator therapy with 6-mercaptopurine (6-MP) or azathioprine to maintain remission in UC patients who have been unable to taper corticosteroids, despite mesalazine maintenance therapy. In a long-term outcome study complete remission was attained in 65% of patients taking 6-MP and partial remission was seen in 24% (52). Complete responders who discontinued immunomodulator therapy, however, had a high relapse rate (87%).

If intravenously administered ciclosporin was used to induce remission, a transition to orally administered ciclosporin is performed at the time of hospital discharge. Many experts suggest a further transition to 6-MP or azathioprine as maintenance therapies, over the next several months, because ciclosporin has not been an effective maintenance treatment and also because of its long-term toxicities.

2.7.3 Surgery

Approximately 25% of patients with severe colitis who fail to respond to medical therapy will require urgent colectomy (53). Clinical signs that suggest failing medical therapy include cessation of bowel movement, abdominal distension, progressive leukocytosis, and progressive hypoalbuminaemia. Surgery should be offered to all patients with severe symptoms who do not improve within a week of treatment with intravenously administered corticosteroids.

Several surgical options exist. The two most common choices today are proctocolectomy with ileostomy and total colectomy with ileoanal anastomosis. In previous years, total colectomy with ileorectal anastomosis was sometimes performed as well as proctocolectomy with the Kock pouch (continent ileostomy).

Elective surgery in UC can be done laparoscopically. The advantages of the laparoscopic approach are a shorter postoperative ileus and less narcotic requirement. Patients can generally be fed sooner, and shorter hospital stays have been reported (54).

Colectomy is indicated when UC is refractory to medical therapies or when it is fulminant and toxic megacolon or perforation are suspected (55). Toxic megacolon occurs in approximately 5% of severe attacks of ulcerative colitis. A final indication for surgery is the development of dysplasia or cancer.

2.8 Course and prognosis

UC is a chronic condition characterised by relapse and remission, the course of the disease can vary widely. Eighty percent of patients with UC have intermittent attacks of their disease but the length of remission varies between a few weeks and many years. Ten to fifteen percent will pursue a chronic continuous course, whereas the remainder will have a single severe

first attack which requires urgent colectomy (56). Spontaneous remission from a flare-up occurs in 20 to 50% of patients, but 50 to 70% have a relapse during the first year after diagnosis. A long-term study by the Copenhagen group showed that only 1% of patients had no relapses during the 18 years following presentation (57). The relapse rate is higher in younger patients and seems to decrease with increasing age (28).

The extent of disease partly determines severity and therefore the course of the disease. Proctitis and proctosigmoiditis affect approximately 46% of patients with UC (58). When inflammation extends to the splenic flexure, the diagnosis is of left-sided disease, which affects 17% of UC patients. In extensive UC, inflammation extends beyond the splenic flexure and may include the entire colon (pancolitis). Pancolitis accounts for approximately 37% of patients with UC and patients with pancolitis are more likely to have severe attacks than those with limited disease (59) (60). A study by Powell-Tuck showed that 29% patients who present with proctitis may subsequently extend their disease after nineteen years (61).

In a long-term study of 95 UC patients, Bresci and colleagues (62) found that although most of the patients experienced a relapse over the course of 10 years, those who had been diagnosed with distal colitis had a lower rate of relapse than those with more extensive disease.

2.9 Changing patterns in UC

Results of a 5-year population-based follow-up study from Norway (63) showed that the disease course and prognosis of UC appears better than previously described in the literature (57), (58), (61). The frequency of colectomy in this study population was low (7.5%) and a relapse-free course was observed in 22% of the patients. The population-based study of changes in the clinical presentation, course, and prognosis of IBD during the last 5 decades in Copenhagen, Denmark (64), revealed a milder initial course of UC in recent years, the introduction of immunosuppressive drugs–only had a minor impact on initial management of the disease. The long-term prognosis remained fairly stable, with no increased risk of CRC or death in patients with UC (65).

Overall mortality associated with UC has diminished markedly from 37% in 1963 (56) to less than 1% in 1978 (66). This decline in mortality is probably related to early interventions, improved surgery and the use of corticosteroids and 5-ASA maintenance. Several studies have shown a normal life expectancy, although there is a slight but significant increased mortality (2%) in the first year after diagnosis (58), (61), (67), (68). A population based study of over 1,000 cases in Leicestershire had similar results with an overall standardized mortality ratio of 0.93 (95% CI 0.75 to 1.1(69), (33).

A steady increase in the incidence of UC has occurred. This may be due to an increase in uptake of medical care and developments in diagnostic

techniques. If hospital admission is an indication of severe disease then the frequency of life threatening fulminant UC seems to be less (70). This would be consistent with earlier diagnosis and better treatment of more patients with less severe disease (71).

The incidence of CRC in UC seems to be decreasing and mortality in UC is equivalent to that of the general population (72). The improved prognosis in UC could be due to a chemopreventive effect of the medications used.

2.10 Concluding remarks

This chapter has presented a broad overview of the disease that is the topic of this thesis, in order to provide context for the studies described in later chapters. The next chapter reviews more specifically the development and the therapeutic use of 5-ASA in UC.

Chapter 3

Background 2: 5-ASA therapy

3 Chapter 3: Background 2 – 5ASA therapy

3.1 Introduction

The previous chapter presented an overview of the broad topic of UC; in this second background chapter, the history of sulfasalazine and 5-aminosalicylates from the first serendipitous observation to the latest randomised clinical trials is reviewed.

3.2 History of sulfasalazine and 5-ASA

The history of the development of 5-ASA dates from the middle of the 20th century and the drug continues to be a topic for further research. The introduction of sulfasalazine by Nana Svartz (1890-1986), Professor of Medicine at the Karolinska Hospital in Stockholm (Fig.3.1) was a major milestone in the treatment of UC.

Figure 3.1: Professor Nana Svartz

Sulfasalazine was developed synthetically as a new therapy for rheumatoid arthritis (73). Professor Svartz decided to combine (via an azo-bond) sulphapyridin (SP), a drug that was active against bacteria, and 5-ASA that was active in connective tissue. Together with the pharmaceutical chemist, Philip Willsted, Professor Svartz produced the compound Salicylazosulphapyridine (SASP) (Fig.3.2) named sulfasalazine (73) (trade name Salazopyrin).

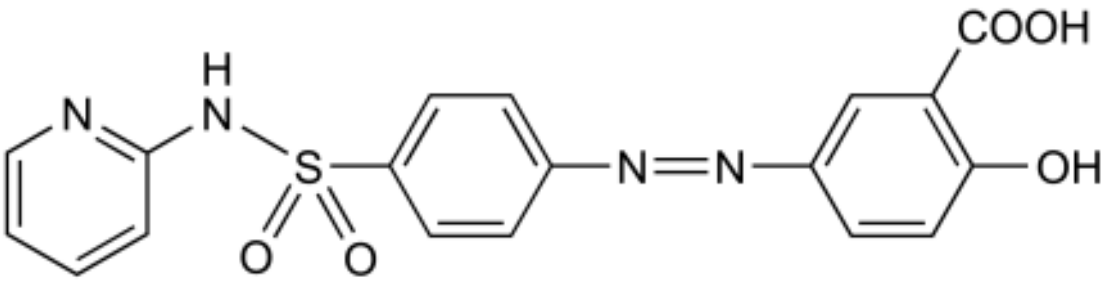


Figure 3.2: Salicylazosulfapyridine

During clinical work on the role of this new drug in rheumatoid arthritis, Professor Svartz and her colleagues found that patients with UC reported a significant improvement in their symptoms (73). Nanna Svartz continued to study SASP and published her first study of 124 patients in 1948 (74). This open study showed that most patients (70-80%) with mild to moderate UC responded well, but relapsed when the drug was discontinued. She suggested that SP was the active agent.

Dr Bargen of the Mayo Clinic introduced SASP in the Unites States and published a large-scale study of patients successfully treated with the new drug (75), (76). In Britain SASP became available only several years later and at the beginning it was not well accepted by doctors or patients due to its frequent side effects. These side-effects included headache, nausea, vomiting, jaundice, leucopenia, agranulocytosis and reversible oligospermia (77).

The first double blind, RCT of sulfasalazine was conducted in 1962 at St Mark's Hospital, London by Baron *et al* (76). Later, the same group of researchers showed for the first time that SASP at a dosage of 2 g/day administered as maintenance therapy for one year was much more effective than placebo in preventing relapses (78). A low incidence of side effects was also observed due to the use of a smaller dose.

The efficacy of SASP as maintenance treatment for up to 5 years was subsequently confirmed by Dissanayake and Truelove (79). The relapse rate in the SASP group was found to be 12%, compared to 54% in the placebo group ($p<0.001$). It was concluded for the first time that maintenance treatment of UC with SASP should be continued "indefinitely", unless contraindicated by side effects. The importance of these observations was particularly relevant from a clinical point of view as controlled trials had shown that corticosteroids were totally ineffective in reducing the number of

relapses (51), (80). SASP therefore became the drug of choice in maintenance treatment for UC throughout the world. However, the mechanism of action was still unknown.

3.3 Advances in the delivery of 5-ASA

In the early 1970s, studies on the distribution of SASP and its metabolites showed that most of SASP reached the colon intact where it was split by bacterial azo-reductase releasing SP and 5-ASA (81). The active component remained unknown.

Azad Khan and Truelove made a significant contribution to the history of 5-aminosalicylates in identifying that 5-ASA (Fig 3.3) was the therapeutic moiety of SASP (82).

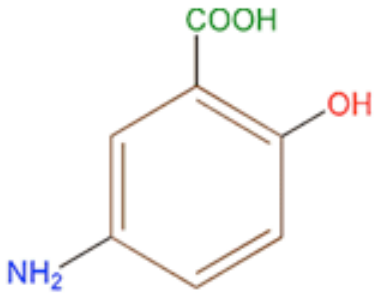


Figure 3.3: 5-ASA molecule

The problem of how better to target the release of 5-ASA in the colon by oral administration without the use of SP was then considered. Truelove experimented with a new compound called disodium azodisalycilate

(Olsalazine) consisting of two salicylate radicals linked by an azo–bond (83). At the same time Lennard-Jones and his team synthesized a pro-drug consisting of the inert compound 4-Aminobenzoylalanine linked to 5-ASA (Balsalazide) (84).

pH-dependent 5-ASA formulations were introduced in 1982 by John Rhodes from Cardiff, who found a gastro-resistant acrylic resin, Eudragit-S, that dissolved in an alkaline medium and therefore could be used to transport a capsule of 5-ASA to the terminal ileum and caecum (Asacol) (85). Another approach was to coat 5-ASA in ethyl-cellulose microspheres that allow slow release of the medication beginning in the duodenum and extend to the proximal colon (Pentasa) (86).

In early 2007, mesalazine with Multi Matrix System (MMX) technology (Liada, Mezavant) was approved for the induction of remission in mild to moderate colitis in a once-daily oral dose (87). This 5-ASA formulation utilizes MMX technology comprising lipophilic and hydrophilic excipients enclosed within a gastro-resistant, pH-dependent coating. The gastro-resistant film, covering the tablet core, delays the initial release of 5-ASA until is exposed to pH 7 or higher, which is normally in the terminal ileum. It is believed that a combination of the high dose of 5-ASA per tablet (1.2g) coupled with MMX drug delivery technology allows an effective quantity of 5-ASA to be delivered throughout the colon in a single daily dose.

Currently 4 types of formulation are available (Fig. 3.4):

1. Compounds that bind 5-ASA to a carrier requiring splitting of the diazo-bond by bacteria (Olsalazine and Balsalazide).
2. Compounds that are pH dependent (Asacol, Salofalk)
3. Time-controlled release microsphere (Pentasa)
4. Multi-matrix (MMX) system (Liada, Mezavant)

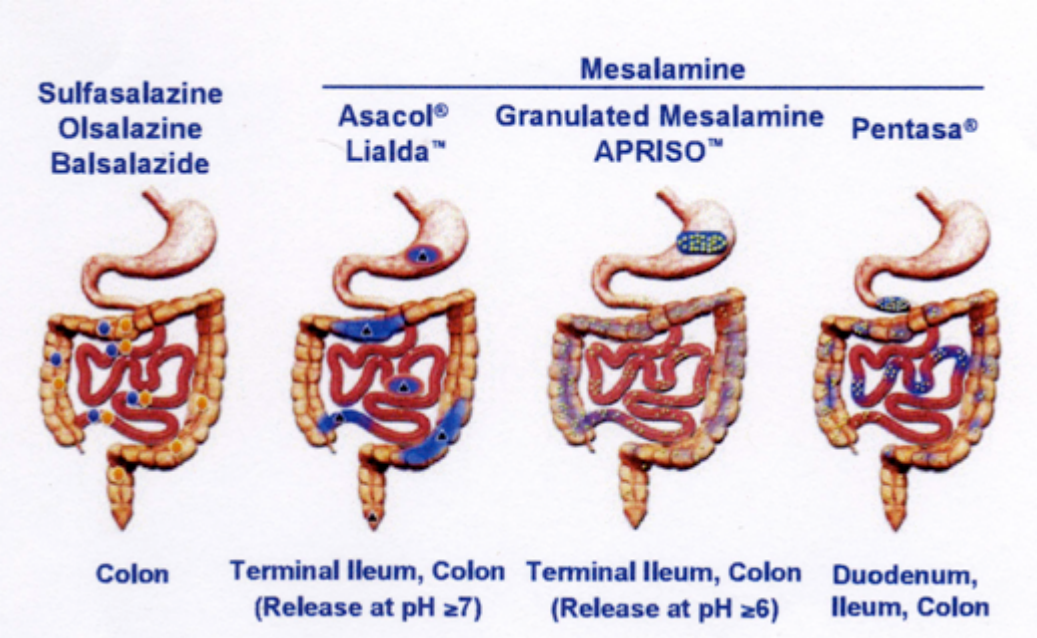


Figure 3.4 : Oral 5-ASA formulations: sites of delivery

Adapted from: Baumgart DC, Sandborn WJ. *Lancet*. 2007; 369: 1641-1657, and from Sandborn WJ. *J Clin Gastroenterol*. 2008; 42: 338-344.

3.4 Pharmacokinetics of 5-ASA

Previous research suggested (88) that all types of oral 5-ASA medication have comparable pharmacokinetics of systematic absorption and urinary excretion of 5-ASA and its metabolites, regardless of formulation and release

characteristics. The pharmacokinetics of 5-ASA is described in Chapter 7.2. This Chapter also presents a pilot pharmacokinetics study that was undertaken in order to confirm that determination of 5-ASA and N-acetyl-5-ASA urinary concentration by HPLC could be used as reliable objective measure of adherence.

3.5 Mechanisms of action of 5-ASA

The mechanisms of action of 5-ASA are numerous and not entirely understood. It has a potent inhibitory effect on a number of pro-inflammatory mediators released by the mucosa, including roms, leukotrienes, interleukin 1 and tumor necrosis factor alpha (TNFα) (89), (90), (91).

Recently it has been shown that the peroxisome proliferator-activated receptor gamma (PPARγ) is the major functional receptor mediating the common salicylate activities in IBD (92). PPARγ is a nuclear receptor which plays a central role in the regulation of the inflammatory signaling pathway, by inhibiting mucosa production of inflammatory cytokines. Recent studies have demonstrated that 5-ASA is a ligand for PPARγ and acts as a PPARγ agonist (93).

The action of 5-ASA is predominantly topical at the site of inflammation. Frieri *et al.,* demonstrated that the anti-inflammatory effect of 5-ASA was closely correlated to its mucosal concentration (94), (95). In order to obtain the best

therapeutic results, it is important to ensure topical availability of the drug on the inflamed mucosa rather than increasing the dose. Indeed, it has been demonstrated that increasing the dose of oral mesalazine did not result in a higher remission rate in UC (96), (97).

3.6 Concluding remarks

This chapter has reviewed the development and use of current 5-ASA formulations. The next chapter will discuss the clinical benefits of 5-ASA medications and importance of adherence issues in the treatment of UC.

Chapter 4

Background 3

Adherence to 5-ASA in ulcerative colitis

"Drugs don't work in patients who don't take them"

C. Everett Koop

4 Chapter 4: Background 3 - Adherence to 5-ASA in ulcerative colitis

4.1 Introduction

The previous chapter has reviewed the development and use of 5-ASA medication; this third background chapter presents an overview of adherence to 5-ASA therapy in UC. The clinical benefits of adherence are then considered, including the role of 5-ASA therapy in relation to remission and the possible role of mesalazine in the prevention of CRC.

4.2 Definition of adherence

Non-adherence to medication is very common and is a particular challenge in the treatment of long-term conditions. “Drugs don't work in patients who don't take them.” This famous observation by C. Everett Koop, former US surgeon general, is reinforced by the findings of a 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 illness, as many as 30-50% are non-adherent (98), (99).

A number of terms: compliance, adherence, concordance and persistence have been used to describe the concept of adherence. Horne *et al.* clearly defined the differences between these terms in their 2006 report for the

National Institute for Health Research (NIHR), (100) and the definitions are summarised in Table 4.1.

Table 4.1: Terminology commonly used to describe the concept of adherence

Terms	Definition
Compliance	The extent to which the patient's medication-taking behaviour matches the prescriber's recommendations
Adherence	The extent to which the patient's medication-taking behaviour matches agreed recommendations from the prescriber
Concordance	A relatively new and more complex concept, predominantly applied in the UK. Defined as a two-way relationship between patient & physician where the treatment decisions are discussed and the treatment choice is the one most acceptable to both parties
Persistence	The continued adherence over time to the prescribed medication, This term describes long-term aspect of adherence in chronic illness

Adapted from Kane & Robinson. *Aliment Pharmacol Ther.* 2010; 32: 1051-1058

In order to be consistent with the recommendations of the NICE and WHO reports, adherence is used as the term of choice in this thesis.

4.3 Rates of adherence

The rates of adherence with 5-ASA medication in clinical trial settings are 80% or more, but adherence rates in community-based studies are much lower ranging from 35% to 72% (101), (102), (103), (104), (105). The latest

results from a large UK pharmacy database have shown that only 30% of patients were adherent to mesalazine therapy (106). Moreover, non-adherence rates might vary considerably between countries. In Europe, a survey of 203 IBD patients identified self-reported non-adherence rates ranging from 13% in France, to 26% in Italy, 33% in the UK and 46% in Germany (107). In this study (107) the overall non-adherence rate was 29% across Europe, where non-adherence was defined as taking less than 80% of prescribed medication. Similarly high rates of non-adherence were reported in a study from Eastern Europe in which overall intentional non-adherence was reported by 38.9% of patients, and 18.6% of the patients discontinued their treatment at least once (102).

Research has shown that adherence rates not only vary between patients but also over time, patients who adhere to therapy during acute UC flares may become less adherent during disease remission (108). A study by Kane *et al* (109) showed that within the first 3 months of diagnosis, a time characterised by higher levels of disease activity, a rapid decline of nearly 40% in patients' medication refills was noted (57% were persistent over the full 3 months). This study showed that decline with time also occurred in the later, chronic, possibly asymptomatic phase, but at a slower rate (109).

Significant differences in adherence rates may exist in children and adolescents, given the complex development challenges unique to childhood and adolescence, including the maturation of cognitive and behavioural

patterns (e.g. health beliefs) that affect self-management. However, only a few studies have examined adherence rates in paediatric IBD, with the results indicating a prevalence of non-adherence ranging from 50% to 66% (110).

4.4 Measurement of adherence

A variety of measures have been used to determine adherence to 5-ASA therapy. Adherence has been measured by objective methods, such as observation of actual drug intake or assays of blood (111) or urine (112), (113). Other objective measures, based on the close correlation between salicylates and 5-ASA, have been used for assessing adherence to 5-ASA therapy (114). However, this test is not routinely available in clinical practice in the UK.

Subjective methods have also been utilised, such as questionnaires, pill counts, clinical questioning, diaries and electronic monitors. This variability has resulted in different estimates of the prevalence of non-adherence and diminished generalizability and validity of data (115).

Special attention should be paid to the method of assessment, because significant differences may be present when objective and self-report methods are compared. Two independent studies of adherence from the UK (112) and Spain (113) have shown a significant discrepancy between self-reported adherence and objectively measured adherence. In a recent paper,

Hommel *et al*., (116) reported an objective non-adherence frequency of 49% for 5-ASA medication, while self-reported non-adherence frequency was as low as 3%.

4.5 Predictors of medication non-adherence

The causes of medication non-adherence are multi-factorial and patients' decisions to adhere to treatment are dynamic and influenced by daily context (117). Traditional approaches to identifying and addressing non-adherence in UC were based on generalized strategies to divide variables associated with non-adherence into groups (such as demographics, treatment related and disease related). A review article (118) identified a number of factors associated with non-adherence in UC (Tab.4.2).

Table 4.2: Factors predicting medication non-adherence in UC

Demographic characteristics	Male gender Single status Younger age Full-time employment Education level
Treatment-related	Efficacy of the medication Three times or more daily dosing Four or more concomitant medications Medication side effects Rectal treatment Prescription costs
Disease-related	New patient status Disease duration Left-sided disease Depression Patient discordance Quiescent disease

Adapted from Hawthorne *et al. Aliment Pharmacol Ther.* 2008; 27: 1157-1166.

Other factors have also been linked to non-adherence, including the approach and attitude of the physician, patient beliefs about necessity of prescribed medication (119), (120). Impact of these factors on patient adherence will be discussed in Chapter 8.

Identifying risk factors that are predictive of non-adherence seems an attractive possibility; however, the largest systematic review challenged these previously-held concepts. This study noted specifically that none of the frequently measured demographic or clinical variables, as well as those related to treatment, were consistently associated with non-adherence (119).

It appears that demographic studies have provided contradictory evidence. For example, Kane *et al.* related poor adherence to male gender. In this study non-adherent patients were statistically more likely to be males (67% vs. 52% in adherent patients, retrospectively) (101). Conversely, in two recent studies, young females proved less adherent than males (110), (121), while other studies could not find a significant difference (122), (102), (110). A higher education level and full time employment was also associated with a non-adherent pattern of behaviour in some (102) (112), (121) but not all, studies (123).

Age seems to be an important factor, as younger patients tend to be less adherent than older patients (102), (113), (121), (103). In a recent Italian

study (122) non-adherence was significantly associated with cases under 40 years (43% vs. 34%, p= 0.041).

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 adherence (101), (103), (124). Conversely, Cerveny *et al*. reported that non-adherent patients were more likely to be chronically active or in relapse (p = 0.002) (102).

The studies specific to UC have failed to demonstrate a consistent significant relationship between dosing frequency and adherence (101), (125). 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 once daily dosing compared with twice daily (119). In addition, no significant differences in adherence have been found between the various oral 5-ASA formulations or different daily dosages.

Taken together, these data suggest that a wide variety of factors play a role in adherence. Therefore, identifying non-adherence, based on generalised strategies focusing on risk factors, is unlikely to reliably predict which patients are non-adherent and will not provide a universal solution to non-adherence in UC patients (108).

4.6 Patient barriers to adherence

It is useful to divide the barriers to adherence into those that are patient-related, physician-related, medication-related, and cost related (126), because each offers a potential point of intervention at which patient compliance can be targeted and improved (Tab.4.3).

Table 4.3: Barriers to patient adherence

Patient-related	Forgetfulness Disease denial Lack of perceived benefit of treatment
Physician-related	Poor interactional style Insufficient support/information
Drug-related	Complicated drug regime (i.e. number of tablets / frequency) Side-effects or fear of side-effects
Cost-related	Cost of prescription

Adapted from Kane SV. *Aliment Pharmacol Ther.* 2006; 23: 577-585

4.7 Clinical benefits of adherence to 5-ASA therapy

The clinical benefits of adhering to prescribed 5-ASA medication are well established in relation to prevention of UC relapse (101) and improving patients' quality of life (127) but there is also some evidence of benefit in relation to prevention of CRC (128), (129).

4.7.1 5-ASA adherence and disease relapse

The clinical outcomes of non-adherence can be detrimental to patients. A correlation has been demonstrated between poor adherence to maintenance 5-ASA therapy and increased frequency of relapses (Fig. 4.1). Kane and colleagues (101) prospectively followed 99 UC patients who had been in remission for more than 6 months and who were taking maintenance 5-ASA. The authors verified medication adherence rates based on pharmacy records, where non-adherence was defined as refilling less than 80% of the prescribed medication. Patients who were not adherent had a more than 5-fold increased risk of relapse than adherent patients (p=0.001). In total, 89% of adherent patients maintained remission over a 2 year period compared with only 39% of non-adherent patients.

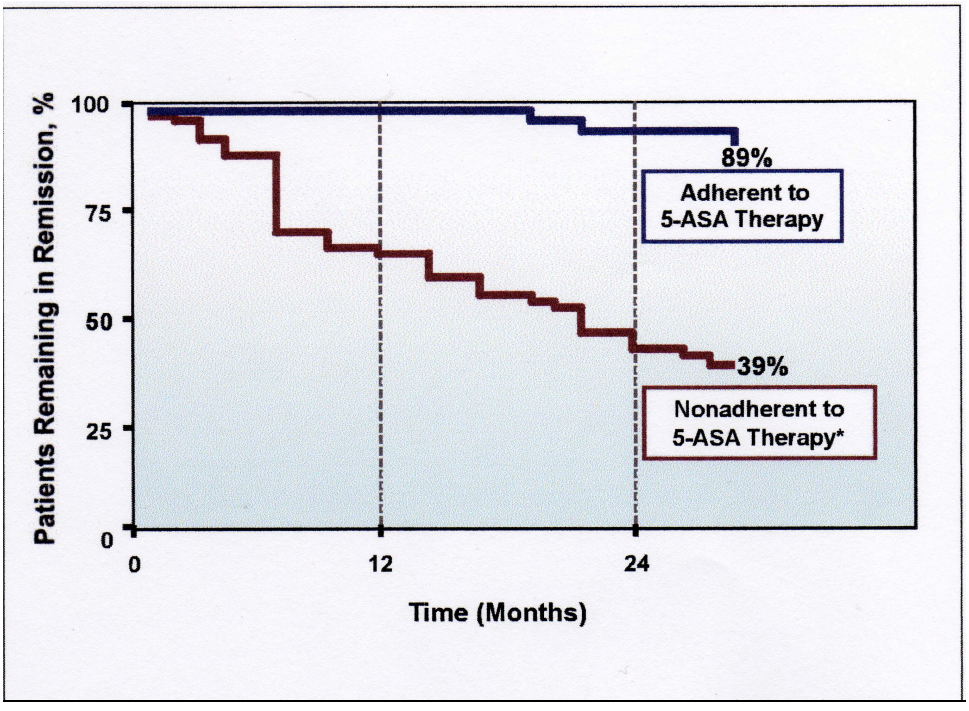


Figure 4.1: Non-adherence is associated with relapse in UC (p<0.001)
Adapted from Kane *et al. Am J Med*. 2003; 114: 39-43.

4.7.2 5-ASA adherence and risk of development of CRC

As mentioned in Chapter 2, CRC is the most serious long term complication of UC. Non-adherence to 5-ASA therapy has been linked to increased risk of developing CRC. Moody *et al.* (130) showed a correlation between non-adherence or discontinuation of sulfasalazine therapy and increased risk of colon cancer; in their study, 5 of 152 adherent patients and 5 of 16 non-adherent patients developed CRC ($p<0.001$)(130). This finding was supported by Eaden *et al*.(131), who conducted a case-controlled study of 102 cases of CRC in UC with matched controls, in which they found that CRC was reduced by 81% in patients receiving regular mesalazine therapy (≥1.2g/day) compared with those receiving no treatment ($p=0.006$) (131). In a study by Ullman *et al*. a daily dose of a least 2.4 g was required to prevent progression to advanced neoplasia. However, the protective effect was not seen in patients who already had low-grade dysplasia (132). A case-control study by Rubin *et al.* found that patients taking 5-ASA at a dosage of 1.2 g/day were 76% less likely ($p=0.024$) to progress to dysplasia or cancer (133). A large epidemiological study from the UK has confirmed the possible preventive effect of 5-ASA in UC patients. Van Staa *et al.* used a general practice research database to identify 18 969 patients, of whom 100 had developed CRC during 5-ASA exposure, most of these cases had a history of UC (76 patients) (134). These results show that regular 5-ASA use is associated with some reduction in the risk of CRC developing in UC. In an earlier study undertaken by the same authors it was noted that mesalazine

conferred CRC protection (OR 0.31, 95% CI 0.11-0.85), while sulphasalazine failed to do so (OR 0.73, 95% CI 0.35-1.50) (135).

In contrast, three negative studies have been published (136), (137), (138). These studies failed to demonstrate a chemoprotective effect of 5-ASA for the majority of patients. According to these results, neither sulfasalazine nor melsalazine use was protective regardless of duration of therapy.

Two recent studies, have provided additional information regarding chemoprotection by 5-ASA (139), (140). These studies accord with Van Staa *et al*., who found that 5-ASA use for less than 2 years was not associated with a significant reduction in CRC incidence (135).

Velayos and colleagues performed a systematic review and meta-analysis (128) of nine studies (3 cohort, 6 case-control) containing 334 cases of CRC, 140 cases of dysplasia and a total of 1932 subjects. Pooled analysis showed a protective association between use of 5-ASA and CRC (OR=0.51; 95% confidence interval (CI): 0.37-0.69) or a combined endpoint of CRC/dysplasia (OR 0.51; 95% CI: 0.38-0.69). 5-ASA use was not associated with a lower risk of dysplasia, although only two studies evaluated this outcome (OR=1.18; 95% CI: 0.41-3.43) (128).

In spite of this evidence suggesting that 5-ASA may be protective against dysplasia and CRC in UC patients, confirmatory randomised controlled trials

have not been reported. However, the drug may share similar molecular targets to other NSAIDs, with its close chemical similarity to aspirin (Chapter 7.4.2). Several sources of evidence suggest that 5-ASA has inherent chemopreventives properties (141), (142), (143) and that protection is not due to a general anti-inflammatory effect. These include studies of molecular targets (144), (91), (145) and the absence of a chemopreventive effect of other anti-inflammatory agents (131) used in IBD.

Because there is still no ideal treatment for CRC and 5-year relative survival rates is low (50% for male and 51% for female), (146) cancer prevention has become an increasingly important consideration in UC. Although the most effective strategy to prevent CRC in high-risk patients with UC is prophylactic colectomy, patients and physicians are generally unwilling to accept surgery as a routine preventive method (147). The second widely approved method is colonoscopic surveillance. Screening has been practised for about 40 years but has proven ineffective. Research has shown that surveillance leads to the detection of early-stage cancer in only a minority of patients and that a significant number of patients develop cancer at an advanced stage despite surveillance (148), (149). Moreover, most patients do not undergo appropriate screening. Research suggests that there is no clinical sense in waiting for “best evidence” that would prove a definitive chemopreventive effect of maintenance 5-ASA therapy. This is because discontinuation of 5-ASA treatment to perform a RCT would be unethical due to its proven efficacy for maintenance treatment of UC (150). Therefore, considering the

potential chemopreventive properties of 5-ASA, it could be postulated that effort would be better directed at ensuring patient adherence with treatment. Such an approach would be safe and cost effective (151) compared to colonoscopy and its attendant risk.

4.8 The impact of 5-ASA non-adherence in UC

Non-adherence with 5-ASA therapy has been associated with increases in disease flares, an impaired social life and poor quality of life (152). As noted above, the risk of clinical relapse is more than five- fold greater amongst individuals who are non-adherent to 5-ASA therapy than among those who are (101). As symptoms of UC are strongly associated with quality of life (153), (154), (155), (156) an increase in the frequency of relapse would probably lead to a concomitant reduction. Indeed, 5-ASA treatment has been shown to lead to improved quality of life in patients with mild-to-moderate active UC (127).

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. In the UK, a single centre retrospective study (157) of IBD patients showed individual patient costs ranged from £73 to £33 254, with a mean 6-month cost of £1256 (95% CI: £988, £1721) per UC patient. The high percentage of non-adherent patients who are at an increased risk of relapse is likely to

contribute to the overall high cost associated with the treatment of UC. Indeed, disease relapse was associated with a 2 to 3 fold increase in cost for non-hospitalized cases and a 20-fold increase in cost for hospitalized cases compared with quiescent cases of IBD (157). Another study of over 4000 UC patients receiving 5-ASA maintenance therapy demonstrated that non-adherence (defined as failure to refill prescriptions) is strongly correlated with higher healthcare costs, with non-adherence being associated with a two-fold increase in inpatient costs compared with adherent patients ($p<0.01$) (158). Figure 4.2 summarizes the impact of 5-ASA non-adherence in UC.

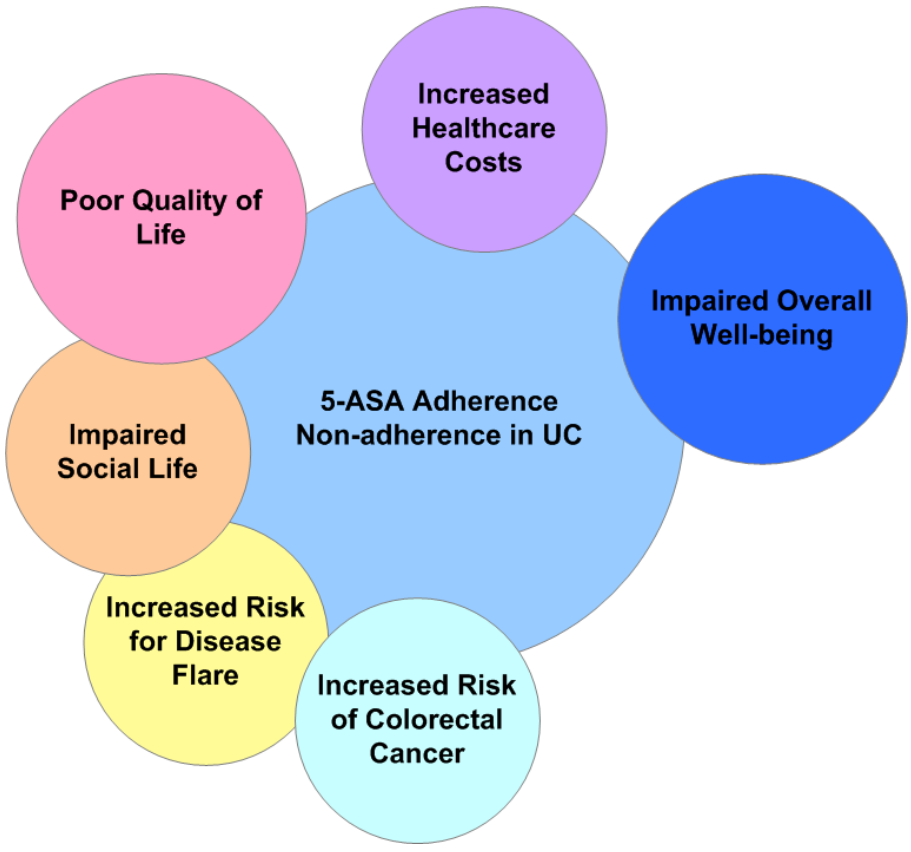


Figure 4.2: The impact of 5-ASA non-adherence in UC

Adapted from Beaulieu & Schwarz MedscapeCME Gastroenterology 2009; cme.medscape.com/viewprogram/30602

4.9 Concluding remarks

5-ASA medication non-adherence in UC patients is an important factor in predicting disease relapse, poor quality of life and is also associated with an increased risk of developing CRC in the long term. The result is increased healthcare costs. Hence, there are strong arguments both clinically and economically for developing strategies to optimise 5-ASA medication adherence in UC. The following Chapter 5 introduces the programme of empirical study and presents the preliminary qualitative study that begins to identify factors that may increase adherence.

Chapter 5

Introducing the programme of empirical study

Preliminary qualitative study

5 Chapter 5: Introducing the programme of empirical study. Preliminary qualitative study.

5.1 Introduction

This chapter introduces the programme of empirical study and presents the preliminary qualitative study. This study begins to identify factors that may increase adherence. The findings from this work provide insight into patient medication-taking behaviour, which subsequently influenced the design of the adherence-enhancing interventions.

5.2 Introducing the programme of empirical study

To summarise the evidence, presented in the background chapters, non-adherence to 5-ASA medication is an important challenge in UC management; therefore successful strategies to improve medication adherence are needed. In order to test the hypothesis that was outlined in Chapter 1, a research programme of empirical study was designed. This comprised 3 studies with different experimental design and methods:

- ➔ qualitative investigation
- ➔ cross-sectional, quantitative survey
- ➔ randomised controlled trial

with the overall aim of investigating barriers to 5-ASA medication adherence in UC and methods of overcoming these barriers.

5.3 Rationale, aims and objectives for qualitative study

Adherence research in IBD has focused mainly on quantification of the problem, with the exception of a few studies (123), (159), (102) that have attempted to identify the factors influencing non-adherence.

The rationale for this study was to gain insight into the factors leading to non-adherence to 5-ASA therapy, in order to enhance our understanding of patients' medication-taking behaviour and patient satisfaction with 5-ASA therapy in an everyday context. It was felt that knowledge of this type would be helpful in understanding and ultimately addressing the complex issue of 5-ASA medication adherence.

The objectives of this initial qualitative stage of the programme were to examine adherence to 5-ASA therapy by patients with UC in a range of communities; to identify and explore the reasons why patients fail to take medication; and to identify factors which might increase adherence. The overall aim was to inform the development of a package of adherence-enhancing interventions which would subsequently be tested for efficacy in a RCT.

In order to achieve the research aim, a qualitative method based on semi-structured interviews was selected. The choice of this approach was based on the fact that:

- a semi-structured interview allows the participant to describe what is meaningful or important to him or her using his or her own words rather than being restricted to predetermined categories, as is the case when using questionnaires or rigidly structured interviews;
- this approach would allow the researcher to probe for more details and ensure that participants have interpreted questions as intended;
- this approach would allow the researcher the flexibility to use the knowledge, expertise and interpersonal skills to explore interesting or unexpected ideas or themes raised by participants.

5.4 Materials and Methods

5.4.1 Approvals and setting

Approval for this study was sought and obtained from the West Midlands Multi-Centre Ethics Committee (ref. number 06/MRE07/9). The relevant R&D approvals were obtained at each site. Patients with UC receiving maintenance 5-ASA therapy were recruited from outpatient clinics at three hospitals in Leicester, Cardiff and Norwich between April and December 2006. All three cities have a detailed community-based register of patients with UC. Office of National Statistics data indicate that approximately 30% of the population of Leicester is of South Asian (mainly Indian) origin whereas in Norwich and Cardiff over 90% of the population is white British.

5.4.2 Sampling and recruitment

Quota sampling was used for purposive sampling based on obtaining data from a varied sample of people in terms of gender, age, ethnicity and time elapsed since diagnosis. A provisional target was to obtain up to 20 interviews in Leicester and a smaller sample in each of the other 2 sites, with the intention of basing the final number on continuing recruitment until saturation had been obtained in terms of the emergence of new themes. Patients with UC were eligible if they were aged 18-80 years, and on maintenance oral 5-ASA therapy. Potential participants were invited to take part in this study and patient information regarding the study was provided verbally and as a patient information sheet (Appendix 1). Participants were recruited from gastroenterology clinics of hospitals in the three cities on a sequential basis using our quota-sampling frame. Patients who took part provided written informed consent for their involvement in the research (Appendix 2). The interviews were all undertaken by myself, with the Leicester site selected for the first round of interviews followed immediately by the Cardiff and Norwich sites.

5.4.3 Data collection and analysis

All interviews were conducted face-to-face within the gastroenterology clinic environment; they were recorded onto audio tape and transcribed verbatim. The duration of each semi-structured interview was approximately 30 minutes. A topic guide was developed by members of the research team for

guidance in conducting the interviews, but this was a flexible instrument allowing scope for additional lines of discussion and revision to incorporate any additional emerging ideas into subsequent interviews. Care was taken to ensure a non-judgemental style (160), using open rather than closed questions wherever possible. The topic guide (Appendix 3) included areas for discussion such as time elapsed since diagnosis and currently prescribed treatment regime; patient self-assessment of medication taking behaviour; views and experiences relating to medication efficacy and any attendant side effects; patient self-assessment of the range and depth of information provided to them about UC (including 5-ASA chemoprevention in CRC development); and also experiences, behaviours and ideas relating to strategies for promoting medication taking behaviour.

A systematic qualitative research methodology grounded in the data was used to explore patients' experiences and the rationale for their medication-taking behaviour (161), (162). A constant comparative approach (163) to data collection and analysis was adopted, taking care to ensure that emerging themes and ideas were a true reflection of the data contained in the transcripts. Data collection and preliminary analysis (involving open coding and discussion between investigators) were carried out concurrently in order to facilitate revision of the topic guide where considered appropriate and to identify saturation in relation to emerging themes. QSR N5 computer software was used to initially open code the transcripts line-by-line using free nodes to ensure that emerging themes were grounded in the data (161),

(164). All interviews were open coded by myself and a proportion of the transcripts were also coded independently by one of the PhD supervisors. Codes identified by these two investigators were compared and used to develop a thematic framework by progressively focussing upon emerging key themes. Framework charting (164), (165) was subsequently used to summarise and organise the data for further analysis based on the key themes identified.

5.5 Findings

The main findings from the qualitative study are summarised below in terms of the key themes identified and explored.

5.5.1 Sample recruited

Twenty-seven patients (of 30 approached, 90% response) from the three sites were recruited in accordance with our quota sampling frame (Table 5.1). These comprised a heterogeneous sample varying in terms of ethnicity, age, sex and time elapsed since diagnosis. Seventeen patients were interviewed from the Leicester site, 4 from Cardiff and 6 from Norwich.

Table 5.1: Characteristics of patients interviewed

Total sample (N)		27
Gender:	Male	11
	Female	16
Age Distribution:	18-30 years	5
	31-45 years	9
	46-60 years	6
	60+ years	7
Time elapsed since diagnosis	1 – 3 years	8
	4 to 10 years	7
	11 to 20 years	6
	20+ years	6
Ethnicity	White	20
	Asian*	7
Oral 5-ASA Prescription Information		**N° of Patients**
	Asacol	11
	Colazide	3
	Pentasa	11
	Salazopyrin	2

*All from the Leicester site

One third of respondents had experienced a change in their prescription of proprietary 5-ASA compound.

Seventeen interviews were undertaken in Leicester, in order to meet the targets of our sampling frame with respect of heterogeneity; theoretical saturation in terms of emerging themes was observed after preliminary analysis. The interview series was concluded when data from Cardiff and Norwich proved consistent with themes identified in Leicester and it was agreed that overall saturation for the 3 sites had been reached.

This study showed that some patients can accept medication and follow the advice of healthcare practitioners without question. Only a few participants in this study followed advice without question. This group can be described as passive acceptors and amongst our interviewees all those in this category were noted to be over 60 years old. The majority of our interviewees are best described as active acceptors. Their decision making and medication taking behaviour are strongly dependent on the result of individual evaluation. Patients take into account the seriousness of their symptoms, the medication's anticipated effectiveness, the necessity of treatment, possible side-effects and their own experience. Personal experience along with understanding of their illness and its treatment form the foundations of patients' beliefs which consequently influence medication taking behaviour.

5.5.2 Balancing benefits and disadvantages

The dominant overall theme related to recognising and balancing the benefits and disadvantages of taking 5-ASA medication. Many patients were clearly convinced about the necessity of prescribed 5-ASA therapy for maintenance of benefits and prevention of flare-ups:

"I didn't have any flare ups for many years and I am happy with this. I will take my medication because I don't want to have any problems. I don't want to reduce the dose, I want to stay on it because it's doing so much good for me." [Interview 22, Norwich];

"*I never forget take my tablets because I don't want to become poorly again, I have suffered enough*." [Interview 17, Leicester].

They can be described as active acceptors after evaluation. For other patients, however, 5-ASA may be ineffective or may cause side effects or both. Patients had difficulty in appreciating the potential benefits of oral 5-ASA medication when they experienced unpleasant symptoms because these adverse effects of medication were important factors in their evaluation of treatment.

"*I took (Branded Mesalazine) tablets. They didn't make me any better and they made me really sick. I don't think that I will stay on it if the medication doesn't work for me."* [Interview 18, Cardiff]

Others perceived no benefit from taking 5-ASA compounds and consequently stopped taking them. These subjects may become rejecters because they are not convinced about the effectiveness and necessity of their 5-ASA treatment.

"I felt that the (Branded Mesalaszie) wasn't making much difference with the other tablets I was taking, because they were a lot stronger than (Branded Mesalazine), so I didn't think it was necessary for me to take it." [Interview 2, Leicester]

Another issue was associated with patient self-evaluation of 5-ASA medication efficacy in UC because this involved the concept of "deferred benefit." The actual benefit of 5-ASA medication in UC is unlike the use of analgesics or antibiotics for other medical conditions. In these cases the effects of treatment are evident within a reasonably short timescale. In evaluating the benefits of 5-ASA therapy it may be difficult for patients to see a clear link between the presentation of symptoms (especially in remission) and the advantages of continued medication adherence.

"I think that the benefit is obviously when you have a flare up of colitis you take the tablets, but… now when its better I don't see the point of taking them." [Interview 7, Leicester]

Concern about taking 5-ASA therapy in the long term was also an issue for patients. They were faced with a dilemma. On the one hand they realised the necessity of taking 5-ASA medication to control UC, but on the other hand they had strong concerns about the long-term risks. Those patients who were worried about the long-term effects of taking 5-ASA compounds appeared to modify their regime to achieve the lowest possible dose.

"I have actually to say that I occasionally reduce the number of pills. Sometimes I am really worried about what would happen with my health in the future." [Interview 20, Cardiff]

Some patients reduced the dose, skipped doses or took “drug holidays” as a way to stop the build-up of toxicity and to ‘cleanse’ their body. Other people minimised their intake of medicines because they felt that long-term use might reduce the effectiveness of the medication.

“I have done that (reduced the dosage) because I believe otherwise the body will get used to the high doses of medication and it wouldn’t have an effect any more.” [Interview 4, Leicester]

In these cases non-adherence was the result of a deliberate decision to adopt a strategy of reducing 5-ASA intake.

Many patients described the temptation to stop taking medication when they began to feel better. This was often despite knowledge of the long term benefits of continuing with 5-ASA compounds. Patients were often aware (or believed in the probable existence) of the benefits of taking 5-ASA medication in the long term but they deliberately chose to reduce or stop the medication despite this knowledge.

“I reduce the dosage myself - depends how I am feeling. You don’t want to be on tablets all the time, do you? You want to be normal and just take yourself off everything.” [Interview 26, Norwich]

We also found that some patients stopped their 5-ASA medication or altered the dose in order to discover the effect of prescribed medication:

"I think that you test yourself and you would like to find out what will happen if you don't take (Branded Mesalazine)… I think sometimes "shall I go and try and find what will actually happen?" [Interview 20, Cardiff]

However, personal experience could also lead to a change in beliefs and related behaviour, after acknowledging the link between persistence with medication and prevention of relapse.

"*In the past I didn't always regularly take it and I had relapses because I didn't probably think that it was important. Then I found if I do regularly take it that it does keep it at bay really. So I don't get as many as flare ups."* [Interview 10, Leicester]

5.5.3 Knowledge and information

It is important to note that the interviews identified perceived benefits and disadvantages and that these perceptions may be contrary to reality. This may result from a lack of information. The degree of information held by the patient, along with balancing benefits and advantages, will logically impact on whether patients accept or reject medication. The study identified that a number of patients perceived that they had been very poorly informed about their disease.

Patient:" *I wasn't properly told what the problem was, they just told me the name of the condition and I went on the NHS website and found out all the problems and symptoms and everything for myself.* "

Researcher: *"Do you mean no-one explained about your condition?"*

Patient: *"That's right, no-one explained what it was properly to me until I researched myself".* [Interview 15, Leicester]

"The information I was given on the tablets was minimal and I couldn't really tell you anything about the drug now. I am not happy about how little information I got. " [Interview 13, Leicester]

Patients were, therefore, potentially making decisions on an ill-informed basis possibly leading to rejection of adherence to prescribed 5-ASA medication.

"Nobody told me that when you are well you will still need to take (Branded Mesalazine). Maybe that could be better explained." [Interview 25, Norwich]

5.5.4 Beliefs about medicines and health

Some patients felt that alternative treatments for UC were better from a quality of life perspective. Their hypothesis appeared to be that most medicines are harmful and addictive. This view was most frequently expressed by patients of South Asian origin.

"*Some people don't believe that tablets are the right thing for their body… They take natural herbs and herbal tablets or ayurvedic tablets."* [Interview 4, Leicester]

Some people expressed the belief that medicines in general are over-prescribed by doctors, a view likely to lead to taking prescribed 5-ASA medication but not as recommended by the doctor.

"*People will do this (minimise the dose of 5-ASA), they think that doctors always advise to take tablets. This is a human mentality.*" [Interview 19, Cardiff]

Individual perceptions of the effects of medications were important in determining perceived necessity. For instance, a few participants described how they had "*tested the water*" by coming off 5-ASA maintenance medication.

"…you test yourself and you would like to find out what will happen I cut my own dosage down to 2 per day that resulted in flare up last year". [Interview 20, Cardiff]

"*In the past I didn't always regularly take it and I had relapses. Then I found if I do regularly take it …I don't get as many flare ups."* [Interview 10, Leicester]

Worsening symptoms strengthened their beliefs about the necessity of continued usage. Those participants unable to identify such a direct link consequently will stop taking their medication.

"I felt that the (Branded Mesalaszie) wasn't making much difference, so I don't think it was necessary for me to take it." [Interview 2, Leicester]

Some patients described an association between their perception of being an 'ill person' and the subsequent willingness or ability to rationalise the requirement to take medication. The logic appeared to be that if a person did not accept their illness then they were unlikely to accept the attendant medication regime.

"You've got to take drugs that will remind you that you have this condition for life every morning, noon and evening. I think that taking drugs is very well connected to your definition of who you are as a well and ill person." [Interview 8, Leicester]

"Young people don't take prescribed medication because they want to forget about their illness and whether there is something wrong with them" [Interview 15, Leicester]

Many study respondents, especially younger patients, were fearful of disclosing their illness to others. This was particularly so amongst Asian

study respondents regardless of age. Instances were described where, rather than take their medication in public and risk disclosing their illness, patients would postpone or forego treatment.

"… people are embarrassed to take their medication in front of other people, especially of their friends." [Interview 17, Leicester]

5.5.5 Patient-healthcare provider relationship

Our data suggest that the effectiveness of the patient-healthcare provider relationship is one of the main determinants of adherence or non-adherence to 5-ASA therapy. The more information a patient received from clinicians about UC and its treatment, the better they were able to participate in decision making related to the management of their illness.

" *I was quite lucky when I was first diagnosed and I came to the first out-patients – I had a couple of nurses and the doctor spend a long time going through everything with me and I sort of came away knowing everything and had the leaflets as well and that's how I've managed to go on…"* [Interview 14, Leicester]

Patients described the fact that effective consultations with clinicians could lead to increased confidence to be involved in the management of their UC symptoms and a greater assumption of responsibility for their own health.

"He (doctor) explained to me that the disease would come back if I did not take the (Branded Mesalazine). He told me: You have to decide yourself - do you want to be a well person who is occasionally ill or an ill person who is occasionally well? I choose to be a well person who is occasionally ill. Therefore I am taking (Branded Mesalazine) regularly. I want to be well and stay well; it's a small price to pay - only 6 tablets a day!" [Interview 21, Cardiff]

Some patients, however, described less effective interactions with healthcare professionals.

"Some registrars just think they are in clinic only to prescribe tablets and say bye." [Interview 8, Leicester]

"I have been told that I have to take (Branded Mesalazine) but I have never been told what they do and how they work or anything like that. People don't know what they do; nobody explains to them properly why they have to take 5-ASA for so long time." [Interview 27, Norwich]

There may be a mismatch between the information doctors and other health care professionals consider important and what patients think and recall. Despite information about the efficacy of 5-ASA medication in terms of long-term cancer prevention being well known amongst health professionals, few respondents were aware of this. Only a minority of patients had been

informed of this by a clinician; during the interviews, However, all respondents evaluated this information as crucial for encouraging adherence.

“Nobody told me about possible effect of 5-ASA on cancer prevention. It would be good for medical professionals every visit to pass information to the patient about what would be the benefits.” [Interview 7, Leicester]

“If a doctor tells a patient that a drug will have effect on something like a cancer, I personally believe that it will definitely effect who will take it and how often!" [Interview 27, Norwich]

"I am sure that if people were told about prevention the risk of cancer it would help them to take their medication." [Interview 19, Cardiff]

5.5.6 Supportive family relationships

The majority of participants’ underlined the positive influence of supportive family relationships in their disease management.

“My husband always asks me whether I have taken my medication. I wouldn’t have gone through like I have done without the support of my husband because he always helped to find information or remind me to take my medication.” [Interview 8, Leicester]

"I think it is important, certainly for young people, children especially for parents and family to be there on a regular basis to encourage them to take tablets. As adults, yes, partners do help… especially when people are depressed because of the disease." [Interview 25, Norwich]

5.5.7 Practical considerations and additional barriers

It was clear that people also evaluated their regime in terms of its fit with their daily routine.

"I was told to take 6 tablets (1x6) a day. It is actually difficult…you forget because you are doing other things." [Interview 7, Leicester]

Acceptability appeared to be described in terms of the degree to which "normal life" was facilitated without significant disruption. It seemed that the frequency of dosage and number of pills was a determinant for adherence or non-adherence. Changing the regime was described as a possible method of facilitating adherence.

"When I took (Branded Mesalazine) 2 tablets three times a day, I found that I was very often missing my midday tablets. Finally I decided to take 3 tablets twice a day." [Interview 21, Cardiff]

The size and shape of the pills themselves were also sometimes described as problematic.

"When I am taking tablets sometimes they get stuck in my throat. I would prefer if (Branded Mesalazine) tablets were in caplet shape or at least smaller in size." [Interview 3, Leicester]

Additional barriers identified from the interview data were prescription costs, forgetfulness and changes to daily routine. The majority of the respondents mentioned forgetfulness as a common reason for non-adherence if 5-ASA compounds were prescribed more than twice a day, if their daily routine changed and also during periods of disease quiescence.

5.5.8 Summary of reasons for non-adherence and ideas from participants

The reasons for non-adherence described by patients are summarised in Table 5.2

Table 5.2: Patient descriptions of reasons for non-adherence

• Lack of knowledge and information
• Side-effects of 5-ASA compounds
• Worries about long term effects
• Forgetfulness, especially when daily routine has changed
• Lack of trust in the medication
• Uncertainty about the benefits of 5-ASA
• A belief that patients can reduce 5-ASA medication when they feel well
• Decision "to have a little break" to prevent medication becoming ineffective
• Cannot afford prescription charge
• Dosage, number and size of tablets

5.5.9 Ideas from participants

At the end of the interview every patient was asked to give his or her suggestions about how to improve adherence to 5-ASA therapy. Ideas raised by respondents are shown in Table 5.3.

Table 5.3: Mechanisms for improving adherence to 5-ASA suggested by participants

• Quality time and information from doctors
• Make regime for medication taking easier
• Reduce prescription charge
• Give information about reducing risk of colon cancer
• Teach people to be responsible for their own actions about their own health and develop self-efficacy
• Family support and involvement
• Use a medication reminder chart or calendar
• Use a beeping fridge magnet (for elderly people)
• Use a key fob reminder with alarms
• Use mobile phone messages
• Use mobile phone alarms
• Use computer messages
• Use a wristwatch or bracelet with alarms.
• Use pill dispenser with or without alarms

5.6 Development of decision model

Based on consideration of study findings, a Therapeutic Decision Model initially developed by Dowell and Hudson (166) and later changed by Pound (167) was adapted for this study with the aim of illustrating the main factors which influence adherence amongst patients with UC and to demonstrate the decision-making process (Figure 5.1).

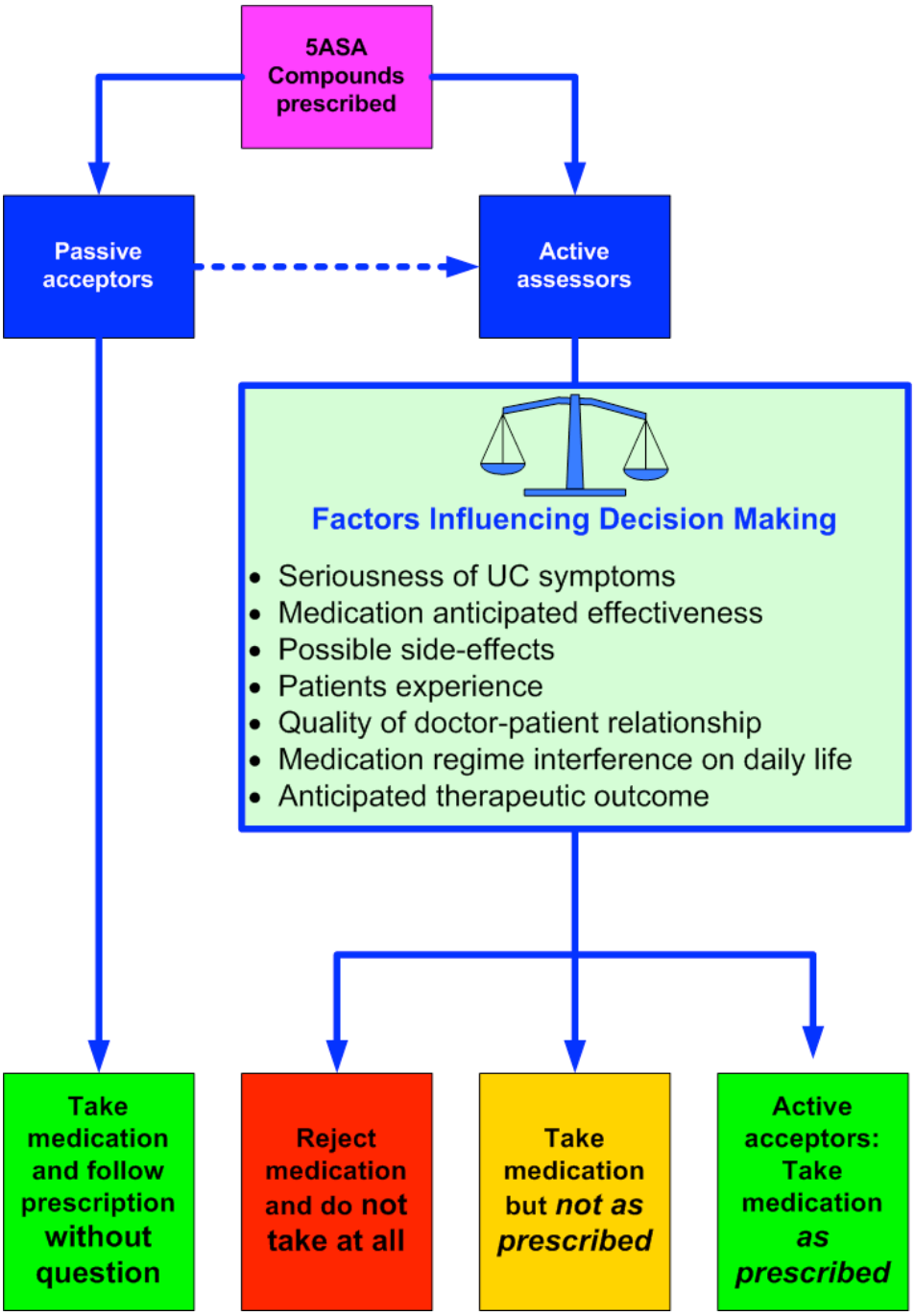


Figure 5.1: Adapted model of 5-ASA adherence in UC

Dowell J, Hudson HA. *Family Practice*. 1997; 14(5): 369-375.
Pound P, *et al. Social Science & Medicine*. 2005; 61(1): 133-155.

5.7 Discussion

This study used a qualitative research design to identify and explore factors responsible for poor adherence to 5-ASA medication amongst UC patients in a range of communities. The results suggest that important determinants of 5-ASA medication adherence in patients with UC include levels of information provided, patient beliefs about prescribed 5-ASA and the effectiveness of the patient-clinician relationship. The study data indicate that patients may be non-adherent to treatment recommendations either intentionally or unintentionally. Factors identified as being associated with increased risk of intentional non-adherence to prescribed 5-ASA therapy included poor understanding of the potential benefits of taking 5-ASA compounds, especially during periods of disease quiescence, absence of anticipated effectiveness, denial of illness, fear of side effects and a sub-optimal relationship with health care professionals. Complicated dosing regimes that interfere with everyday life, less active disease, younger and also older age, new patient status, forgetfulness and absence of adequate information from health care practitioners were associated with increased risk of unintentional non-adherence.

The patient's intention to adhere to medication regimes appears to depend on a deliberate decision based on need, effectiveness, and safety of the medication concerned. Active acceptors and rejectors make decisions about taking medication based on a varying degree of idiosyncratic evaluation of

the information (or absence of information) available. Information provided or gathered is supplemented by personal experience and underlying health beliefs. From this study it would appear that patients weigh up their beliefs on regarding the necessity to take medication and its benefits against the disadvantages, and this evaluation influences their adherence behaviour (168), (169).

These findings suggest that patients rarely remain passive acceptors when medication results do not meet expectations. It is therefore possible to infer that the majority of patients are, or will over time become, active acceptors or rejectors. Rejection may take the form of complete or partial deliberate non-adherence to the medication regime as prescribed. Adherence to medication may involve a change in the patient's perception of self (as a person with a chronic condition) and in the perceived need to continue the medication regime. Changes to these perceptions over time, coupled with the patient's own assessment of 'wellness', appear to create a set of conditions within which patient medication behaviour may vary unpredictably.

5.7.1 Comparison with other studies

Different factors associated with non-adherence to 5-ASA therapy among patients with UC such as lack of adequate information, fear of side effects, denial of disease, forgetfulness, full-time employment, inconvenient dosing regime, inability to see the need for medication during periods of disease quiescence have been reported previously (124), (120), (112). These issues

were consistent with the findings from the work presented in this chapter. Central to these findings is the importance of the patient-clinician dynamic relationship. This is supported by a previous study which described a communication theory of adherence (103).

In contrast to my findings, a study from Spain (123) found that the patient-doctor relationship was assessed as excellent by both patients and physicians. However, similar levels of satisfaction were not observed among the majority of my study participants. Another noticeable discrepancy related to the degree of satisfaction of information about UC and its treatment. The majority of participants in the Spanish study were satisfied with the information provided by their clinicians; only a few described it as insufficient. In contrast, a lack of perceived benefit and paucity of information about the condition and its treatment were identified as barriers to adherence in my study. Differences between findings from my study and those from Spain suggest that factors affecting adherence may vary between settings and populations.

It is evident that many of the issues relating to adherence in other chronic diseases (168), (170) apply also to patients with UC. However, a distinguishing feature influencing the behaviour of patients with UC was identified by our study in relation to the relapsing and remitting nature of the condition. Patient expectation of the efficacy of 5-ASA may initially be high; however, unlike some other chronic conditions, symptomatic relief is not

always apparent and there may thus sometimes be a lack of perceived association between taking 5-ASA and management of symptoms.

The findings of this qualitative study are compatible with a study which examined the effect of health beliefs in 31 patients with IBD (17 of whom had UC) on treatment behaviour using semi-structured interviews and focus groups (169). The balance of concerns and acceptance of concepts developed by Hall *et al.* (Figure 5.2) is very similar to concepts of the Decision Making Model (Figure 5.1) developed by this study. Patients' attitudes and beliefs towards medication were found to be based on an ongoing balance between three main groups of factors: 1) acceptance and perceived necessity of medication; 2) fears and concerns and 3) the perceived impact of the disease (Figure 5.2). In addition, patients' experience of the illness, knowledge and the relationship with the health care provider can also be influential in this process (169). These findings mirror that of my qualitative study.

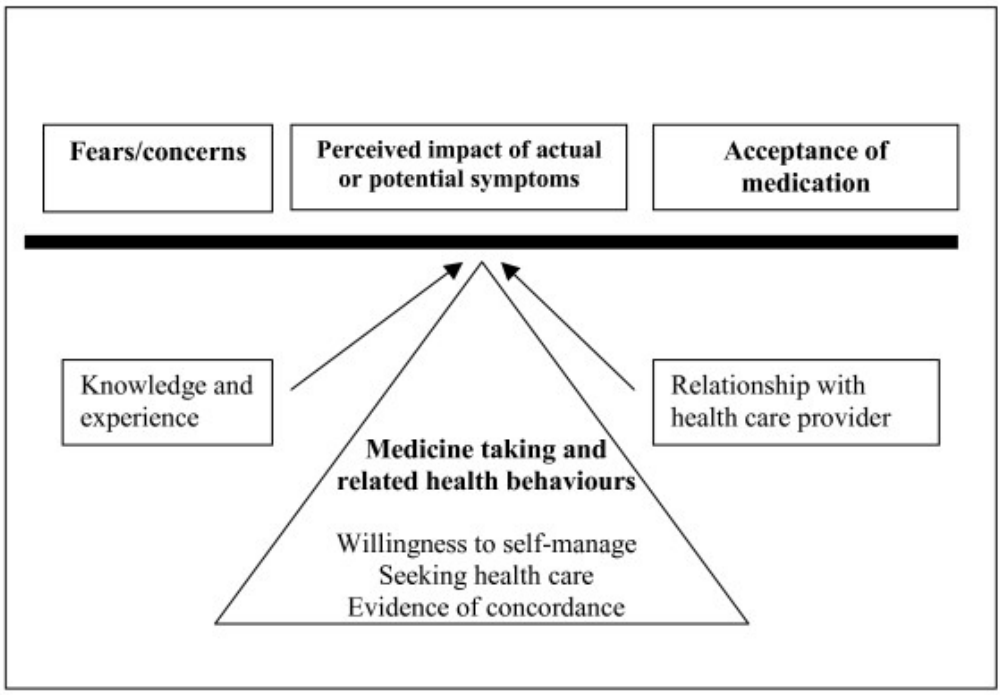


Figure 5.2: Factors influencing medication-related behaviour

Adapted from Hall *et al*. BMS Gastroenerol 2007; 7:20

5.8 Concluding remarks

The value of the qualitative methodology used in this study lies in the potential to identify and explore patient medication taking behaviour through in-depth investigation. Confidentiality was guaranteed and the methodology included encouraging honest responses, whose meaning could be clarified through discussion.

In conclusion, the patients' knowledge of the disease and its treatment, beliefs about medication and the effectiveness of relationship with their physicians influence patients' adherence to 5-ASA medication. This study

also suggests that a medication adherence change over time, therefore, needs regular reinforcement and the patient-clinician relationship has a crucial role to play.

One of the hypotheses underlying the programme of study was that factors affecting medication-taking behaviour could be identified and this study was designed to determine these factors. The findings from this qualitative study were therefore then tested for generalisability using larger scale survey methods. This is described in detail in Chapter 6.

Chapter 6

Cross-sectional, quantitative survey

6 Chapter 6: Cross-sectional, quantitative survey

6.1 Introduction

This chapter presents an observational study with a cross sectional design. This method was chosen within the research programme in order to assess the prevalence of, and factors associated with, non-adherence to 5-ASA therapy in a range of communities, including the South Asian population in Leicester. The qualitative work presented in the previous chapter had shown that important determinants of adherence are: levels of information provided, patient beliefs about prescribed 5-ASA and the effectiveness of the patient-clinician relationship. The quantitative survey described in the present chapter was used to further investigate the issues explored in the qualitative study. This included testing the qualitative findings for generalisability using a larger sample.

6.2 Aims and objectives

This study aimed to determine rates and predictors of non-adherence to oral 5-ASA therapy in a sample of patients with UC, using two different adherence measures; also to examine the agreement between these measures. Specific objectives included an investigation of the relationship between patients' beliefs about prescribed 5-ASA therapy and medication adherence. Additional objectives were measurement of patient satisfaction with

information received regarding 5-ASA therapy and an exploration of the relationship between non-adherence with 5-ASA medication and satisfaction with information.

6.3 Materials and Methods

6.3.1 Ethical considerations

The study was approved by the West Midlands Multi-Centre Ethics Committee (reference number 06/MRE07/9) and relevant R&D approvals were obtained from each research site.

6.3.2 Participants and procedure

Patients with UC, who were aged 18-80 years and receiving maintenance 5-ASA therapy, were recruited from out-patient clinics at four hospitals in Leicester, Cardiff and Norwich, UK. Potential participants were approached either by letter or personally when attending clinic appointments (Appendix 4). Patients who took part provided written informed consent (Appendix 5) for their involvement in the research. Participants completed a questionnaire booklet which contained a study specific questionnaire (Appendix 6), the Beliefs about Medication Questionnaire (168) (BMQ)-Specific scales (Appendix 7) and the Satisfaction with Information about Medicines Scale (SIMS) (171) (Appendix 8). They also provided a spot sample of urine while at the clinic. Samples were coded to retain blinding and kept at -22^{o}C until analyses were performed using high-performance liquid chromatography (HPLC). Participants' age,

gender, ethnic group, disease duration and prescribed 5-ASA medication were also recorded.

6.3.3 Psychological variables

Beliefs about medicines were assessed using the scales from the BMQ-Specific instrument (168) (Appendix 7). This 11-item validated questionnaire assesses patients' beliefs about their perceived need for medication (Specific Necessity subscale, five items) and their concerns about potential adverse effects of medication (Specific Concerns subscale, six items). Individual scale items are scored using a 5-point Likert-type scale providing options ranging from Strongly Disagree (scored 1) to Strongly Agree (scored 5). Scale scores are computed by adding individual item scores and dividing by the number of items in the scale, providing adjusted scale scores ranging from 1 to 5, with higher scores indicating stronger agreement with the scale constructs. Psychometric data suggest that this measure is both reliable and valid in a variety of medical populations including those being treated for asthma, diabetes, cardiac problems and psychiatric illness (168). It has also recently been used in patients with rheumatoid arthritis (172) and inflammatory bowel disease (173), (121).

In addition to the main analyses relating to predictors of non-adherence, an attitudinal analysis (173), (174) was conducted in order to further explore the relationship between adherence and beliefs about medication in a clinically meaningful way. Patients were divided into one of four groups based on whether they scored above or below midpoint (<3, ≥3) (175) on the BMQ

specific Necessity and Concerns scales: Accepting (high necessity, low concerns), Ambivalent (high necessity, high concerns), Sceptical (low necessity, high concerns) or Indifferent (low necessity, low concerns).

The SIMS (171) assesses the extent to which participants are satisfied with 17 aspects of information considered essential for the optimum use of medicines (Appendix 8). The questionnaire does not focus on the specific information provider or specific formats of information (e.g. written, verbal); rather it assesses the patient's overall satisfaction with information about 5-ASA compounds prescribed for UC. Nine items relate to information regarding the action and usage of the medication (Action and Usage subscale) and eight items relate to information regarding the potential problems associated with the medication (Potential Problems subscale). Participants are asked to rate the amount of information about prescribed 5-ASA they have received, indicating: "too much", "about right", "too little", "none received" or "none needed". For each item, participants responding "about right" or "none needed" are classified as satisfied and those responding "too much", "too little" and "none received" are classified as dissatisfied. Scores are summed for each subscale, resulting in an Action and Usage satisfaction score (possible range 0-9) and a Potential Problems satisfaction score (possible range 0-8).

6.3.4 Measures of adherence including analytical methods for urine analysis

A 12-item self-report questionnaire (Appendix 6) was developed specifically for this study to collect information relating to adherence to 5-ASA. Two items provided a free-text opportunity and 10 items had a series of “options” to tick for answering questions. One of the questions asked for a yes/no response about non-adherence in the past two weeks. This question was worded in terms of whether any doses had been ‘missed’, thus potentially including both intentional and non-intentional non-adherence. The study specific questionnaire also provided a free-text opportunity for participants to disclose reasons for not taking their 5-ASA medication as prescribed.

Adherence was also measured objectively testing the spot urine samples provided by participants. HPLC was used for determination of 5-ASA and N-acetyl-5-ASA urinary concentrations. Chapter 7.1 of this thesis reports the development and use of this method.

6.3.5 Statistical methods

Analyses were conducted using SPSS v16. A separate model was determined for each adherence measure: self-reported and urinary mesalazine excretion (analytically detected). Self reported non-adherence was included as a binary variable (based on yes/no responses) in the analyses. For the measure based on analysis of urine samples (Chapter

7.2.5), complete non-adherence was defined as undetectable (0 μg/ml) levels of 5-ASA or N-acetyl-5-ASA. Concentration of 5-ASA with values <30μg/ml and of N-acetyl-5-ASA with values <90μg/ml was defined as partial non-adherence, and concentration of 5-ASA ≥30μg/ml and N-acetyl-5-ASA ≥90μg/ml was deemed to indicate adherence. Partial and complete non-adherence were subsequently combined to form a single category which was compared with complete adherence to create a binary variable.

The same set of potential predictor variables was used for the analysis of each of the two separate outcomes, namely: age, ethnic group (Caucasian/ South Asian), disease duration, BMQ specific necessity (SN) and specific concerns (SC) scores, SIMS score, and Indices of Multiple Deprivations (IMD) score. Age, duration of disease, SIMS, IMD, SN and SC scores were treated as continuous variables. The Indices of Multiple Deprivations scores for England (IMD 2004) and Wales (WIMD 2005) were calculated and analysed separately as they are not compatible. Significant predictors from univariable models were entered into multivariable models for each outcome. Backwards stepwise logistic regression was used for two separate models to identify any independent predictors of self-reported non-adherence and analytically detected non-adherence. Variables with p values below 0.2 were selected for inclusion in the stepwise process. Phi correlation was used to assess the correlation between the two measures of adherence.

6.4 Results

6.4.1 Sample characteristics

One hundred and seventy questionnaires were completed (100-Leicester, 46-Cardiff, and 24-Norwich). The self-report question about non-adherence in the past two weeks was completed by 169 people and, of these, urine samples were available for a sub-cohort of 151 cases. The mean age of participants was 49 with an age range from 18 to 88 years. Eighty-four participants (49%) were female, and 33 (19%) were of South Asian origin. Patients had been taking a range of oral 5-ASA formulations, most frequently mesalazine formulations (Table 6.1).

Table 6.1: Characteristics of study sample (n= 170)

		Number	Percentage
Gender	Male	86	51%
	Female	84	49%
Age distribution	18 – 45 Years	76	45%
	46 – 88 Years	94	55%
	Mean	49 Years	
Geographical location	Leicester site	100	59%
	Cardiff site	46	27%
	Norwich Site	24	14%
Ethnicity	Caucasian	137	81%
	South Asian (31 from Leicester site)	33	19%
Time elapsed since diagnosis	1 – 3 Years	41	24%
	4 - 10 Years	51	30%
	11 - 20 Years	62	36%
	20+Years	16	10%
Oral 5-ASA prescription information	MESALAZINE (Asacol)	87	51%
	(Pentasa)	57	34%
	BALSALAZIDE (Colazide)	12	7%
	OLSALAZINE (Dipentum)	2	1%
	SULPHASALAZINE	12	7%

6.4.2 Adherence to medication

The adherence rates were 66% (111/169) when assessed using the self-report measure and 60% (90/151) when assessed by urine analysis. There was no significant correlation between the urine analysis and self-report methods of assessing adherence. The phi correlation between these two binary variables was 0.029 (p=0.725).

In terms of the self-report measure of adherence, 58 participants (34%) indicated that they had missed their medication in the previous two weeks; they were classified as low adherers. In response to the free-text question about reasons for non-adherence, 21 (12%) said that they “just forgot” (unintentional non-adherence) and 9 (5%) sometimes decided to miss their medication (intentional non-adherence). Using univariable analysis, significant predictors of non-adherence were age, low perceived need for treatment and high levels of concern about potential adverse effects of treatment (Table 6.2).

Table 6.2: Univariable predictors of non-adherence to 5-ASA medication, from analysis of data based on self-report and analysis of urine samples

	Self-reported non-adherence				Non-adherence measured by urine analysis			
Predictor	N	OR	95% CI	p	N	OR	95% CI	p
Age	169	0.949	0.927 to 0.972	<0.001	151	1.006	0.986 to 1.027	0.562
Centre	169	-	-	0.082	151	-	-	0.020
2 v 3	70	0.449	0.157 to 1.288	0.136	61	0.657	0.195 to 2.215	0.498
1 v 3	145	0.452	0.219 to 0.931	0.031	127	2.312	1.022 to 5.229	0.044
2 v 1	123	0.994	0.373 to 2.651	0.99	114	0.284	0.097 to 0.830	0.021
Gender	169	0.982	0.520 to 1.854	0.956	151	0.635	0.330 to 1.222	0.174
Ethnicity	169	1.003	0.446 to 2.255	0.994	151	2.940	1.303 to 6.638	0.009
Duration of UC	169	0.999	0.996 to 1.002	0.492	151	1.001	0.998 to 1.004	0.431
SIMS	169	0.949	0.881 to 1.022	0.166	151	0.999	0.926 to 1.078	0.983
Specific Necessity score	169	0.506	0.329 to 0.780	0.002	151	0.829	0.538 to 1.277	0.394
Specific Concerns score	169	1.565	1.032 to 2.374	0.035	151	1.303	0.861 to 1.971	0.210
Deprivation (IMD-2004)	124	0.977	0.946 to 1.010	0.174	114	1.003	0.975 to 1.031	0.853
Deprivation (WIMD - 2005)	45	1.001	0.958 to 1.045	0.970	37	0.987	0.936 to 1.041	0.642

SIMS (The Satisfaction with Information about Medicines Scale)
IMD- (The Indices of Multiple Deprivations scores for England)
WIMD- (The Indices of Multiple Deprivations scores for Wales)

Logistic regression revealed that, from the potential predictors studied, younger age (p<0.001) and low perceived need for treatment (p=0.019) were significant independent predictors of non-adherence (Table 6.3).

Table 6.3: Results for self-reported non-adherence in 169 patients: significant predictors remaining after stepwise logistic regression modelling.

Predictor	OR	95% CI	p
Age	0.954	0.932 to 0.976	<0.001
Specific Necessity	0.578	0.366 to 0.913	0.019

Of the 151 participants providing urine for analysis, 20 (13%) had no 5-ASA or its metabolites in their urine and 41 (27%) had drug levels well below those expected. Urine testing also showed that 59% (19 out of 32) of South Asian participants were low adherers (8 had no evidence of having taken 5-ASA medication and 11 had levels much lower than expected). Significant univariable predictors of non-adherence were (a) location of research centre attended and (b) South Asian ethnicity (Table 6.2). Logistic regression modelling revealed that South Asian participants were significantly more likely to be low adherers than non Asian participants (p=0.009), but no other independent predictors were identified (Table 6.2).

6.4.3 Adherence and patients' beliefs about their prescribed 5-ASA medication

Some degree of doubt regarding personal need for 5-ASA medication (SN score <5) was indicated by the BMQ-Specific responses of 20/170 (12%) participants and 43/170 (25%) indicated some degree of concern (SC score <5) about potential adverse effects of the medication. Non-adherence was associated with low perception of necessity and high levels of concern as identified from questionnaire responses. Independent samples t-tests revealed that patients of South Asian origin had significantly higher concerns about treatment than non-Asian patients ($p<0.001$) (Figure 6.1), but there were no differences in necessity scores across ethnic groups.

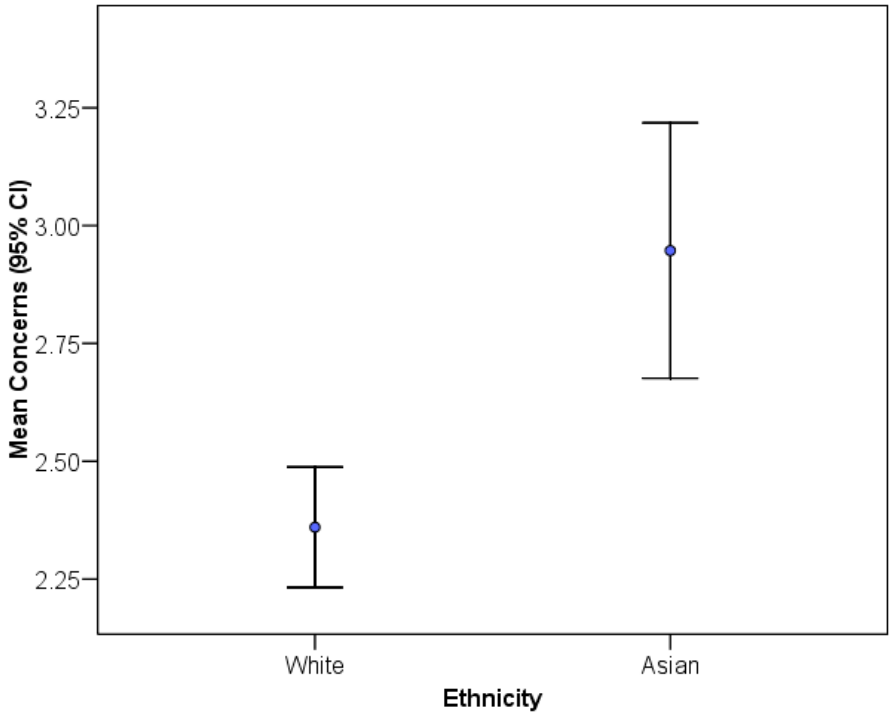


Figure 6.1: Ethnic group differences in SC score

There was a significant correlation between age and necessity scores across 170 cases (Spearman's rho 0.200, p=0.009) and also between age and specific concerns scores (Spearman's rho-0.242, p=0.001), suggesting that older participants had a higher perception of necessity but lower concerns (Figure 6.2). There were no differences in necessity or concerns scores between males and females.

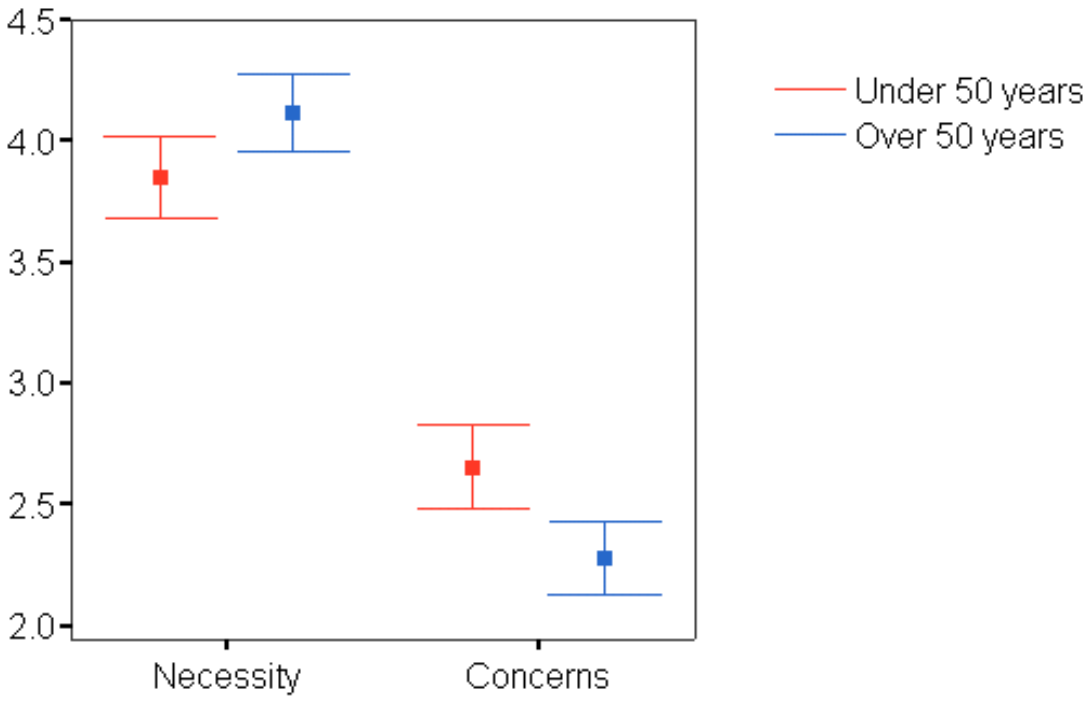


Figure 6.2: Age differences in SN and SC scores

The attitudinal analysis (Figure 6.3) showed that the majority of patients perceived a need for medication and were classified as Accepting (High Necessity, Low Concerns, 67%, n=114)) or Ambivalent (High Necessity, High

Concerns, 21%, n=36). However, 7 (4%) patients were Sceptical about medication (Low Necessity, High Concerns) and 13 (8%) were Indifferent (Low Necessity, Low Concerns). According to both the self report and urine analysis, those in the Accepting group were significantly less likely to be classified as low adherers than those in the other three attitudinal groups (Chi-square=9.955, p=0.002; Chi-square=4.832, p=0.028 respectively).

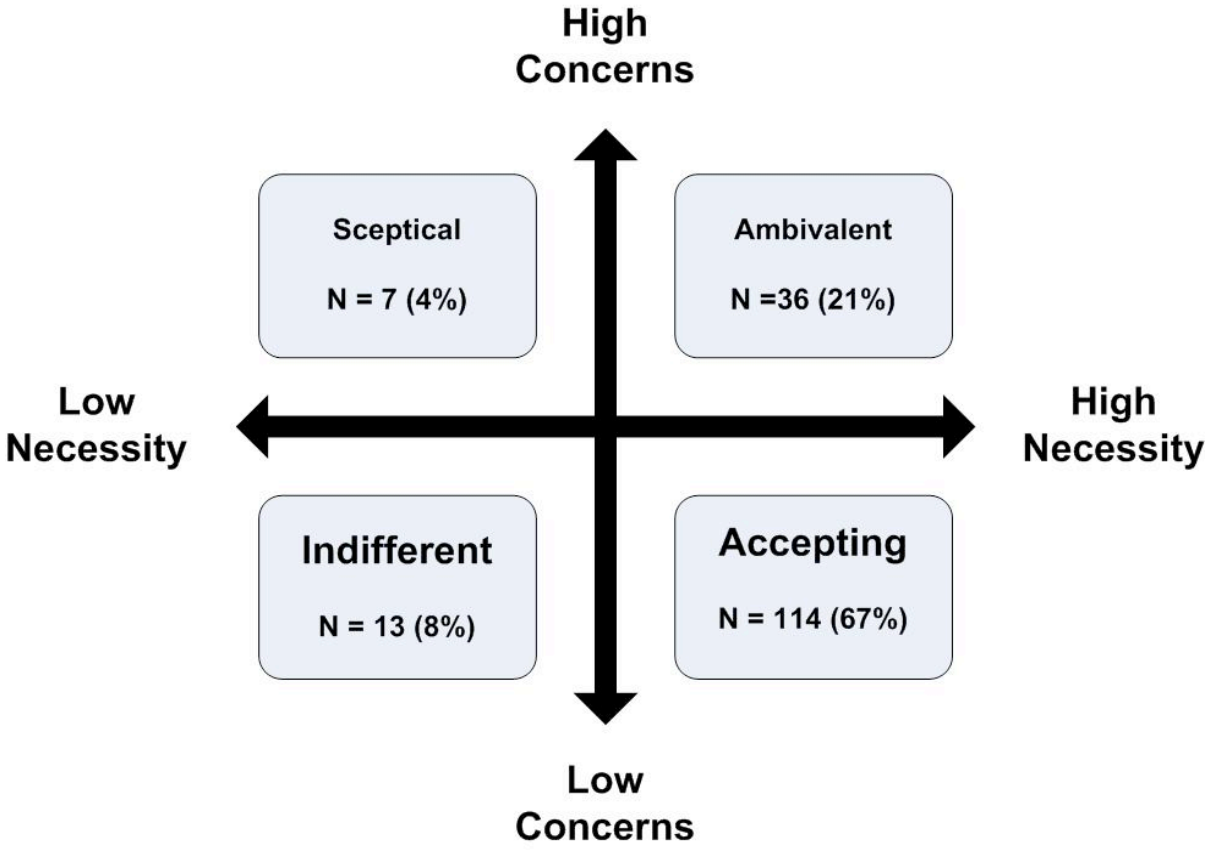


Figure 6.3: Patient profile derived from the attitudinal analysis

Adapted from: Horne R, *et al*. *Inflamm Bowel Dis.* 2009; 15(6): 837-844.
Aikens JE, *et al*. *Am Fam Med.* 2005;3: 23-30.

6.4.4 Patients' perceptions of information received about 5-ASA medication

In response to the SIMS questions (Figure 6.4 and Figure 6.5), almost half of the participants (47%, 80 out of 170) indicated that they were dissatisfied with the information that they had received about how their 5-ASA medicines work, and over a third of participants (38%, 65 out of 170) reported dissatisfaction with the information they had received about how long these medicines take to act and 39% (66/170) how long they would need to take the medicines. In terms of the potential problems associated with medicines, almost half of the participants were dissatisfied with the information they had received about whether the medication would affect their sex life and whether the medication would interfere with other medicines (47%, 80 out of 170 for both questions). Furthermore, 40% (68/170) of participants were dissatisfied with the information they had received about the risks of getting side effects, 37% (63/170) -what they should do if they did get side effects and 34% (59/170) whether they could drink alcohol while taking the medication. However, in this sample, a significant relationship between satisfaction with information received and levels of adherence was not identified. (Table 6.2)

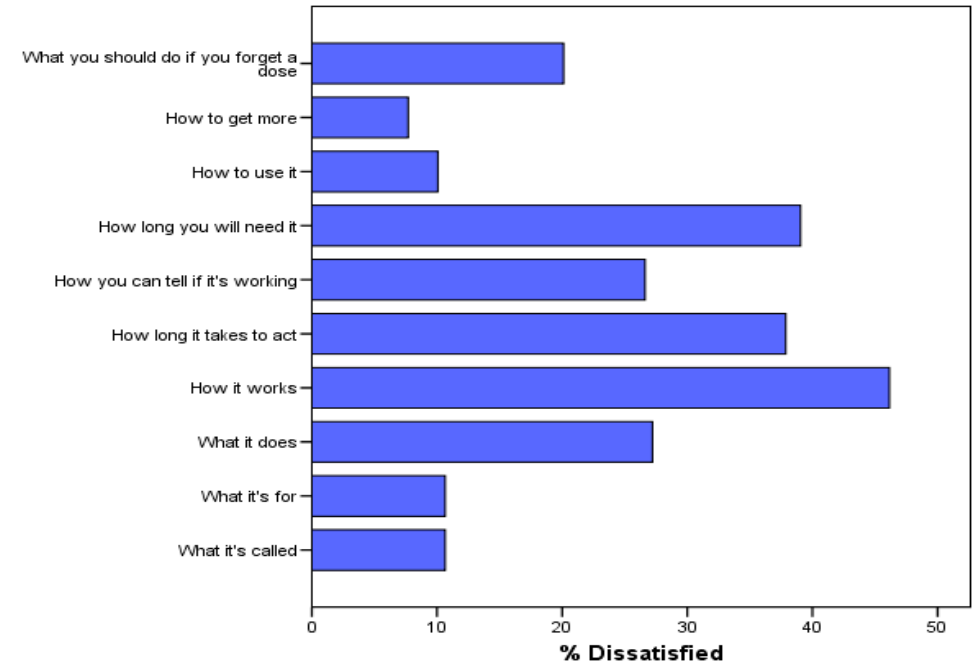


Figure 6.4: Dissatisfaction with information regarding the action and usage of 5-ASA medication

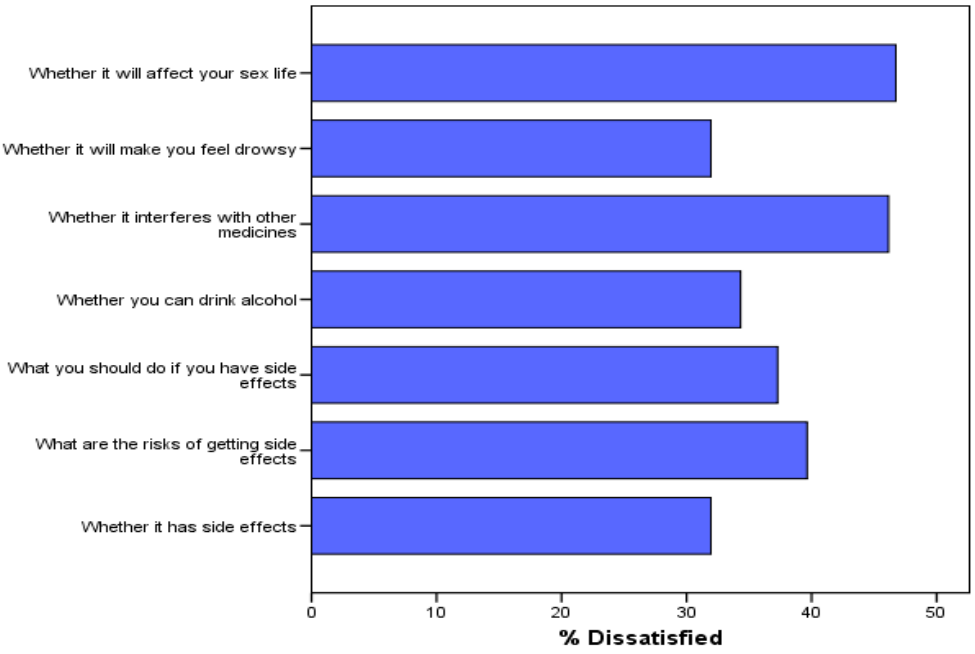


Figure 6.5: Dissatisfaction with information regarding the potential problems associated with 5-ASA medication

6.5 Discussion

6.5.1 Summary of main findings

This study considered adherence to 5-ASA medication in three UK communities including people from the South Asian population in Leicester, using self-report and urine analysis. The study was conducted using different methods to investigate levels and predictors of adherence in patients with UC in a “real world” environment. Questionnaires and spot urine samples were obtained from consenting patients with no prior knowledge of the fact that they would be involved in the study.

6.5.2 Comparison with other studies

The rates of adherence identified are generally consistent with previous adherence data relating to the management of patients with IBD (176), (122), (121), (102). However, analysis of data for the two measures identified a lack of correlation between these measures and inconsistency between adherence rates and independent predictors of non-adherence. These observations confirm the difficulty of accurately determining levels of medication adherence in the absence of a truly reliable measure that can be regarded as a gold standard.

Two independent studies of adherence in patients with inflammatory bowel disease, from the UK (112) and from Spain (113) have also shown a

discrepancy between self-reported adherence and analytically determined adherence. Lopez San Roman *et al.* identified that urine from 13% (2 out of 40) showed a complete absence of mesalazine metabolites in the urine. Shale and Riley, who also measured urinary 5-ASA and N-acetyl-5-ASA levels, found that 12% of urine samples (12 out of 98) had no detectable metabolites of 5-ASA. They suggested that self-reporting of medication non-adherence identified only 66% of patients who were indeed non-adherent according to their urinary drug measurement (112).

Objective measures are generally regarded as being more reliable than those based on subjective self-reporting. However, it is acknowledged that the objective measure used in this study, based on analysis of urine samples, has limitations. Although spot urine samples were obtained from consenting patients with no prior knowledge of the fact that they would be involved in the study, it is possible that a single sample cannot capture the complexity of adherence behaviour and reflect true adherence levels over a period of time. An additional problem that arises from using data based on urinary mesalazine level is a possible wide variation of results among people who are equally compliant due to different factors. These include changes in diet, dosage variation of different 5-ASA formulations (prescribing inconsistency), and pH of the colon and colonic transit time (177). Although genetic differences may influence rates of acetylation at individual patient level (178), rates of recognised slow acetylator mutations have been found to be broadly similar in people of Indian Asian (the predominant South Asian group in our

study population) and white ethnic origin (179). In addition, some 5-ASA compounds (olsalazine, balsalazide) are not easily detected in urine (180), (181), (182), (183). Therefore, this method may have limited reliability as an adherence measure, particularly for partially adherent patients. In terms of relevance to clinical management, urinary mesalazine measurement by HPLC is expensive, time consuming and gives a picture of recent consumption only, rather than being able to provide a longer term picture as is the case with glycosylated haemoglobin measurement for determining blood glucose levels in people with diabetes. Moreover, it could be argued that performing urinary mesalazine measurement might have a detrimental effect on the level of trust between physician and patient.

Self-report and urine analysis measures applied to the same patients identified different demographic predictors of non-adherence: younger age and South Asian ethnicity respectively. No other demographic predictors were identified after adjustment for potential confounding variables using logistic regression modelling. Our findings in terms of predictors of adherence, therefore, differed in some respects from those described in other studies. Gender has been implicated as a significant predictor of adherence in previous research (101), (113) whereas no difference in adherence was apparent between males and females in our sample. Previous findings have suggested that disease duration may have an impact on medication adherence (122), but the present study results did not support this assumption. The data involving self-reporting did, however, confirm previous

observations (176), (121), (102) relating to a predictive role for age, with younger patients in my sample being more likely to report low adherence than older participants. However, age differences were not evident according to urine mesalazine measurement.

Literature searching suggests that this is the first study to explore the relationship between ethnicity and adherence to 5-ASA medication in UC. The study findings based on analysis of urine samples suggested that patients of South Asian origin are more likely to be non-adherent than Caucasians. South Asians had significantly higher concerns about treatment than non-Asian patients and it can be surmised that these concerns may have had an impact on their levels of adherence. This is a new finding for patients with UC but seems to be consistent with previous research in rheumatoid arthritis and depression (172), (184). Reasons for the observed non-adherence disparity between Caucasian and South Asian people with UC should be studied further, for example, using qualitative methodology. Methods of addressing this disparity also require further investigation.

Identifying groups of patients in whom there is a greater likelihood of non-adherence is important in relation to epidemiological understanding and is also clinically relevant in terms of highlighting those groups who may need to be specifically targeted in terms of adherence advice. However, demographic characteristics such as age and ethnic origin cannot be altered and it is particularly important to identify and understand any modifiable predictors of

non-adherence. This study found a relationship between adherence to medication and patients' potentially modifiable beliefs (Necessity and Concerns) about treatment. This is supported by the qualitative study findings described in Chapter 5.5.4. In line with previous research into adherence to medication in chronic illnesses (168) including IBD (173), the findings from the present study suggested that low perceived personal need for treatment and high concerns about potential adverse effects of treatment are associated with low adherence. This was particularly the case in respect of the relationship between levels of perceived necessity and self-reported adherence. It has been suggested that interventions designed to increase adherence interventions should provide patients with a clear rationale for the need for treatment and elicit and address their concerns about treatment (185). Demographic groups at higher risk of low adherence reported significantly greater concerns about medication (patients of South Asian origin and younger participants) and younger patients reported a significantly lower perceived need for treatment than other participants. These groups may be particularly good targets for belief-based interventions. In contrast to the qualitative study (Chapter 5.5.3), the cross-sectional, quantitative survey failed to demonstrate a significant relationship between satisfaction with information received and non-adherence. Nevertheless, poor patient knowledge may still be an important cause for non-adherence to 5-ASA therapy.

6.6 Concluding remarks

A variety of factors were identified within the qualitative and quantitative studies that might be addressed in order to improve adherence to 5-ASA therapy. These provided a framework upon which to develop a package of patient-tailored adherence enhancing interventions (described in Chapter 8) and test the effectiveness of these interventions using a RCT (Chapter 9). Prior to this, Chapter 7 reports the results of collaborative work with Department of Chemistry, Loughborough University, including results from a pilot pharmacokinetics study that addresses the question raised earlier in this chapter (6.5.2).

Chapter 7

Analytical Chemistry -

Development of method and practice

Section 1:	**Development of a simple and rapid chromatographic method for the determination of 5-ASA and its acetylated metabolite N-acetyl-5-ASA in urine.**
Section 2:	**Pilot pharmacokinetics study.**
Section 3:	**Determination of a simple method for detection of non-adherence to 5-ASA therapy.**

7 Chapter 7: Analytical Chemistry – Development of method and practice

7.1 Introductory guidance to chapter 7

The work presented in this chapter was carried out in collaboration with Professor Roger M. Smith and his MSc and BSc project students, from the Department of Chemistry, Loughborough University. The partnership with this academic department was essential to achieve the objectives of the adherence project. Together with Professor Smith and Professor Mayberry I conceived the strategy and four specific research studies were then designed:

I. An ion-pairing high performance liquid chromatographic method for determination of 5-ASA and its metabolite in urine – Jun Wang MSc, September 2007.

II. A high performance liquid chromatography method to study the pharmacokinetics of 5-ASA and its metabolites in patients with UC – Enas Zarrugh Ismail MSc, September 2008.

III. The identification of extra peaks observed in urine from patients taking 5-ASA medication for UC using ion-pairing high performance liquid chromatography - Ting Diu MSc, September 2008.

IV. Determination of a simple method for detection of non-adherence to 5-ASA therapy in clinical settings – Kate Hilling BSc, July 2007; Rebecca Bowley BSc, July 2008.

These research projects form the basis of this chapter and are divided into three sections. The students, mentioned above, designed and undertook the experimentation and analysed the resulting data. Details of my contribution to the work presented in this chapter are provided in Chapter 1 on page 20. All projects were conducted under the supervision of Professor Smith, who provided technical support and conceptual advice.

7.2 Section 1: Development of a simple and rapid chromatographic method for the determination of 5-ASA and its acetylated metabolite N-acetyl-5-ASA in urine

7.2.1 Introduction

The development of a rapid and sensitive analytical method for the determination of 5-ASA and its acetylated metabolite, N-acetyl-5-ASA in the urine was an important precondition to achieve the aim of the overall project. This method was developed and validated by Jun Wang, MSc (September 2007) Loughborough University. This section outlines this method.

7.2.2 Background

High-performance liquid chromatographic (HPLC) methods are considered the gold standard test for quantification of 5-ASA and its metabolites and have been used previously by researchers as the objective measure of 5-ASA medication adherence (112) (114). Several HPLC methods have been developed, validated and applied to the determination of 5-ASA and N-acetyl-5-ASA in biological samples (186), (187), (188). These previous HPLC methods required extraction of 5-ASA and N-acetyl-5-ASA from the biological samples (189), (190). However, the extraction of these compounds and their chromatographic analyses are complicated. Based on the suggestions that all types of oral 5-ASA medication have comparable pharmacokinetics of systematic absorption and urinary excretion of 5-ASA and its metabolites, regardless of formulation and release characteristics, (88) it was decided to

develop a simplified approach for the simultaneous determination of 5-ASA and N-acetyl-5-ASA in human urine by HPLC without extraction.

7.2.3 Aim and objectives

In order to assess medication adherence, the aim of this study was to develop a simple, rapid and sensitive analytical method for the determination of 5-ASA and N-acetyl-5-ASA in the urine by HPLC without extraction.

7.2.4 Method and procedure

Urine samples were defrosted on the day of analysis and prepared by filtering the urine into glass HPLC sample vials using disposable plastic syringes and Whatman filters (Whatman Ltd, UK) (0.2 µm NYL W/GMF). The 5-ASA standard compound (>97%) was provided by Fluka Sigma Chemical Co (Fluka Holding AG, Switzerland). Acetic anhydride and HPLC grade methanol and acetonitrile were from Fisher Chemicals (Fisher Scientific Ltd, UK). N-acetyl-5-ASA was synthesised at Loughborough from 5-ASA by acetylation with acetic anhydride and purified by recrystallisation with ethanol and identified by melting point and spectroscopy. Anhydrous theophylline (99%), sulfapyridine (>99%) and sulfasalazine were purchased from Sigma-Aldrich (Sigma-Aldrich Company, Ltd, UK) whilst 4-ASA (98%) and 6-methylthiopurine (97%) were from Alfa Aesar (Alfa Aesar GmbH εt Co KG, Germany). Components for the mobile phase included anhydrous EDTA, anhydrous disodium hydrogen phosphate (Na_2HPO_4), both from Sigma-

Aldrich (Sigma-Aldrich Company, Ltd, UK) , and also 36% hydrochloric acid (HCl), 1-heptane sulfonic acid/sodium salt and tri-sodium citrate from Fisher Chemicals (Fisher Scientific Ltd, UK). The chromatographic urine sample separation, quantitative determination and the calibration curves were performed using an HPLC Agilent 1100 system (Fig. 7.1) that consisted of a 1322A 1100 vacuum degasser, a 1311A 1100 binary pump, a 1313A 1100 autosampler, and a 1314A 1100 variable wavelength detector. The separations were carried out on an analytical 50x 4,6mm i.d. X Bridge C_{18} column (Waters, UK). The mobile phase consisted of a mixture of anhydrous disodium hydrogen phosphate (1.419g), EDTA (0.0292g), tri-sodium citrate (29.410g) and sodium 1-heptane-sulfonate (0.809g). The pH was adjusted to 3.0 with 36% hydrochloric acid and then acetonitrile (20 ml) was added at a ratio of 98:2. The injection volume was set at 1µl per sample, the UV wavelength was set at 313nm, and the mobile phase was delivered at a flow rate of 0.8ml/min.

Standard solutions of 5-ASA, N-acetyl-5-ASA, 4-ASA (internal standard) were prepared and analysed every 5-7 days to determine their retention times for identification of any extra peaks in the samples. The calibration curves of both 5-ASA and N-acetyl-5-ASA were plotted at the beginning of HPLC analysis for quantitative determination of the peaks. The selectivity and reliability of the method were evaluated from spiked urine samples. Routinely, each sequence was started with a reference solution and this was repeated after every 10-15 samples. The reproducibility of the analyses was

tested by repeating the test on the same vial of urine sample after every 10-15 samples. These arrangements minimised the risk of false negative results. The chromatographic data management was automated using Agilent Chemstation software (Fig. 7.1).

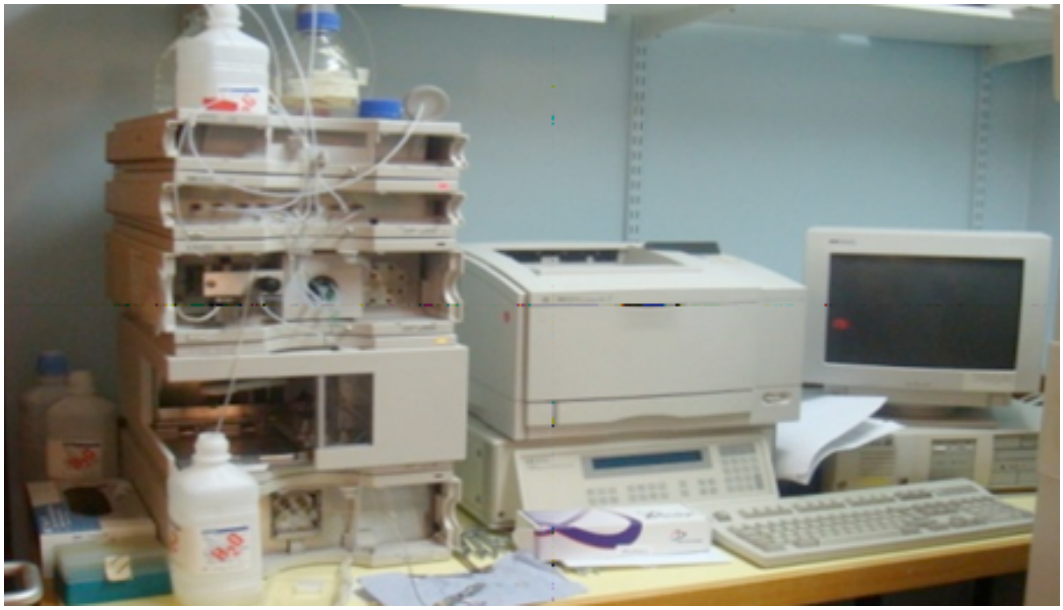


Figure 7.1: HPLC Agilent 1100 series (LGH laboratory)

7.2.5 Results and Discussion

This method was used as an objective measure of adherence in cross-sectional, quantitative survey (Chapter 6). One hundred and fifty one urine samples were analysed by HPLC, analysis run time was 8-13 minutes for each sample. The results of this study showed large individual variations in 5-ASA (7.0-1268 µg/ml) and N-acetyl-5-ASA (9.7-1903.9 µg/ml) urine concentrations. The limit of detection was 7.0 µg/ml for 5-ASA and 9.7 µg/ml

for N-acetyl-5-ASA. Typical chromatogram derived from the urine sample of a compliant subject is shown in Figure 7.2.

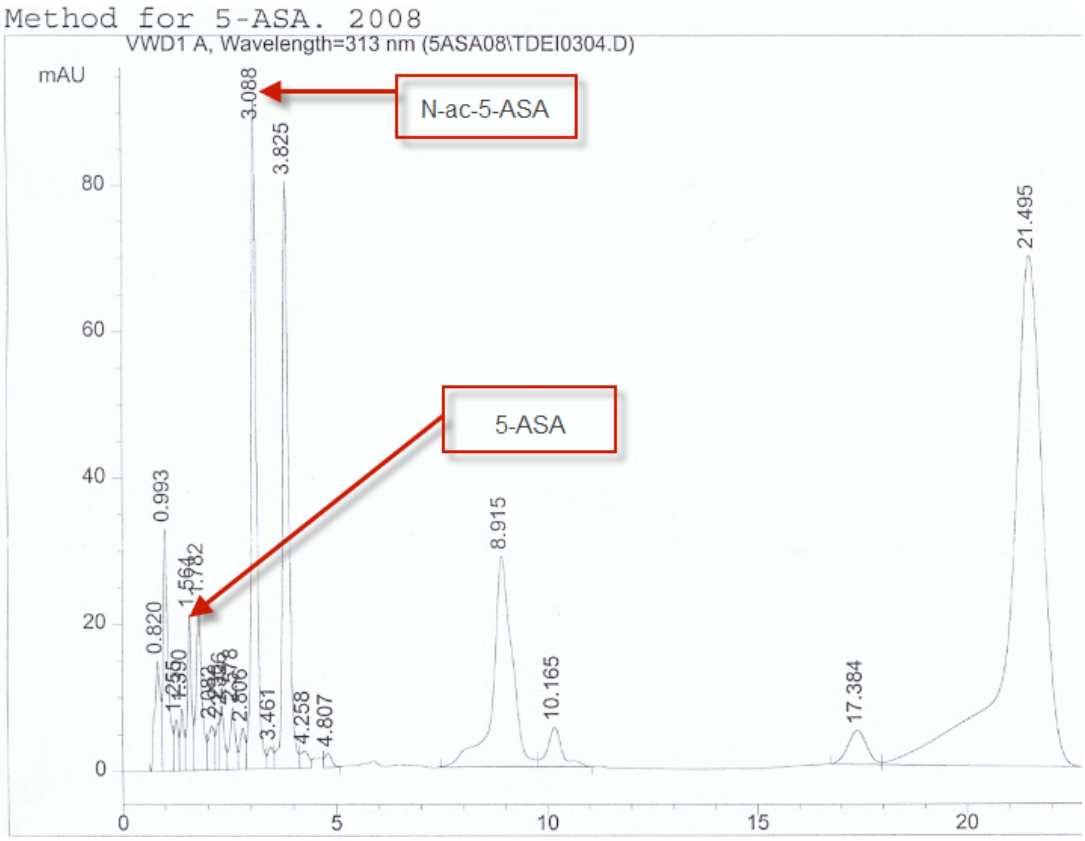


Figure 7.2: Typical chromatogram derived from the urine sample of subject compliant with 5-ASA medication

The retention times for 5-ASA and N-acetyl-5-ASA were 2.0 min and 4.8 min respectively (Fig 7.3 and 7.4) [personal communication Jun Wang, MSc, 2007].

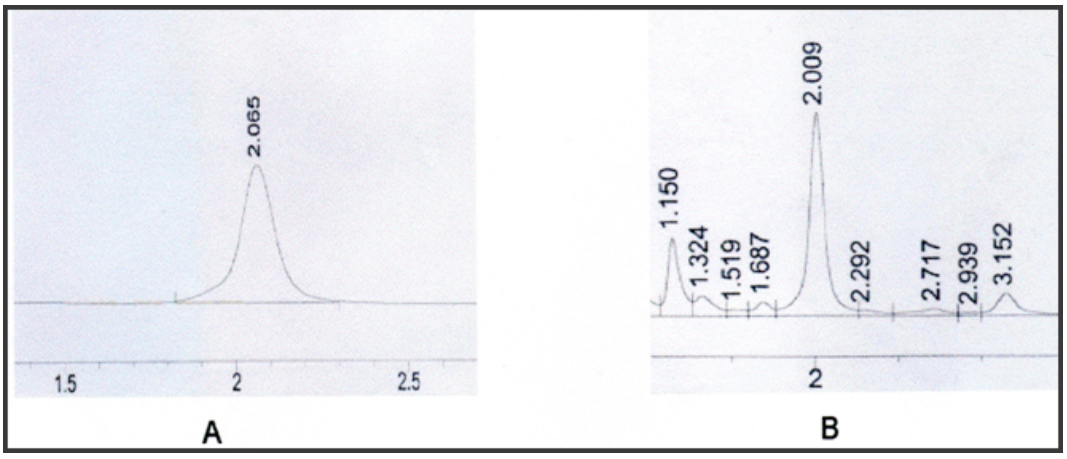


Figure 7.3: Graph A shows the retention time of 5-ASA in standard solution and B gives the retention time of 5-ASA in urine samples

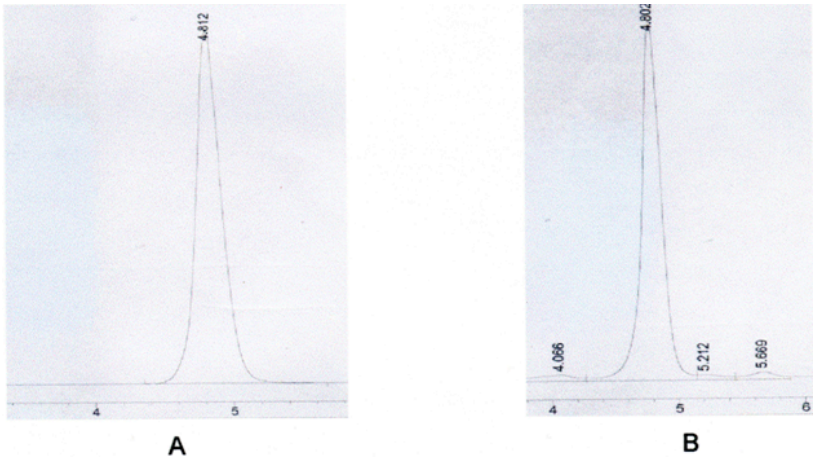


Figure 7.4: Graph A shows the retention time of N-acetyl-5-ASA in standard solution and B gives the retention time of N-acetyl-5-ASA in urine samples

Twelve chromatograms exhibited some extra and carry over peaks [personal communication Jun Wang, MSc, 2007]. Figure 7.5 shows a comparison of an expected chromatogram and one that had multiple peaks [personal communication Ting Diu, MSc, 2008].

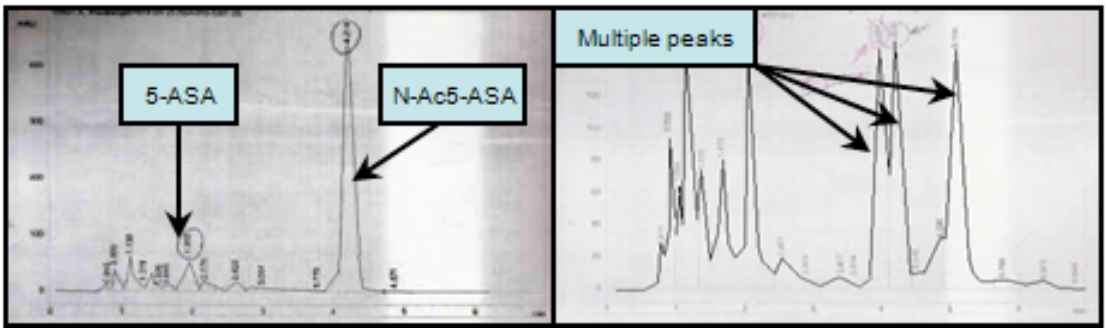


Figure 7.5: A comparison of an expected chromatogram and one that had multiple peaks

Appearance of multiple extra peaks could mislead analysis; therefore 25 samples (12 and other related by sequence) were rerun using current HPLC setting with increased run time to 30 minutes instead of 8 minutes. The previous record made possible to construct a sequential picture of chromatograms that were run in the same order to pinpoint the cause of extra or carry over peaks [personal communication Ting Diu, MSc, 2008].

After careful examination of this phenomenon it was established that multiple peaks was mainly observed in patients taking sulphasalazine. Sulphasalazine is metabolised in the colon by bacterial azo-reduction, releasing active free 5-ASA, N-acetyl-5-ASA and at least three other metabolites: suphapyridine, N-acetylsulphapyridine and 5-hydroxysulphapyridine, there are also other minor metabolites. This means that on the chromatograms of patients who takes sulphasalazine at least three extra peaks can be expected in addition to the main 5-ASA and N-acetyl-5-ASA peaks (Fig. 7.6).

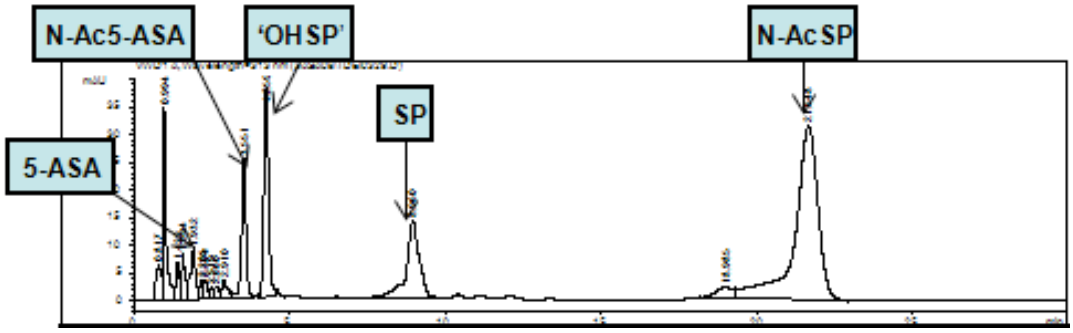


Figure 7.6: Identifying the peaks observed in urine of patient who takes sulphasalazine

Based on the analysis of urine samples, complete non-adherence was defined as undetectable (0 µg/ml) levels of 5-ASA or N-acetyl-5-ASA. Concentrations of 5-ASA with values <30 µg/ml and of N-acetyl-5-ASA with values <90 µg/ml were defined as partial non-adherence, and a concentration of 5-ASA ≥30 µg/ml and N-acetyl-5-ASA ≥90 µg/ml was deemed to indicate adherence.

The chromatograms analyses found that the 5-ASA peaks were usually very small and not clearly distinguished, in contrast the N-acetyl-5-ASA peaks were usually larger and increased with the increase of 5-ASA peaks (Fig.7.7). In addition, there were fewer interfering peaks near the N-acetyl-5-ASA peak than in the 5-ASA region [personal communication Jun Wang, MSc, 2007].

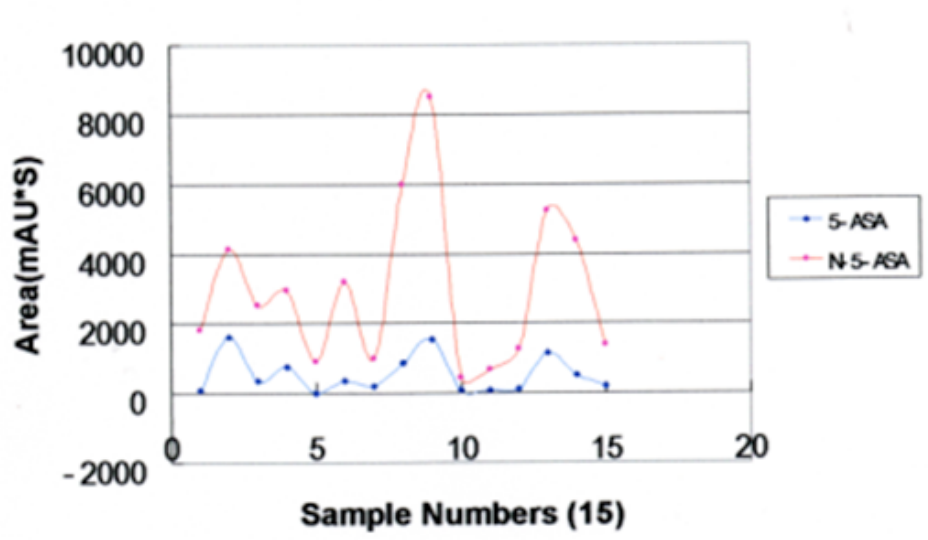


Figure 7.7: The relationship between of areas between 5-ASA and N-acetyl-5-ASA in typical set of urine samples

7.2.6 Concluding remarks

This method can be used for the determination of 5-ASA and its acetylated metabolite N-acetyl-5-ASA in urine without requiring an extraction procedure. The presence of N-acetyl-5-ASA may be more significant than the presence of 5-ASA when assessing adherence. It was established that extra peaks were due to the presence of sulphasalazine metabolites; therefore, to avoid appearance of extra and carry over peaks the run time was increased to 30 minutes. To address the question raised earlier in Chapter 6.5.2, additional pharmacokinetics studies were needed to confirm that a spot sample of urine can provide an accurate, objective measure of adherence.

7.3 Section 2: Pilot pharmacokinetics study

7.3.1 Introduction

This section briefly describes a pilot pharmacokinetics study. The pilot was undertaken in order to confirm that the objective measurement of adherence described in section 1 could be utilised in a subsequent randomised control trial. This was added to the protocol as Amendment Number 1 and gained a favourable ethical opinion by Leicestershire, Northamptonshire & Rutland Research Ethic Committee 2 (06/Q2502/100). The study was carried out as two MSc student projects undertaken in June - September 2009 by Enas Ismail and Ting Diu from Loughborough University.

7.3.2 Background

As already discussed in Chapters 2.7 and Chapter 3, 5-ASA (mesalazine) is the active moiety in the treatment of UC (191). If the drug is not specially formulated, it will be absorbed from the small intestine into the blood. It is metabolized into N-acetyl-5-ASA by the liver. Both 5-ASA and N-acetyl-5-ASA are excreted by the kidney into the urine. Because the mechanism of action of 5-ASA is generally perceived to be topical, the optimal delivery site for the treatment of ulcerative colitis is the large intestine (192).

A number of different tactics for delivering 5-ASA to the colon without absorption by the small intestine have been devised, resulting in the development of multiple approved oral and topical preparations (described in Chapter 3.3, Figure 3.4).

5-ASA pro-drugs include sulphasalazine (sulphapyridine linked to 5-ASA), olsalazine (a 5-ASA dimer) and balsalazide (5-ASA linked to 4-aminobenzoyl-β-alanine, an inert carrier). After ingestion, pro-drugs are metabolised in the colon by bacterial azo-reduction, releasing active free 5-ASA.

5-ASA can also be delivered as a monomer and is available in several formulations. Delayed-release (pH dependent) preparations (Asacol, Salofalk) are designed to release 5-ASA in the terminal ileum and colon where the pH is known to be 7 or greater. A prolonged-released preparation (Pentasa) is released partially in the small bowel, where about 50% of the drug is available, with the remainder released in the colon (193).

Free 5-ASA when administered orally undergoes rapid and nearly complete systematic absorption from the proximal small intestine depending on concentration and local pH. This is then followed by extensive metabolism to N-acetyl-5-ASA, by the N-acetyl-transferase enzyme, which is present in intestinal epithelial cells and the liver. It is then excreted in the urine as a mixture of free 5-ASA and N-acetyl-5-ASA (194), (195), (196), (181). The excretion of these compounds and its chromatographic analysis were used by previous researchers as objective measures of medication adherence (112) and this was therefore selected as an appropriate measure in our study. This approach was based on a systematic review of the primary literature (177) published by Sandborn and Hanauer in 2003. They noted

that the urinary excretions of 5-ASA were comparable for all oral 5-ASA formulations and pro-drugs, including sulfasalazine, olsalazine, balsalazide, Asacol, and Pentasa. In contrast, Levine (197) demonstrated a marked variability in 5-ASA metabolism and distribution following oral dosing of different 5-ASA formulations. As already discussed in previous section 7.1.5 and in Chapter 6, preliminary findings similarly showed large individual variations in 5-ASA and N-acetyl-5-ASA urine concentrations in patients receiving maintenance therapy with different 5-ASA preparations and dosage regimes.

7.3.3 Aim and objectives

This pilot study aimed to compare the range in urinary excretion of 5-ASA or N-acetyl-5-ASA in UC patients receiving maintenance therapy with different 5-ASA preparations and dosage regimes in order to further investigate whether urinary drug excretion in a spot sample could be used as an objective measure of adherence. Specific objectives were to define the level above which adherence can be determined and to identify any differences in drug excretion between South Asian and Caucasian patients.

7.3.4 Methods and procedures

From the intervention group cohort, 15 patients with UC prescribed various formulations and dosage regimes of 5-ASA compounds were asked to participate in an additional, optional, pharmacokinetic study in order to

develop a table of urinary excretion characteristics. The necessity for 5-ASA medication compliance was impressed upon this group and patients were informed of the purpose of this pharmacokinetic study (Appendix 9). All participants in this optional pharmacokinetic study gave specific additional written consent (Appendix 10).

Seven urine samples were collected in plastic containers from each participant at 3 hourly intervals over a 24 hour period. Patients prescribed twice daily medication administered the medication between 7 am - 9 am and 7 pm – 9 pm and patients prescribed three doses per day administered the medication between 7 am - 9 am, 12 pm - 2 pm, and 7 pm - 9 pm. Urine samples were coded with an anonymous identifier to retain blindness and were kept at -20 C until the analyses were performed. The concentrations of 5-ASA and N-acetyl-5-ASA in the urine were determined by HPLC (as described in 7.2.4).

7.3.5 Results

Participants comprised 8 males and 7 females, between the ages of 24 and 66 years. Five participants were of South Asian origin and 10 were Caucasian. There was no deviation from protocol, and all patients were compliant.

The highest concentrations of 5-ASA and N-acetyl-5-ASA were detected between 4 to 10 hours after drug administration. This reflected use of delayed-release formulations.

The summary data of 5-ASA prescription information and the range and mean for urinary excretion of 5-ASA and N-acetyl-5-ASA for each participant are shown in Table 7.1 [personal communication Enas Ismail, MSc].

Table 7.1: The summary data of 5-ASA administered as different formulations and the range and mean for urinary excretion of 5-ASA and N-acetyl-5-ASA [personal communication Enas Ismail, MSc]

		Asacol				Pentasa					Colazide			Olsalazine	Sulfasalazine	
Patient Number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Dosage (mg)		800	800	800	800	1000	1000	1000	500	1000	1500	750	750	50	500	500
Frequency		TDS	TDS	BD	BD	BD	BD	BD	TDS	BD	TDS	BD	TDS	BD	BD	BD
5ASA Concentration Range (µg/ml)	Minimum	0.0	7.27	0.0	43.71	19.98	15.78	68.24	69.73	22.13	40.71	112.32	0.00	56.19	0.00	26.86
	Maximum	0.0	19.9	137.82	224.64	268.52	369.44	713.11	119.76	173.14	332.64	233.79	0.00	147.95	247.36	91.93
	Mean	0.0	12.46	22.97	117.72	105.92	202.75	262.73	115.43	73.738	126.00	167.26	0.00	89.24	56.75	53.41
N-Acetyl-5ASA Concentration Range (µg/ml)	Minimum	89.41	51.97	105.89	789.43	250.09	146.92	353.12	371.35	355.40	160.89	542.47	250.13	162.62	255.08	71.73
	Maximum	444.77	238.16	739.98	1139.86	1211.35	1178.22	1679.81	1237.46	905.62	1603.70	1207.44	910.84	387.06	2516.94	457.22
	Mean	286.16	106.45	302.92	909.53	663.77	375.27	843.18	708.60	749.4	573.48	1068.20	634.81	280.44	735.82	229.89

It was found a lower level in urinary excretion of 5-ASA (38.29 μg/ml median value) and N-acetyl-5-ASA (401.27 μg/ml median value) after Asacol treatment which indicates a more distal release from this preparation compared to Pentasa (295.38 μg/ml and 671.61 μg/ml median values, respectively for 5-ASA and N-acetyl-5-ASA) (Table 7.1) [personal communication Enas Ismail, MSc].

The highest urinary excretion of N-acetyl-5-ASA (758.83 μg/ml median value) was found after Colazide treatment and the lowest urinary excretion of N-acetyl-5-ASA (280.44 μg/ml median value) was noticed after Olsalazine treatment (Table 7.1) [personal communication Enas Ismail, MSc]. After administration of different 5-ASA formulations, especially of the pro-drugs, 5-ASA was not always detectable in the samples of compliant patients (subjects 1, 3, 12, 14) but N-acetyl-5-ASA was detected in all these cases. Therefore, the presence of N-acetyl-5-ASA in urine (Fig. 7.8) was chosen as the most clinically valuable measurement of adherence.

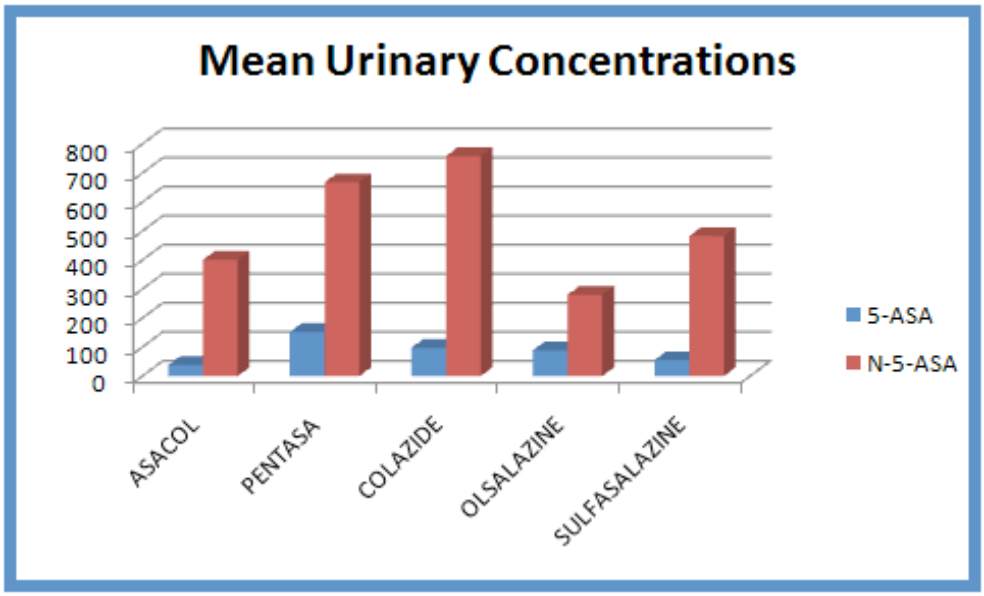


Figure 7.8: Bar chart showing a comparison of 5-ASA and N-acetyl-5-ASA urinary concentration for different 5-ASA formulation

The relative concentrations of 5-ASA and N-acetyl-5-ASA from each subject were plotted. Patients were grouped according to the prescribed 5-ASA formulations and the N-acetyl-5-ASA concentrations were plotted against time.

Patients 3 and 4 took 1.6 g/day of Asacol administered twice daily and two others (1, 2) - 2.4 g/day administered three times daily. Unexpectedly, the excretion of N-acetyl-5-ASA was greater in patient 4 who was on the same dose as patient 3 and a lower dose compared to patients 1 and 2 (Fig 7.9) [personal communication Enas Ismail, MSc].

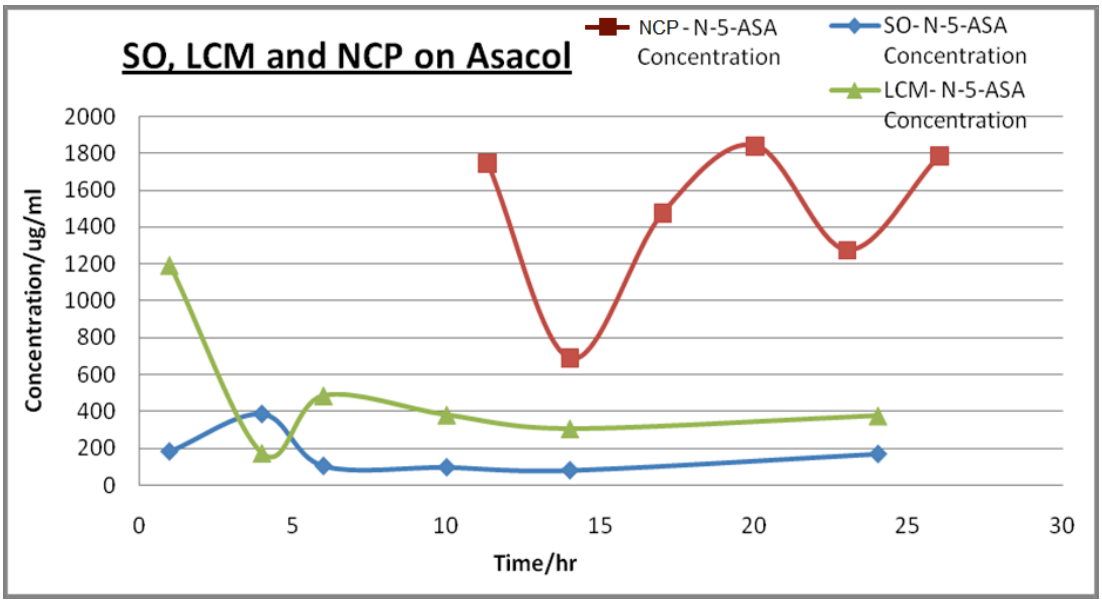


Figure 7.9: Excretion of 5-ASA and N-acetyl-5-ASA during 24 hours

Four patients took 2 g/day of Pentasa administered twice daily and patient 8 took 1.5 g/day administered three times daily. All these patients seem to have similar concentration curves (Fig 7.10) with some possibly taking their medication slightly later than others.

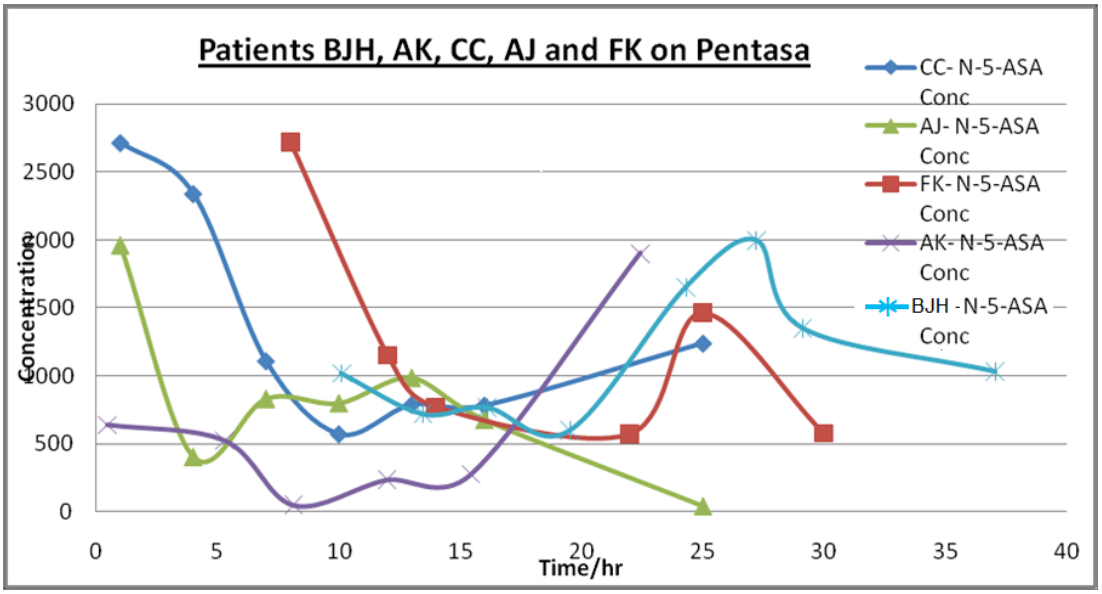


Figure 7.10: Excretion of 5-ASA and N-acetyl-5-ASA during 24 hours

It was noted that the urinary excretion for both 5-ASA and N-acetyl-5-ASA did not appear to increase with a slight increase in oral dose from 1.5 g to 2.0 g (Pentasa) and from 1.6 g to 2.4 g (Asacol) [personal communication Enas Ismail, MSc].

Two patients (10 and 11) took 4.5 g/day of Colazide and patient 12 took 2.25 g/day administered three times a day. All these patients seemed to have similar concentration curves (Fig. 7.11) [personal communication Enas Ismail, MSc].

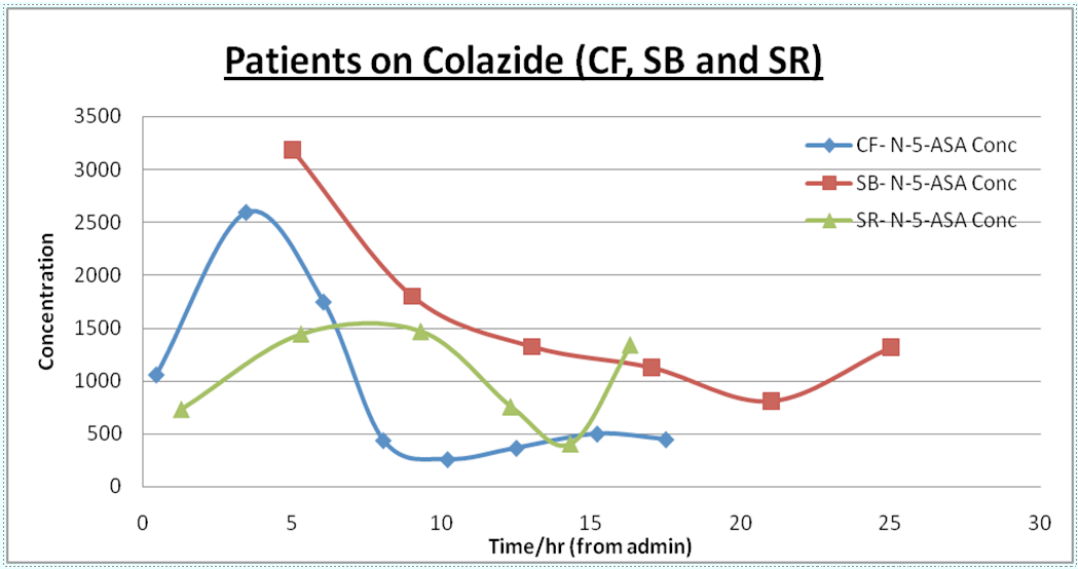


Figure 7.11: Excretion of 5-ASA and N-acetyl-5-ASA during 24 hours

For the patient taking balsalazide 2.25 g/day, 5-ASA was not detectable (0 µg/ml) in any of the seven samples, but the concentration for N-acetyl-5ASA was detected in range of concentration: 404 - 1470 µg/ml [personal communication Enas Ismail, MSc].

Despite the fact that patients 14 and 15 were of the same ethnicity and on the same dose of sulphasalazine (1 g/day administered twice a day), very different N-acetyl- 5-ASA concentration profiles were found (Fig. 7.12) [personal communication Enas Ismail, MSc].

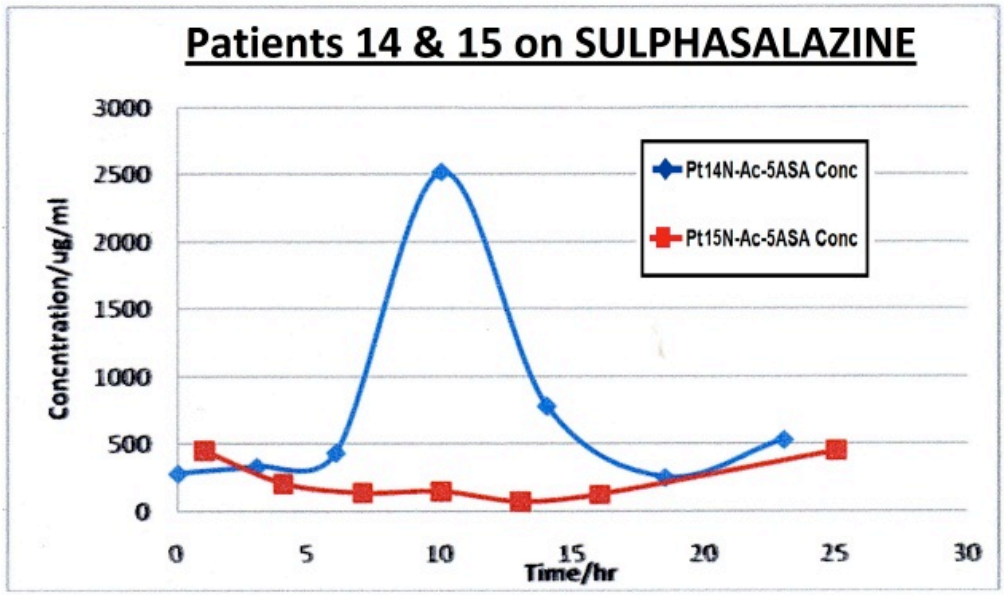


Figure 7.12: Excretion of 5-ASA and N-acetyl-5-ASA during 24 hours

7.3.6 Discussion

Even given that all 5-ASA formulations are metabolised by the same pathway to N-acetyl-5-ASA, this study showed that free 5-ASA was not always detectable in urine. We suggest that the presence of N-acetyl-5-ASA in urine is the most clinically valuable measurement of adherence, due to the peak area of N-acetyl-5-ASA being larger than that of 5-ASA and having less interfering peaks [personal communication Jun Wang, MSc 2007; Ting Diu,

MSc 2009]. Previous work also shows that material excreted in the urine contains 86% of N-acetyl- 5-ASA (195).

This study demonstrates that urinary excretion of 5-ASA and N-acetyl-5-ASA was greater in subjects treated with Pentasa compared to Asacol. This increased urinary excretion may be explained by larger systemic absorption due to proximal release of Pentasa (181).

A greater proportion of urinary 5-ASA is unacetylated in those patients receiving mesalazine compared with patients receiving 5-ASA pro-drugs. This confirms findings from a number of previous pharmacokinetic studies (198), (199).

Some patients in the mesalazine group showed unexpectedly high levels of urinary 5-ASA and N-acetyl-5-ASA concentrations. This disproportional pattern of excretion may be explained by differences in diet and individual N-acetylation polymorphism (88), (178). Surprisingly, we found that a slight increase in the oral dose of mesalazine did not always increase drug excretion. This could be due to some IBD patients having abnormally low colonic pH values, thereby reducing bioavailabllity of 5-ASA from pH-dependent formulations (200).

The highest urinary excretion of N-acetyl-5-ASA (758.83 µg/ml median value) was found after Colazide treatment. This could be explained by the fact that

absorption is less, and acetylation proportionately greater, for pro-drugs compared with mesalazine preparations (196), (181).

The lowest urinary excretion of N-acetyl-5-ASA was noticed after olsalazine treatment. Previous work reports that olsalazine has a lower systematic delivery of 5-ASA than other mesalazine preparations (180). Campbell and Berglindh noted that the material excreted in the urine was found to comprise approximately 90% N-acetyl-5-ASA, 5% free 5-ASA and 5% olsalazine (201). Conclusions should not, however, be drawn from our study as only one patient was prescribed olsalazine.

We did not find differences in drug excretion between South Asian and Caucasian patients. This confirmed an earlier report that the rates of recognized slow acetylator mutation have been found to be broadly similar in people of Asian and white ethnic origins (179).

It is acknowledged that this study has limitations. It was too small for providing generalisable results and a larger-scale pharmacokinetic comparative study with a larger and controlled set of data is needed. However, the study did help to clarity the levels of 5-ASA urinary excretion which would be likely to indicate good compliance with treatment.

7.3.7 Concluding remarks

The presence of N-acetyl-5-ASA in urine is the most clinically valuable measurement of adherence. The baseline below which non-adherence should be assumed is <90 µg/ml for N-acetyl-5-ASA, using our HPLC method in spot samples from UC patients on maintenance 5-ASA therapy. This was determined as the lowest level that had been detected in the cohort of patients known to be adherent. The viability of this method for use is therefore confirmed and the method was agreed for use in the RCT study (Chapter 9).

7.4 Section 3: Determination of a simple method for detection of non-adherence to 5-ASA therapy.

7.4.1 Introduction

Urine dipstick tests are widely used in many areas of health care including routine examinations, treatment monitoring, self-monitoring, general preventive medicine and to determine the presence or absence of specific parent drugs or their metabolites. No dipstick test is currently available to determine 5-ASA medication compliance. This section briefly describes the process developed to determine whether such a test was feasible. The preliminary stages of this work were carried out as student projects [personal

communication from Kate Hilling BSc (July 2007), Rebecca Bowley BSc (July 2008) and Enas Ismail MSc (September 2009) Loughborough University].

7.4.2 Background

The current gold standard for monitoring 5-ASA and its metabolites in urine is HPLC method (189), (190) described in section 7.2. However, this method is costly, time-consuming, and test results are not always easy to interpret. It was considered that a simple dipstick test for detection of 5-ASA and its metabolites could be devised and would have considerable clinical value. This test should be efficient, immediate, near patient and cost-effective so as to provide physicians with accurate bedside information on adherence to 5-ASA treatment and so improve management of UC. 5-ASA is derivative of salicylic acid (SA). Ferric chloride ($FeCl_3$) and Trinder's Reagent (contains ferric nitrate ($Fe(NO_3)_3$), mercuric chloride ($HgCl_2$) and hydrochloric acid (HCl)) have both been used to identify salicylates in the urine of patients presenting with possible drug overdose (202), (203), (204). The chemical similarity between 5-ASA and SA was also used by Shaw *et al*. (114) for the development of a simple solution method to assess compliance by patients with 5-ASA therapy. This method was based on a test previously described by Trinder (205). Following a literature review, $FeCl_3$, (202), (206) was identified as the preferred colour test for salicylic acid detection – because it avoided the use of mercury salts. This test is based on the formulation of coloured complexes (Figure 7.13) between salicylates and the iron (III) ion.

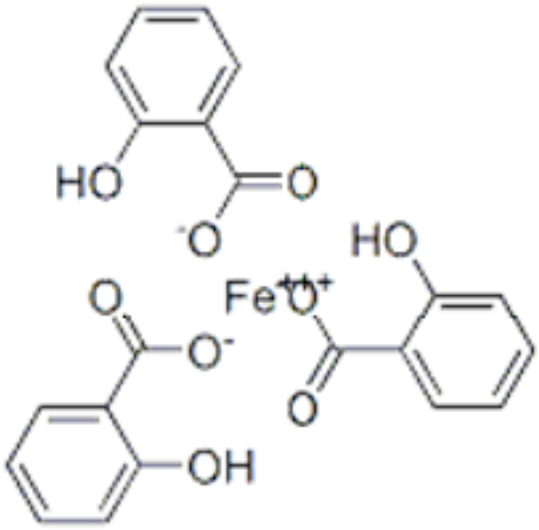


Figure 7.13: Coloured complex between salicylate and iron (III) ion

Ishizawa and co-workers (207) published their work on the development of a salicylic acid detector tube and a dipstick test device (208) based on a colour-forming reaction with ferric chloride. Both devices were developed for the emergency screening of salicylic acid in cases of acute poisoning with aspirin.

7.4.3 Aim

The aim of this study was to devise and evaluate the feasibility of a dipstick-type test for detection of 5-ASA and its metabolites in urine which could be used to assess patients' adherence to this medication.

7.4.4 Methods and procedure

Taking into consideration the chemical similarity of 5-ASA and SA, the proposed dipstick test was centred on the formation of a coloured complex from the reaction between SA and ferric salts (202), (205), (206). To avoid the use of solutions of reagents, the concept was to immobilise the reagent in a dry form on a dipstick or test strip in a similar way to the glucose test strips used to monitor diabetes. It was therefore necessary to initially determine the most effective media within which the ferric ion could be suspended in preparation for subsequent detection of SA, 5-ASA and N-acetyl-5-ASA.

Two media types were tested: filter paper strips and strips of an ion exchange membrane (Nafion®). Both were impregnated with ferric ion and the efficacy of each medium was evaluated within the laboratory by exposure to reducing concentrations of SA, 5-ASA and N-acetyl-5-ASA. Once the preferred suspension medium was determined, a prototype test sample was then evaluated using urine collected from patients with UC on maintenance 5-ASA therapy.

7.4.4.1 Preliminary tests

Preliminary tests were conducted in order to discover a coloured complex produced by SA, 5-ASA and N-acetyl-5-ASA solutions with ferric ion and to identify a detection limit for SA, 5-ASA and N-acetyl-5-ASA. Concentrations of SA, 5-ASA and N-acetyl-5-ASA solutions were prepared in diminishing

concentrations, starting at 500 µg/ml and decreasing until the limit of detection with one drop of 10% ferric chloride solution was discovered. After addition of one drop of 10% ferric chloride the solutions turned from deep purple/blue (concentration of 5-ASA 150 µg/ml) to light purple (concentration of 5-ASA 20 µg/ml) [personal communication Kate Hilling BSc, July 2007, Loughborough University]. The same process with similar result was carried out for serial dilutions of the SA solution (500-50 µg/ml). However, very little or no colour change was observed in N-acetyl-5-ASA solutions [personal communication Kate Hilling BSc, July 2007, Loughborough University].

7.4.4.2 Filter paper tests

Filter paper was investigated as a ferric ion suspension medium candidate. Impregnated paper strips were prepared by cutting disks of filter paper into strips (5 x 1 cm) and then dipping them in ferric chloride solution (10% m/V). They were left to dry at room temperature before use. The strips were then dipped into the serial dilutions of SA, 5-ASA and N-acetyl-5-ASA (1000 to 50 µg/ml) and the reaction colours compared [personal communication Rebecca Bowley BSc (July 2008) Loughborough University]. The strips used to test the stock 5-ASA solution turned a purple/blue colour complex (Figure7.14).

Figure 7.14: Ferric chloride strip testing 5-ASA solution

On testing, the colour changes described above were rapidly evident for 5-ASA and SA solutions, but not for N-acetyl-5-ASA solutions. The Detection limit for SA was 60 µg/ml and the detection limit for 5-ASA was 100 µg/ml. However, in 15-20 seconds the colour complex leached into the surrounding liquid and it did not remain evident on the filter paper for any length of time [personal communication Rebecca Bowley BSc (July 2008) Loughborough University].

In order to make a decision as to which ferric salt was the most suitable to use for the remainder of the project, a direct comparison was made between solutions of ferric chloride and ferric nitrate. Each solution was made to be 10% m/V (5 g of each solid was dissolved in deionised water and then diluted to 50 ml). These were used to impregnate filter paper strips, as before and tested with a range of 5-ASA dilutions. Three tests were carried out on each solution: one using a ferric chloride strip, one using a ferric nitrate strip and

one using a strip consisting of a mixture of the two (equal volumes of ferric chloride and ferric nitrate were mixed in a sample vial and then a paper strip was dipped in the solution) [personal communication Rebecca Bowley BSc (July 2008) Loughborough University].

The results from each set of three strips were almost identical. This suggests that there was little difference in the ferric nitrate and ferric chloride solutions. However, with the ferric nitrate there was less leaking of product colour into the test solution. This was considered an advantage over ferric chloride; therefore ferric nitrate was used as the source of ferric ions for the remainder of the project.

Given the less than ideal results (detection limits were not sufficiently low and the colour of the product leaked into the test solution) it was decided to investigate other ferric ion suspension medium candidates and exclude N-acetyl-5-ASA solutions for further testing.

7.4.4.3 Nafion® strip tests

Nafion® was investigated as a ferric ion suspension medium candidate. Nafion is a sulfonated tetrafluoroethylene discovered in the late 1960s by Walter Grot. It is the first of a class of synthetic polymers with ionic properties which are called ionomers. Loh *et al.* (209) described the use of ion exchange particles on a probe to test for salicylates and so identified a new method to

test for chemicals. It utilises an ion exchange material that allows ferric ions to be immobilised on the surface, whilst still letting them react as they would normally.

Nafion® membrane was cut into 5 cm^2 squares and soaked overnight in ferric nitrate solution (20%). The following day, the membranes were recovered from the solution, blotted dry and then a strip was cut from them. The squares were reduced in size to 1 cm^2 and used to test the 5-ASA and SA solutions (1000 to 50 µg/ml) [personal communication Rebecca Bowley BSc (July 2008) Loughborough University]. On testing 5-ASA solutions, the colour of the strip changed to a purple/blue colour (Figure 7.15) within 3-5 seconds.

Figure 7.15: Nafion® strip with immobilised Fe3+ ion having tested 5-ASA

The signals from reflectance of the squares were measured using a reflectance spectrometer. The signals at 600nm are shown in Table 7.2.

Table 7.2: Signal from ASA from Nafion® after being soaked in varying ferric nitrate solutions

Concentration of ferric nitrate solution (%)	Signal at 600 nm	
	Blank	100 µg/ml ASA
2.5	0.048	0.239
5	-0.1	-0.035
7.5	-0.108	0.004
10	0.057	0.153
15	0.059	0.2
20	0.061	0.219

An optimum concentration of 20% ferric nitrate was then determined by experimentation. The optimum exposure time of 60 seconds was similarly determined by experimentation and is described in Table 7.3 and Figure 7.16.

Table 7.3: Signal values of Nafion® after varying time frames

Time (sec)	Signal from 100 µg/ml ASA at 600 nm
0	0.011
15	0.122
30	0.179
60	0.193
90	0.206
120	0.255
180	0.238

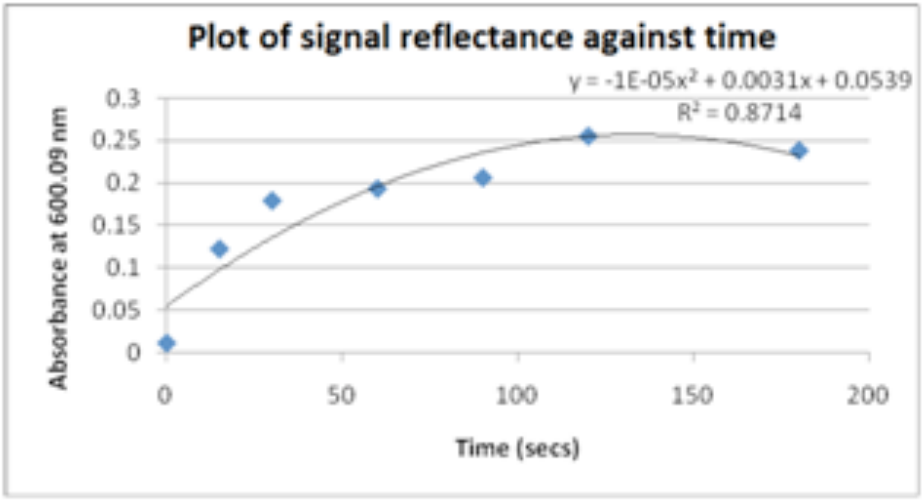


Figure 7.16: Determination of optimal expose time

From this initial test, the results looked promising [personal communication Rebecca Bowley BSc (July 2008) Loughborough University]. Firstly, the colour of the reacted Nafion® was intense and could be easily distinguished from the blank, unreacted Nafion® (Fig. 7.17).

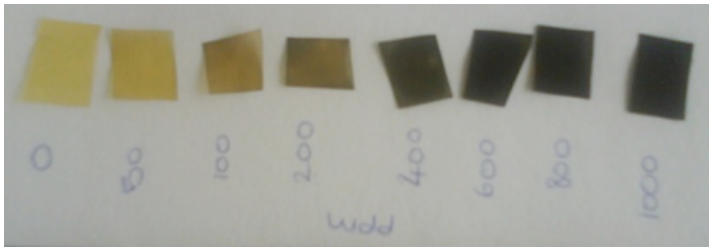


Figure 7.17: Calibration tests of 5-ASA (concentration range: 0-1000 µg/ml)

Secondly, as the ferric ion, and therefore the product, were immobilised on the surface of the membrane the colour stayed on the strip. The 5-ASA molecules had clearly complexed with the ferric ions on the surface of the

membrane and remained there. This property would have great advantages for dipstick test use in clinical settings.

7.4.4.4 Urine tests

The final stage of dipstick development was the investigation of whether 5-ASA and its metabolites were detectable in a sample of urine. Impregnated Nafion® strips, prepared as described earlier by soaking in 20% of ferric nitrate solution, were dipped into the urine samples and the test was interpreted as positive if the urine changed the colour of Nafion® strips from yellow to purple/blue after 1 minute and negative if no colour change was observed.

The test was carried out on 197 urine samples for which the concentrations of 5-ASA and N-Acetyl-5-ASA had previously been determined by HPLC testing. Forty two of 197 (21%) samples caused a purple/blue reaction and were classified as being positive. This group was, noted as having very high concentrations of 5-ASA / N-acetyl-5-ASA (in excess of 100 µg/ml). Eleven of 197 (6%) showed a dark-brown colour reaction despite the fact that HPLC testing determined that these samples contained no detectable level of 5-ASA or N-acetyl-5-ASA. The colour change to dark-brown was therefore interpreted as a reaction to other products within the urine. The remaining 144 samples (73%) showed no colour reaction despite the majority were shown by HPLC testing to contain low levels (20-90 µg/ml) of 5-ASA and its

metabolites [personal communication Enas Ismail MSc (September 2009) Loughborough University].

7.4.5 Discussion

In this study we sought to develop a simple dipstick-type colour test for the detection of 5-ASA and its metabolites in urine. We suggest that this method could be used repeatedly in clinical practice as a follow-up method for patients with UC who take 5-ASA therapy. Research findings (210) in latent tuberculosis infection showed that a similar colour test type provides the physician with immediate information about patient non-compliance. In that case a trusted and immediate diagnostic test proved significantly beneficial and ultimately led to improved adherence to Isoniazid therapy.

However, the proposed method for 5-ASA detection has limitations. The colour changes of Nafion® strips soaked into 20% of ferric nitrate solution were suitable for the detection of 5-ASA and its metabolites in pure solution, but when applied to urine, the colour-reactions were not so clear. Moreover, the colour test was incapable of detecting a major metabolite of 5-ASA (N-acetyl-5-ASA) that predominantly presents in the urine of UC patients on maintenance 5-ASA therapy. An additional problem was that the ferric ion may complex with other compounds present in urine, such as bilirubin, creatinine, urea, uric acid, metabolites of phenylalanine, producing false results. Such compounds in the urine may mask the purple/blue colour of the

ferric complex with 5-ASA. Also, relatively high concentrations of 5-ASA and its metabolite must be present in order for there to be a detectable and characteristic colour change.

7.4.6 Concluding remarks

Despite the theoretical potential of the test, its practical application assessed against predetermined concentrations of 5-ASA and N-acetyl-5-ASA was disappointing because only high levels of adherence proved to be detectable. This test, therefore, was not sufficiently effective to meet the overall aim as it was unable to detect 5-ASA concentration lower than 100 µg/ml. It was therefore determined that the clinical application of the test method investigated in this project would be ineffective. For this reason, no further development work relating to the dipstick method of testing was undertaken.

Chapter 8

Rationale for and design of the adherence enhancing intervention

8 Chapter 8: Rationale for and design of the adherence enhancing intervention

8.1 Introduction

This chapter presents existing evidence regarding adherence enhancing strategies and considers theories about how these strategies may have the desired effect. It describes the development of the adherence enhancing intervention to be tested in the randomised controlled trial. The design of the adherence enhancing intervention was informed by the existing evidence from the literature, appropriate theories, and also by the findings from the qualitative (Chapter 5) and quantitative (Chapter 6) studies.

8.2 Adherence enhancing strategies

Despite a general awareness of the need to enhance medication adherence strategies, studies evaluating adherence interventions in patients with IBD are scarce (211), (212). As was discussed in Chapters 4, 5, and 6, the causes of medication non-adherence are multi-factorial and patients' decisions to adhere to treatment are dynamic and influenced by the daily context (117). No single, specific adherence enhancing strategy has been found that will effectively enhance adherence in all, or even the majority, of patients (213), (214). It was therefore clear that there was a need to design a complex intervention utilising a range of adherence enhancing strategies

(215), targeting the underlying causes of non-adherence and tailored to the needs and preferences of individual patients (216), (217).

Many strategies to improve adherence have been suggested. They have been categorised broadly as educational, behavioural, and affective (218), (219). Later, in the UK, Horne et al proposed a rationalisation of this approach and suggested the use of perceptual (motivational), practical and combined strategies (100). This classification is also used in the NICE clinical guideline for medicines adherence (99) and I have used it for the intervention modelling. However, for the purpose of understanding the rationale, I have used the traditional (educational, behavioural, affective) classification (218), (219), (219), since the available theoretical evidence base which uses this system of classification is wider and more established. In order to identify relevant components of the intervention for the trial, the three types of strategy (218), (219) were defined as follows:

Educational strategies: knowledge-based interventions designed to convey information via oral or written material.

Behavioural strategies: interventions that seek to improve adherence by targeting, shaping, or reinforcing patterns of patient behaviour.

Affective strategies: interventions that appeal to the patient's feeling or emotions or attempt to influence the patient's social relationship and social support.

8.2.1 Rationale for educational strategies

The “Educate Before You Medicate” programme that has been successfully run by the National Council on Patient Information and Education (NCPIE) for many years in the United States and has shown that patient education is the touchstone of effective medication prescription and administration. The chronic nature of UC requires a high level of patient responsibility for successful day-to-day management. In order to make informed decisions about taking medication patients require adequate information. Previous research has found an association between satisfaction with information and adherence to medication in chronic illness (220), (221), (222). However, despite the routine use of educational materials in outpatient clinics, patients often feel that they need more information (223), (224). When patients with UC were asked what they wanted to know about their disease, they placed the risk of developing cancer at the top of their list, followed by new treatments, symptoms, psychological factors, diet and aetiology (225). Up to 75% (226), (227) of patients with UC consider themselves insufficiently informed about their disease. A recent study reported that only 50% of the 192 patients with IBD (both Crohn’s disease and UC) surveyed were aware of any link between their condition and bowel cancer, and 79% felt that their adherence would be improved if they were informed of the chemopreventive potential of 5-ASA medication (228). My qualitative study (Chapter 5) similarly observed a paucity of knowledge about UC and its treatment. In addition, few patients were aware of the possible role of 5-ASA medication in the long-term prevention of colorectal cancer, but all participants evaluated

this information as crucial for encouraging adherence. The cross-sectional, quantitative survey (Chapter 6) also found a high prevalence of perceived dissatisfaction with information about 5-ASA medication across a range of informational topics considered essential in determining informed choice and safe usage. Both the qualitative and quantitative studies suggested that the level of disease related information provided and the level of understanding of associated treatment approaches, are important determinants of adherence. Therefore, the time and attention devoted to orienting patients to their course of treatment are likely to make an important contribution to successful compliance (229).

A large body of evidence supports the premise that educational interventions have a positive impact on medication adherence in chronic conditions (230), (231), (232), (233). According to Krueger *et al*., (234) the reported impact of educational strategies on adherence ranges from 6% to 25%. Educational interventions with guided self-management programmes in patients with IBD have demonstrated a reduction in hospital visits and greater confidence in the patient's ability to cope with IBD (235), (236).

Educational interventions may help to prevent non-adherence that would occur because of misunderstanding about the use of a medication (213). As part of the educational intervention, commonly held patient misconceptions (for example, that the medication can be stopped when the condition comes under control, or that the medication should be taken only when symptoms

are present) should be anticipated and addressed (237). In UC treatment, there is a need to clearly explain to patients that 5-ASA medication should be taken even when the condition is well controlled. A study in IBD patients demonstrated improvements in knowledge and patient satisfaction, and a positive (though statistically non-significant) trend towards greater adherence (211). Education for partners, carers, family and friends may also be beneficial, as these people play an important role in supporting patients and encouraging adherence (233), (212).

Patients are keen to receive educational material in a variety of forms (238). An Italian study (225) has reported that the media preferred by patients with IBD were: specifically prepared books (73%), video cassettes (20%) and leaflets (25%). Ninety percent felt that specially prepared educational material could be very useful. Booklets and leaflets for patients with IBD have been shown to be an effective means of imparting disease related information (239), (240) and have become an important adjunct to the standard doctor-patient consultation. The aim of most booklets is to help the patient to understand the rationale behind their treatment or diagnostic procedure. In this way, it provides a context for the patient's treatment, procedure or medical condition. In the field of gastroenterology, it has been shown that an educational leaflet increases the level of compliance with screening for colorectal cancer (241). Written information is more effective when reinforced verbally (242), although it has also been shown that patients forget more than half of the information from a verbal explanation

immediately after they hear it (229). This suggests that oral information alone is likely to be inadequate.

In summary, being well informed appears to be beneficial in terms of allowing patients to make informed decisions regarding prescribed medication and compliance with general disease management.

8.2.2 Rationale for behavioural strategies

Human behaviour plays a central role in medication adherence. Krueger et al., (234) estimate the reported impact of behavioural strategies on adherence to be 15%, with a range of 0% to 24%. Models of behaviour change have been developed to guide strategies to promote healthy behaviour and facilitate effective adaptation to illness. A chronic condition such as UC can have a strong impact on day to day living as well as attitudes, fears, and beliefs. Due to the fact that UC requires lifelong treatment, medication adherence must be considered within a framework of medication-taking behaviour. Any approaches to the enhancement of medication adherence must therefore contain strategies that directly modify or support patients' behaviour.

8.2.2.1 Learning and conditioning

Discovery of classical conditioning (243) (learning theory) at the beginning of the 20th century by the Russian physiologist Ivan Pavlov was a key milestone

in the field of psychology (244). Classical conditioning is a learning process that occurs through associations between an environmental stimulus and a naturally occurring stimulus (243). Pavlov was studying digestive process in dogs when he discovered that the dogs salivated before they received their food. In fact, after repeated pairing of the laboratory assistant and the food, the dogs started to salivate at the sight of the laboratory assistant. Pavlov noted that dogs were not only responding to the biological need (hunger), but also a need developed by learning. In classic conditioning an organism learns to associate one stimulus with another. The organism learns that the first stimulus is the cue for the second stimulus. Thus classical conditioning introduced concepts that have been particularly important in the design of health-related interventions, such as reinforcement, stimulus-response relationships, modelling, cues to action, and expectancies (244). Classical conditioning formed the basis of what became behavioural psychology.

The aim of increased adherence is to form and maintain a medication taking habit. Habits are the result of the development of different conditioned responses with different levels of complexity. However, the difficulty in maintaining behaviour changes, due to behavioural habits being eliminated (or “extinguished”) is a major problem in health-related interventions, especially those that target alcohol use, smoking and diet (245), (246), (247). Pavlov, who first observed extinction, recognised it as essential to any organism in order for it to continue adapting to a changing environment. He noted that extinction may not be permanent and recovery can occur (243).

An example of a potential retrieval cue is the role of a reminder card, as have been used by Marlatt and Gordon (246) in their relapse prevention program following treatment of alcohol and drug addictive behaviour.

Clearly humans do not respond exactly like Pavlov's dogs. People demonstrate goal-seeking behaviour and have decision-making ability. Personal decisions are therefore based on developing informed choices, which are influenced by motivation or willingness to undertake or reject a task. Thus, medication taking behaviour can be influenced only where there is personal agreement and willingness.

Conditioned response is an important psychological model that can be related directly to aspects of modification of medication-taking behaviour and habit development. For example, an electronic alarm is a neutral stimulus until an individual learns to associate the alarm with remembering to take their medication; the alarm then becomes a conditioned stimulus which produces the conditioned response of remembering to take medication. According to Pavlov’s theory (243), (244), development of new medication taking habits requires at least 4-6 weeks of stimulus exposure. An electronic pill box incorporating an alarm provides both visual and audible stimuli; therefore the conditioned response of remembering to take medication might develop faster. After regular use of the same electronic pill box over a period of 1-3 months, an individual may have developed sufficient association for recollection of medication taking to occur spontaneously without the

continued use of the alarm function, or possibly even without the need to use a pill box system at all. However, this is based on the assumption that the daily routine is reasonably stable and not changing, for example, due to events such as a holiday, business trip, new job or new baby. An event of this type may break the established routine and the associated recollection of the need to take the medication fails. In this example, the conditioned response of remembering to take medication has been temporarily extinguished by a change in environment and routine.

The antagonist for extinction is known as reinstatement (243), (248), (249) and this phenomenon may be beneficial in adherence enhancing interventions. In the example above, temporarily extinguished conditioned responses will be reinstated if the person returns to using the same electronic pill box with the alarm set for required times. Reinstatement results from the resumption of the visual and audible stimuli and their association with the context in which the pill box was originally used during the conditioned response development phase. Reinstatement may also be spontaneous; for example, when the patient returns home from a business trip to a familiar environment, the association triggering recollection may return without the need for re-introducing the use of the alarm.

8.2.2.2 Prospective memory

Another behaviour-related concept that has been reported to be important in relation to medication adherence is prospective memory (250). Prospective memory has been defined as the memory for intentions that are delayed, and has been closely associated with retrospective memory, attention, and planning. In prospective memory research, the dependent variable is the *probability of recall,* in other words, the likelihood that the intention of the action will be remembered and executed in the future. The content of this intention includes information about the presence of an intent (i.e., that there is something that needs to be done), the action to be recalled (i.e., what to do), the retrieval criteria (i.e., when to do it), and some record of whether this intent has been satisfied (i.e., whether it has been completed) (250).

Two types of prospective memory tasks have been identified in the literature – both of which focus on the retrieval criteria element:

- Time-based tasks (e.g., setting an alarm)
- Event-based tasks (e.g. leaving a reminder note, or marking the calendar).

My qualitative study suggested that forgetfulness is the most common reason for poor 5-ASA adherence, especially if 5-ASA compounds have been prescribed more than twice a day, if the daily routine changes, and also during periods of disease quiescence (Chapter 5.5.7). The cross-sectional, quantitative survey also found that 12% of patients were unintentionally non-

adherent because they “just forgot” to take prescribed 5-ASA medication (Chapter 6.4.2).

Classical conditioning and prospective memory theories are highly relevant to the design of interventions that endeavour to influence patients’ ability to adhere to the agreed treatment by targeting, shaping or reinforcing specific patterns of behaviour. This group of behavioural interventions has been classified as practical (100). Some examples of practical interventions are categorised and described below, but there are many other practical interventions, such as refill reminders (234), telephone calls (251) and mobile phone SMS messaging (252).

8.2.2.3 Practical interventions based on behavioural strategies.

Simplifying the dosing regime. Previous research has suggested that simplifying or otherwise modifying the dosing regime should be a first-line strategy for improving adherence (253). Simplified dosing regime will increase “*probability of recall”* because this is a way of reducing the need for people to develop associations by making what needs to be remembered easier. Systematic reviews of interventions to enhance adherence to medication in chronic illness have found that the only consistent successes have been associated with simplifying the dosing regime (254), (255).

Medication reminder charts. Research has shown that medication reminder charts can help patients who are taking multiple medications to remember which medications are to be taken at what time (256), (229). In this case, there is an event-based prospective memory task and also an external visual cue which may indicate what to take, when to take it and what to do if the medication is missed. The use of fridge magnets as visual cues operates in a similar way.

Dosing cues. Dosing cues help to create a mental link between medication-taking and constant features of a patient's schedule (229), (237). This type of intervention is based on Pavlov's theory, where the first stimulus is a cue for the second stimulus. For example, a man who shaves every morning might keep his daily medication near his razor; people who drink coffee every morning might keep their daily medications near the coffeepot (229). Associating medication taking with brushing one's teeth is a popular dosing cue (237), (257).

Pill organisers. It has been shown that pill organisers can remind patients to take their medications, as well as provide a visual check of doses that have been consumed (237). A number of pill organisers now incorporate electronic alarms that can be programmed for multiple daily alerts that beep, vibrate, or give pre-recorded voice prompts when a dose is due. The purpose of pill organisers is to help patients to develop a medication taking habit. The mechanisms of action of these devices are based on both learning and

prospective memory theories. Recent research in hypertension (258), HIV (259), (260) and elderly patients (261) has also suggested that pill box organisers are simple and effective in helping patients to take their medications as prescribed.

8.2.2.4 Understanding patient health beliefs in UC and its treatment

Research has shown that, in patients with IBD, the perceived necessity of medication is weighted against general and specific concerns as well as outcome expectancies (169). These findings are consistent with the results of my qualitative study. The therapeutic decision model (Fig. 5.1) described in Chapter 5.6 and its application to this research shows that few people 'blindly' follow health advice given by health care practitioners, but the majority of people interpret the advice given and make a decision about whether or not to follow it. This process is related to acceptance of their diagnosis and prescribed treatment. Thus, it was suggested that if we want to explain peoples' actions in relation to medication-taking behaviour we should first understand their beliefs about medication (262).

Previously, a number of theoretical models from health psychology such as the Health Belief Model, Theory of Planned Behaviour and Common Sense Self-regulatory Model of Illness, have been used to try to explain the relationship between beliefs and health-related behaviour (263). Social

cognition models (264), such as the Health Beliefs Model (265) and Theory of Planned Behaviour (266), were primarily developed to help us to understand variations in preventive health behaviour (for example, taking regular exercise, giving up smoking), while others such as the Self-regulatory Model of Illness theory (267) were developed to explain illness-related behaviour.

The authors of the BMQ, however, argued that a separate, specific measure to gauge patients' beliefs about medicines would add to the explanatory power of such models (268) Horne suggested that "if we want to explain peoples' behaviour in relation to medicines we should first understand their beliefs about medication" (262). The beliefs about medicines framework integrates some of the constructs within several models (264), (265), (266), (267). For example, the health belief model specifies the benefit and cost of treatment and these are assimilated as necessity beliefs in the beliefs about medication framework. The theory of planned behaviour relates attitude (the product of positive and negative value judgments) towards taking the treatment to the intention to do so. The necessity-concerns differential refers to a patient's "attitude" to their medication.

The beliefs about medication is summarised under four themes (or factors), two themes for beliefs about medicines in general and two themes for beliefs about specific prescribed medication (175). These four themes form the scales of the BMQ (168). The beliefs about medicines framework speculates

that people have beliefs about medicines in general as well as beliefs about medication prescribed for specific illnesses. Two major themes relate to beliefs about medicines in general. The first entitled “general-harm” comprised beliefs about the intrinsic nature of medicines and the degree to which they are perceived as harmful. The second factor was labelled “general-overuse” and comprised beliefs about the way in which medicines are used, particularly the extent to which they are perceived to be over-prescribed by doctors.

Similarly, two themes, necessity and concerns, have been identified for beliefs about medicines prescribed for specific illnesses (168). This was an important step in understanding how patients’ beliefs influence decision making and behaviour in relation of specific medicines prescribed for their illness. Research has shown that patients’ beliefs about treatment (necessity beliefs and concerns) have an important influence on adherence (173). The Necessity-Concerns Framework has been shown to be a useful theoretical model for understanding key attitudes towards prescribed medication (269), (174), (173).

The attitudinal analysis (Fig. 8.1), previously used in cross-sectional, quantitative survey (Chapter 6.4.3), (Fig. 6.3), based on the Necessity-Concerns Framework classifies patients as Accepting (High Necessity, Low Concerns), Ambivalent (High Necessity, High Concerns), Sceptical about medication (Low Necessity, High Concerns) and Indifferent (Low Necessity,

Low Concerns). This attitudinal analysis model provides a simple conceptual scheme for understanding patients' beliefs about medication that are associated with adherence. It suggests that interventions to facilitate optimal adherence for IBD patients should be based on Necessity- Concerns Framework in order to address such perceptual barriers (173).

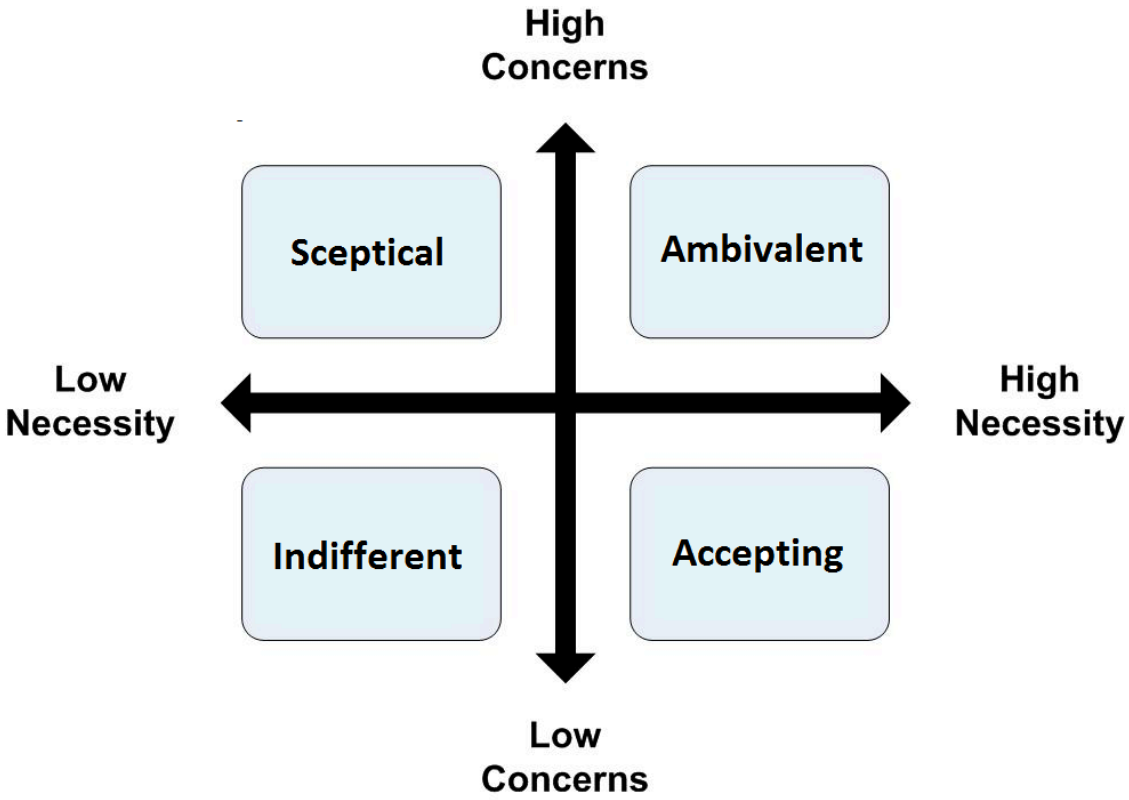


Figure 8.1: Attitudinal analysis model

Adapted from: Horne R, *et al. Inflamm Bowel Dis.* 2009;15(6) :837-844.
Aikens JE, et al. *Am Fam Med.* 2005;3:23-30.

The findings from the qualitative stage of this research suggested that some patients, predominantly those of South Asian origin, are inclined to believe that most medicines are harmful and addictive and that alternative treatments for UC were therefore better from a quality of life perspective (Chapter 5.5.4). This research also revealed that younger patients, and South Asian patients regardless of age, were fearful of disclosing their illness to others. The qualitative study therefore supports the premise that patients' beliefs about disease and treatment are important determinants of adherence. This was also supported by the findings from the cross-sectional, quantitative survey (Chapter 6.4.2), which found that 5% of patients appeared to be intentionally non-adherent and suggested a correlation between adherence and patients' beliefs about their 5-ASA medication. As in the qualitative study, some variations in health beliefs between people of different ages and ethnic origin were identified by the survey, reinforcing the importance of ensuring that interventions that address health beliefs are tailored to the needs of the individual patient.

8.2.3 Rationale for affective strategies

8.2.3.1 Family support of the patient

The positive influence of supportive family relationships is widely accepted in the scientific community (270), (271), (272), (273). Family relationships have greater emotional intensity than do most other social relationships, and research suggests that there is a substantive, positive association between

the specific bonds within families and chronic-disease management outcomes (274). A chronic disease such as UC is a long-term source of stress for the patient and family members alike. Family members create a shared social reality that is linked to health, and it is in this environment that most disease management takes place, whether by the patient alone or with other family members (275).

Family dysfunction has been linked to worsening disease symptoms (276) and poorer adherence (277), (278) in the adolescent patient. Thus, as suggested by Rapoff (277), psychological interventions that assist families in setting appropriate rules and consistently implementing appropriate consequences for behaviour may result in improved medication adherence among adolescents. Two different interventions aimed at improving family functioning resulted in significantly improved adherence compared with comparison groups in adolescents with diabetes (279), (280).

Nicholas *et al.* (281) revealed that social support had a positive effect on coping with IBD in young people, suggesting that adolescents valued honesty and open communication from their families regarding their diagnosis and sensitive issues such as bowel symptoms and their treatment. This led to the development of more effective coping strategies and adaptation, increased feelings of control, and alleviated unfounded fears about IBD. In another study, female teenagers and their mothers were invited to participate in monthly support groups for one year (282). The adolescents and their

mothers reported that sessions were helpful and the adolescents showed significant improvement in emotional and social functioning from baseline to post-treatment.

Whilst relevant research in the field of family support has focused on young people, the findings from both, qualitative study (Chapter 5.5.6) and quantitative survey (Chapter 6) suggest that there is scope for improving social support relating to medication adherence in adults. Slightly less than a third (54/170 - 32%) of the cross-sectional survey participants reported the involvement of family members in prompting or reminding their medication-taking behaviour.

8.2.3.2 Patient-physician relationship

A large body of evidence supports the importance of the physician-patient relationship in achieving higher patient medication-adherence rates (283), (284), (285). In a study of 193 primary care patients, the only element of the process of care that was related to resolution of the patient's symptom at one month, was physician-patient agreement about the nature of the problem (286). Patients with unresolved symptoms were followed for an additional two months, and late resolution was associated with the physician's recording of attention to the patient's psychosocial problems. In addition, the physician's willingness to allow patients to contribute input during the initial medical visit has been suggested as facilitating treatment decisions that are meaningful to

both parties (287). Non-adherence is more common among patients who report a lack of confidence in their physician's ability to help or who are dissatisfied with the concern shown by their physician (285). A waiting room survey of 370 patients in 14 randomly selected New Zealand primary care practices showed that trust in the physician and continuity of care by the same doctor was also important to patients (288). Patients who reported high levels of concordance with their physician (as determined by series of questions evaluating the extent of agreement between the physician and patient) were 33% more likely to adhere to their treatment (288). This supports the findings reported in a Canadian prospective study of IBD patients, which showed a direct correlation between patient-physician discordance and non-adherence (103). Moreover, a large survey from Netherlands (1 067 IBD patients, 450 of them with UC) demonstrates patients' desire to be actively involved in the decision-making process related to the treatment of their disease (224). It has also been suggested that patients show better adherence when they are actively involved in the decision-making process (289).

The qualitative findings reported in Chapter 5.5.5 also suggested that the effectiveness of the patient-physician relationship is one of the main determinants of 5-ASA adherence. These findings underline the fact that effective consultation with clinicians could lead to increased patients' confidence to be involved in their own UC management and a greater

assumption of responsibility for their own health, resulting in a positive impact on medication adherence.

8.3 Development of a complex intervention

The evidence presented in this chapter suggests that a combination of educational, behavioural and affective strategies, tailored to individual patients, may be the most effective way of optimising 5-ASA medication adherence. As was mentioned at the beginning of this chapter, the classification used by Horne *et al.* (100) has been used for intervention modelling. Perceptual, practical and combined interventions have been suggested (99), but there is a lack of evidence about effective approaches relating to 5-ASA treatment in UC. Thus, it was reasonable to postulate that a combination of perceptual and practical strategies with some supporting affective strategies (support from family or friends) would need to be used. Taking into account that patients with the same illness, prescribed the same medication, differ in their perceptions of personal need, adherence enhancing intervention should be targeted to the underlying cause or causes of non-adherence and tailored to the needs and circumstances of each individual patient.

Figure 8.2 shows a working model for an RCT to facilitate informed adherence to 5-ASA in UC patients. I developed the model on the basis of the theoretical perceptions-practicalities approach originally proposed by

Horne (100) and accepted in the NICE guidelines (99). This approach includes:

- determination of causal factors for individual non-adherence;
- targeting the individual perceptual barriers such as beliefs and preferences;
- targeting the individual practical barriers such as forgetfulness and complexity;
- involving patients in the decision-making process.

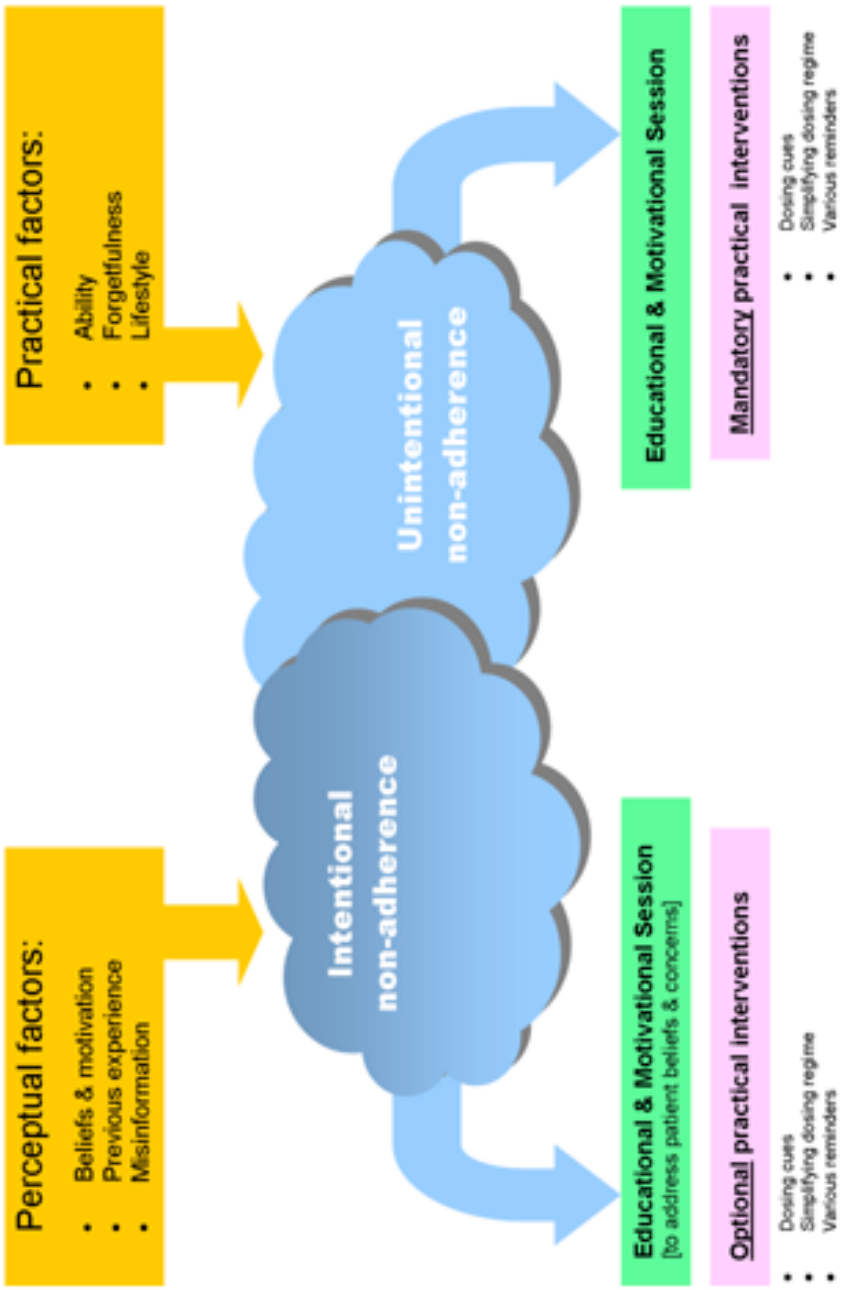


Figure 8.2: A perceptions-practicalities approach to facilitate adherence
Adapted from Horne, *et al.* A conceptual map and research priorities. 2006.

Prior to the start of the RCT, potential components of the intervention were considered. The following elements were determined as components of the complex intervention:

- One-to-one education and motivation sessions (with or without family members) (Appendix 15).
- Patient-focussed educational leaflet (Appendix 16)
- Family/supporter-focussed educational leaflet (Appendix 17)

In order to involve patients in the decision-making process of their treatment, the range of practical medication reminders were offered to patients for self-selection (Tab. 8.1)

- Self-selected practical medication reminders such as:

Table 8.1: Range of practical medication reminders

✓ Simplifying of dosing regime (if clinically appropriate)
✓ Medication reminder charts (Appendix 18)
✓ Visual medication reminders for fridges and bedside cabinets (Appendix 19)
✓ Daily electronic pill box organisers with alarms (3 different types) (Appendix 20)
✓ Weekly electronic pill box organisers (2 types) (Appendix 21)
✓ Weekly non- electronic pill box organisers (2 type) (Appendix 22)
✓ Mobile telephone alarm set-up

Education was identified as an essential component of the overall adherence enhancing intervention for the trial. Evidence suggested that the educational aspect of the intervention should include both oral (education and motivation session) and written (leaflets) components; it was considered that these should be compulsory for all participants assigned to the intervention group. The education and motivation session was designed to motivate, convince and educate. The purpose of this session was to identify individual reasons for non-adherence and to provide targeted information regarding UC, its effects, complications and a "common-sense" (267) rationale for the necessity of 5-ASA treatment. The session was designed as a structured dialogue allowing the patient to comment and ask questions. The session could be used to elicit and address individual concerns about prescribed medication as well as tailoring a convenient regime and addressing practical barriers.

The availability of patient information leaflets regarding 5-ASA medication was ascertained by discussion with a range of clinical and non-clinical staff within the hospital. This information was found to be absent within University Hospitals of Leicester NHS Trust. Such information was noted to be available nationally (produced by at least 2 pharmaceutical companies) but was determined as unfit for purpose in relation to this study as the language used had a medical bias and may not be easily understood by patients. In addition, these leaflets did not focus upon the issue of adherence. The leaflet for relatives/supporters of patients taking 5-ASA medication was

unavailable nationally or locally. In order to support the education and motivation session and help patients to understand the rationale behind their treatment, patient-focussed and family/supporter-focussed educational leaflets were therefore developed. Figure 8.3 shows the process of developing the educational leaflets. These leaflets were prepared by two authors (myself and Prof JF Mayberry). My PhD supervisor proofread and edited the text and then it was reviewed and approved by University Hospitals of Leicester Patient Reader Panel. The text of the leaflets and the educational session script mirrored each other so that an equivalent amount of factual information was imparted in both components.

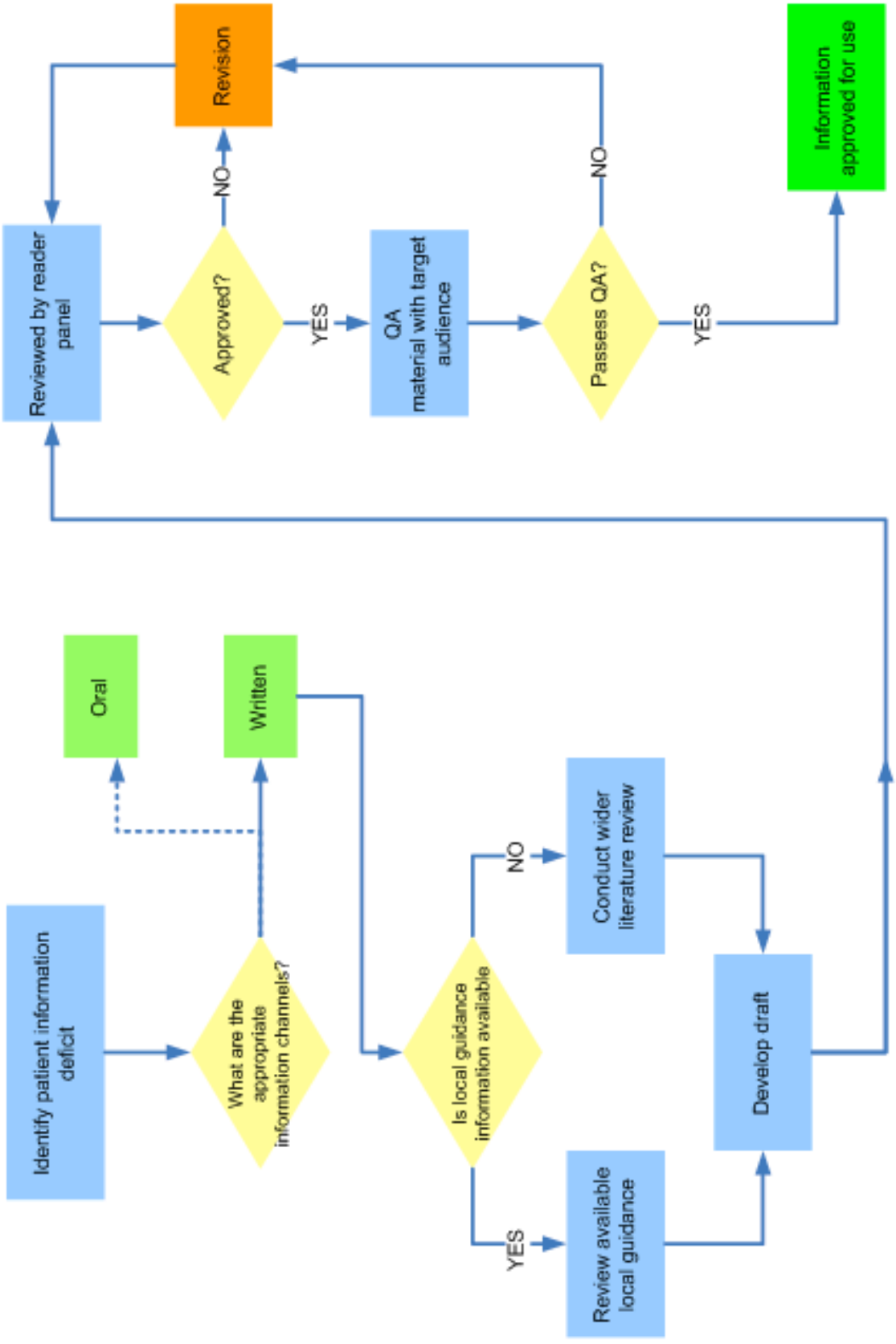


Figure 8.3: The process of educational leaflet development

In addition, for ethical reasons, it was agreed that all patients in the control group would receive the educational materials after the end of the study.

Following the education and motivation session, up to 3 practical interventions could be selected by patients from the range provided (Table 8.1). Patients would be encouraged to examine all types of reminders to assess their suitability. During the trial patients would be also able to exchange practical reminder for an alternative version.

8.3.1 Concluding remarks

Taking into account the existing evidence and also the findings from the qualitative (Chapter 5) and quantitative (Chapter 6) studies a complex adherence enhancing intervention was designed. The involvement of patients in the intervention development; the self-selection of practical reminders' and the fact that the degree of family/supporter involvement in the intervention was determined by the patients themselves provided a novel approach in this study. Chapter 9, which follows, describes the RCT that was used to test the effectiveness of the complex intervention.

Chapter 9

Exploratory randomised controlled trial

9 Chapter 9: Exploratory randomised controlled trial

9.1 Introduction

This chapter presents an exploratory RCT, the final phase of the overall programme of work relating to 5-ASA adherence. The evidence presented in the previous chapter concluded that an effective strategy to change individual medication-taking behaviour would require a multifaceted approach to helping people to adopt, change, and maintain adherent behaviour. Taking into account this conclusion together with psychological theories and the existing evidence discussed in Chapter 8, a multi-faceted adherence-enhancing intervention was designed. The design of the intervention was also informed by the findings from a qualitative study (Chapter 5) and quantitative survey (Chapter 6) and therefore incorporated the patient perspective. The RCT design was chosen as the most appropriate method of evaluating the effectiveness of the intervention.

9.2 Aims of the RCT

The primary aim of the RCT was to evaluate a multi-faceted adherence-enhancing intervention over a 12 month period. The secondary aim was to compare changes in beliefs and satisfaction with information about 5-ASA between intervention and control group participants over the study period.

9.3 Materials and Methods

9.3.1 Ethical considerations

The study was approved by the Leicestershire, Northamptonshire & Rutland Research Ethics Committee 2 (approval reference: UHL 09788, 06/Q2502/100; ClinicalTrials.gov Identifier: NCT00398593) and relevant R&D approval was obtained from the research site.

9.3.2 Participants and procedure

The study was conducted between November 2007 and May 2009. Patients on the gastroenterology outpatient registers of Leicester General Hospital, UK, were eligible if they were aged 18-80 years, with UC, and on maintenance oral 5-ASA therapy. Any not meeting these criteria or who were unwilling or unable to provide informed consent were excluded. Potential participants were approached either by letter or personally when attending clinic appointments. In order to enable informed decision, written information about this study was provided to patients (Appendix 11).

This was an exploratory study, as recommended by the MRC guidelines (1), (2) and discussed in Chapter 1, therefore the number of participants was based on realistic recruitment over a defined period of time rather than on a formal power calculation.

A computer-generated randomisation schedule was used to assign each subject to an intervention or control arm. Sequentially numbered, opaque, sealed envelopes containing a computer generated randomisation sequence were prepared by my PhD supervisor, who was not involved in any way in patient recruitment or delivery of the intervention. Preparation of the randomisation sequence involved blocking to ensure comparable final numbers in the intervention and control groups and also stratification by gender, duration of disease and ethnicity, to ensure comparable participant characteristics in the two groups. I was blinded to the content of the envelopes prior to opening. However, it was not possible for myself (since I delivered the intervention) or patients in either the intervention or control groups, to be blinded to group allocation after the point of randomisation. Prior to randomisation, participants provided written informed consent (Appendix 12) and completed a questionnaire booklet which contained a study specific questionnaire (Appendix 13), the BMQ– Specific and General Scales (168) (Appendix 14), and the SIMS (171) (Appendix 8). A spot sample of urine was provided by patients whilst at the clinic for determination of baseline adherence. Participants' age, gender, ethnic group, disease duration, prescribed 5-ASA compound and concomitant medications were also recorded.

9.3.2.1 Intervention group

Participants who were assigned to the intervention group attended a one-to-one education and motivation session conducted by myself. The rationale for, and content development of, this education and motivation session (Appendix 15) are described in Chapter 8.3. During this session participants were encouraged to identify practical barriers to 5-ASA medication use (for example, difficulties in remembering to take doses or problems associated with complicated dosing regimes), as well as perceived barriers to adherence (including concerns about the medication and doubts about personal need for the treatment). Strategies for overcoming these barriers were also discussed. Sessions lasted for 20-30 minutes and were intended to deliver individualised support to each patient. At the end of the session patients were offered an educational leaflet (Appendix 16) specifically developed for this study (Chapter 8.3). Patients had the option of being accompanied to these educational sessions by a relative or friend and any accompanying person was also offered a leaflet (Appendix 17) specifically written for relatives and friends (Chapter 8.3). During the session, patients were offered a free choice of up to three practical adherence enhancing interventions, such as simplifying of dosing regime, medication reminder charts and different types of pill boxes (Table 8.1, Chapter 8.3).

Taking into consideration that practical problems and adherence may change over time (117), participants had the option of changing these interventions at any time during the study and at weeks 4 and 24 they were formally asked

whether they wished to change the interventions. One brief follow-up telephone call was made to patients in the intervention group at week 4. During the mid-study visit (week 24) a 10 minute reinforcement session was held during which the importance of adherence to prescribed 5-ASA medication was reiterated, beliefs regarding medicine taking were reassessed and any practical problems were discussed. All intervention group patients were given a telephone number which enabled them to obtain advice at specified times or leave a message for a return call.

9.3.2.2 Control group (usual care)

Patients in the control group continued to receive standard prescribed care from their clinical team. The treatment regime for these patients was not changed in any way as a result of involvement in the study and no reminders or other additional adherence support was offered by the research team. Participants in the control group provided three urine samples at 0, 24, and 48 weeks and completed questionnaires during baseline and end of study visits.

At the end of the study control group participants were given the educational leaflets that intervention group participants received at the beginning of study.

9.3.3 Outcome measures

A single measure of adherence was used as the primary outcome measure for this study. Chapters 7.2 and 6 of this thesis report the development and use of this method. Briefly described, it involves the use of HPLC for determination of 5-ASA and N-acetyl-5-ASA concentration in the urine samples collected from both intervention and control group participants during visits at baseline, mid-study (24 weeks) and at the end of study (48 weeks). As a secondary outcome measure, disease activity (flare-up) data were collected from medical records during the study period; a flare up was defined as an unscheduled hospital appointment or admission related to UC. Descriptive data about the intervention were collected by keeping a record of any interventions selected and changed and also by obtaining feedback from intervention group patients using a brief study-specific questionnaire. Analysis of data collected in these ways was used to consider qualitatively the usefulness of specific aspects of the intervention.

General beliefs about medications as a whole were assessed using the BMQ-General scales (168) (Appendix 14). This 8-item validated questionnaire measures beliefs within two domains (General-Harm and General-Overuse). High scores on the General-Harm and General-Overuse scales of the BMQ indicate greater concerns and negative attitude towards medications. Beliefs about prescribed 5-ASA medication were assessed using the BMQ-Specific instrument (168) (Appendix 14). This validated questionnaire, described in Chapter 6.3.3 and used in the quantitative survey,

assesses patients' beliefs about their perceived need for 5-ASA medication and their concerns about potential adverse effects of this medication. The SIMS (171) (Appendix 8), also described in Chapter 6.3.3 and used in the quantitative survey, assesses the extent to which participants are satisfied with information considered essential for the optimum use of 5-ASA medicines.

9.3.4 Statistical methods

The definitions "complete adherence", "complete non-adherence" and "partial non-adherence", based on the concentration level of 5-ASA or N-acetyl-5-ASA in the spot urine sample, were established (Chapter 7.2 & 7.3) and used previously in the quantitative survey (Chapter 6). In order to focus on identifying factors determining full adherence, partial and complete non-adherence were subsequently combined to form a single category for comparison with complete adherence.

Due to lack of complete data for relevant outcome measures in patients withdrawn from the study, a strict intention to treat approach was not feasible and the main analysis was therefore conducted using data for the 71 people who completed the trial. However, to address this limitation, a sensitivity analysis was conducted, including cases where follow up data were unavailable, in order to test the robustness of our main finding relating to adherence levels.

Analyses were conducted using SPSS v16. Multivariable, backward stepwise binary logistic regression analysis was performed to identify significant predictors of non-adherence. The criterion for entry into the model was p=0.1 at the univariable analysis stage and the criterion for retention in the model was p=0.05. The main predictor variable of interest was intervention/control group status. The other candidate predictor variables used in the analysis relating to predictors of adherence were age, gender, ethnic group (Caucasian/ South Asian), disease duration, BMQ general overuse (GO), BMQ general harm (GH), BMQ specific necessity (SN), BMQ specific concerns (SC), overall SIMS score and baseline non-adherence. Additional analyses included the use of the generalised estimating equations (GEEs) approach, which was used to define changes in adherence over time when comparing the two groups. Chi-square analysis was used to assess the level of correlation between non-adherence and frequency of flare ups. Additionally, the mean differences in changes in questionnaires scores were compared between intervention and control groups using the following paired psychological variables: SN, SC, GO, and GH at baseline and at the end of study, with adjustment for potential confounders.

9.4 Results

The flow of patients through the study is shown in Figure 9.1. Eighty-four patients were recruited to this study. Overall, 84 of the 200 (42%) people approached agreed to participate in the trial. Uptake was much higher (55/80, 69%) in patients approached in the clinic setting, compared to those who were contacted by mail (29/120, 24%). Three subjects were withdrawn for medical reasons and 10 subjects were lost to follow up. Withdrawal rates were similar in the intervention 6/43 (14%) and control 7/41 (17%) groups.

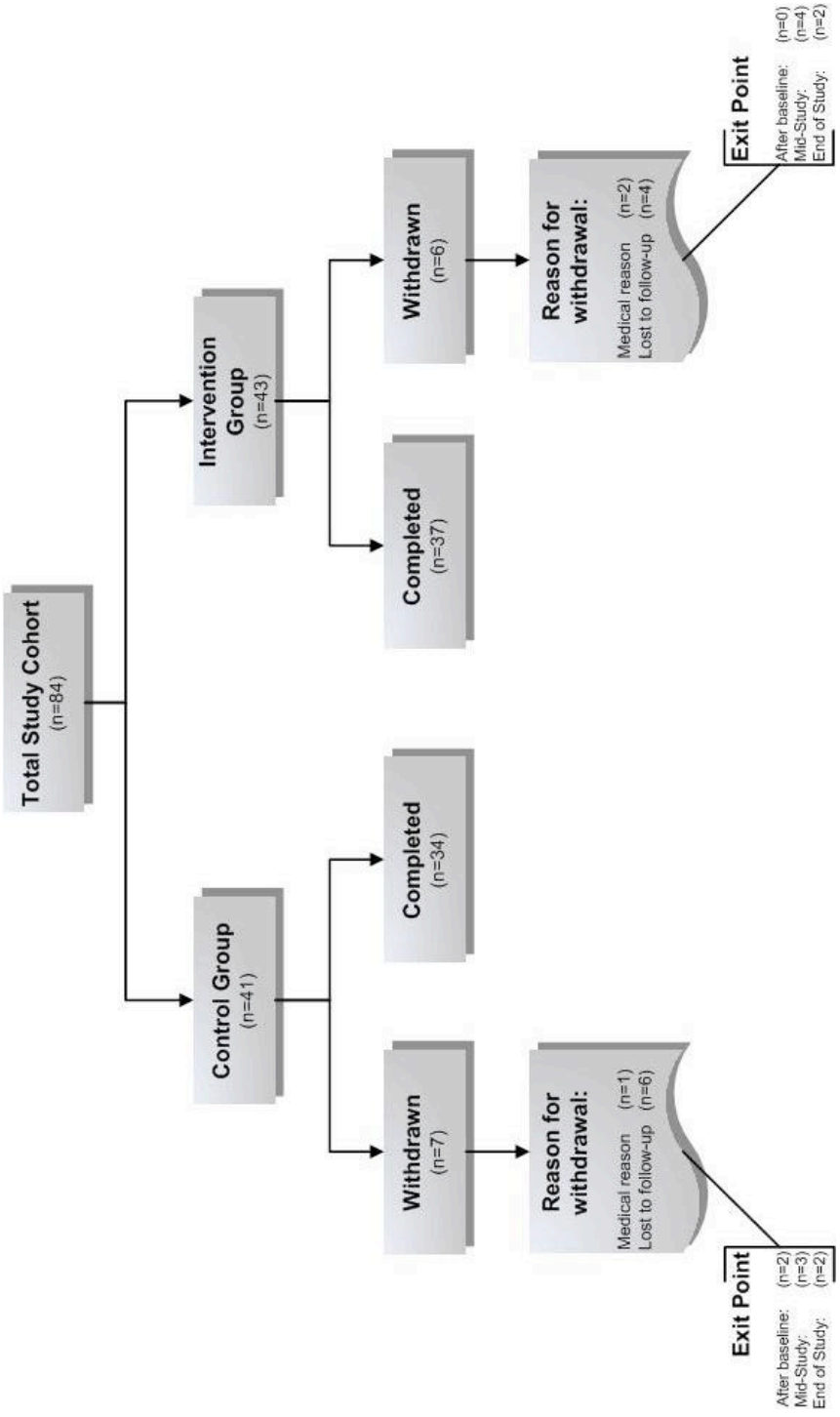


Figure 9.1: The flow of patients through the study

Table 9.1 shows the baseline and demographic characteristics of the 71 patients who completed the study.

Table 9.1: Characteristics of study sample (n=71)

		Control group n = 34 (48%)	Intervention group n = 37 (52%)
Age distribution:	23 – 45 Years	11 (32%)	14 (38%)
	46 – 82 Years	23 (68%)	23 (62%)
	Mean	49 Years	
Gender:	Male	19 (56%)	16 (43%)
	Female	15 (44%)	21 (57%)
Ethnicity:	Caucasian	24 (71%)	25 (68%)
	South Asian	10 (29%)	12 (32%)
Disease duration:	1 – 3 Years	9 (27%)	8 (22%)
	4 - 10 Years	11 (32%)	12 (32%)
	11 - 21 Years	10 (29%)	13 (35%)
	22+ Years	4 (12%)	4 (11%)
Oral 5-ASA prescription information:	MESALAZINE		
	Asacol	16 (47%)	20 (54%)
	Pentasa	11 (32%)	13 (35%)
	Mesren	2 (6%)	1 (3%)
	BALSALAZIDE		
	Colazide	2 (6%)	2 (5%)
	SULPHASALAZINE	3 (9%)	1 (3%)
Concomitant steroid medication		8 (24%)	10 (27%)
Concomitant immunosuppressive medication		7 (21%)	11 (30%)
Adherence at baseline:		24 (71%)	30 (81%)

Note: No statistically significant difference identified on comparing intervention and control group participants

No significant differences were detected in demographic/medical characteristics or key variables between the two groups prior to the intervention. Although adherence in the control group was 71% (24/34) compared to 81% (30/37) in the intervention group, this difference was also non-significant (p=0.30).

A decline in overall adherence levels over the study period was noted in the overall sample. However, at follow-up, adherence in the intervention group was 44% greater than in the control group: 28/37 (76%) compared to 11/34 (32%), p=0.001. For the sensitivity analysis including the 13 patients who withdrew from the study, we assumed that at follow up a strong majority of those in the intervention group (5/6) were non-adherent and a strong majority (6/7) in the control group were adherent. This comparison of 29/43 adherent patients in the intervention group and 17/41 adherent in the control group was still significant ($\chi 2 = 5.72$, $p = 0.017$), suggesting that our significant finding based on patients who completed the trial is valid. Of the 17/71 patients who were non-adherent at baseline, 14 (82%) remained non-adherent at the end of the study visit. In addition, 18 out of 54 patients (33%) identified as adherent at baseline had become non-adherent at the end of study.

Table 9.2 shows the odds ratios (ORs) and 95% confidence intervals (Cls) for the variables appearing in the final model of the backward stepwise multivariable regression analysis. Control group status (p<0.001) and non-

adherence at baseline (p=0.002) were significant predictors of non-adherence.

Table 9.2: Significant predictors of non-adherence remaining after backward stepwise logistic regression modelling

Predictor	OR	95% CI	p
Control group status	7.69	2.34 to 25.29	0.001
Non-adherence at baseline	11.41	2.47 to 52.77	0.002

Order of removal of variables during stepwise logistic regression modelling:

a. on step 2: general overuse (baseline)
b. on step 3: specific necessity score (baseline)
c. on step 4: age
d. on step 5: SIMS (baseline)
e. on step 6: duration of UC
f. on step 7: general harm (baseline)
g. on step 8: specific concerns (baseline)
h. on step 9: ethnicity
i. on step 10: gender

From discussions during the education session, 25 out of 37 participants (68%) were determined to be unintentionally non-adherent (forgot to take medication) and 10/37 (27%) were classified as intentionally non-adherent (7 took a lower dose than instructed and 3 periodically stopped taking their medication). Efficacy of 5-ASA medication was rated by 30 out of 37 (81%)

participants as the most important medication attribute. However, 8 out of 37 participants (22%) had doubts about the efficacy of 5-ASA medication (such as consistent symptom relief and flare-up prevention).

The mean difference in change in questionnaires scores between control and intervention groups from baseline to end of study (Table 9.3) confirmed the benefit of the education and motivation sessions for study participants in terms of satisfaction with information received (difference in SIMS scores $p<0.001$). Although statistically significant differences were not identified in relation to changes in beliefs when comparing BMQ General and Specific scores in patients in the two groups, a positive trend was noted (Table 9.3).

Table 9.3: Mean difference in change in Questionnaires scores between control and intervention group participants from baseline to end of study

Questionnaires	Control group		Intervention group		p value for interaction (group and time)*
	Change	P value	Change	P value	
General overuse	0.02	0.67	0.01	0.77	0.78
General harm	- 0.01	0.85	- 0.08	0.06	0.20
Specific Necessity	- 0.02	0.81	0.14	0.23	0.26
Specific Concerns	-0.06	0.18	- 0.11	0.12	0.50
SIMS	0.77	0.004	3.57	0.001	0.001

*Using ANOVA

Figure 9.2 shows the initial intervention choices made by patients together with their selection changes over the course of the study.

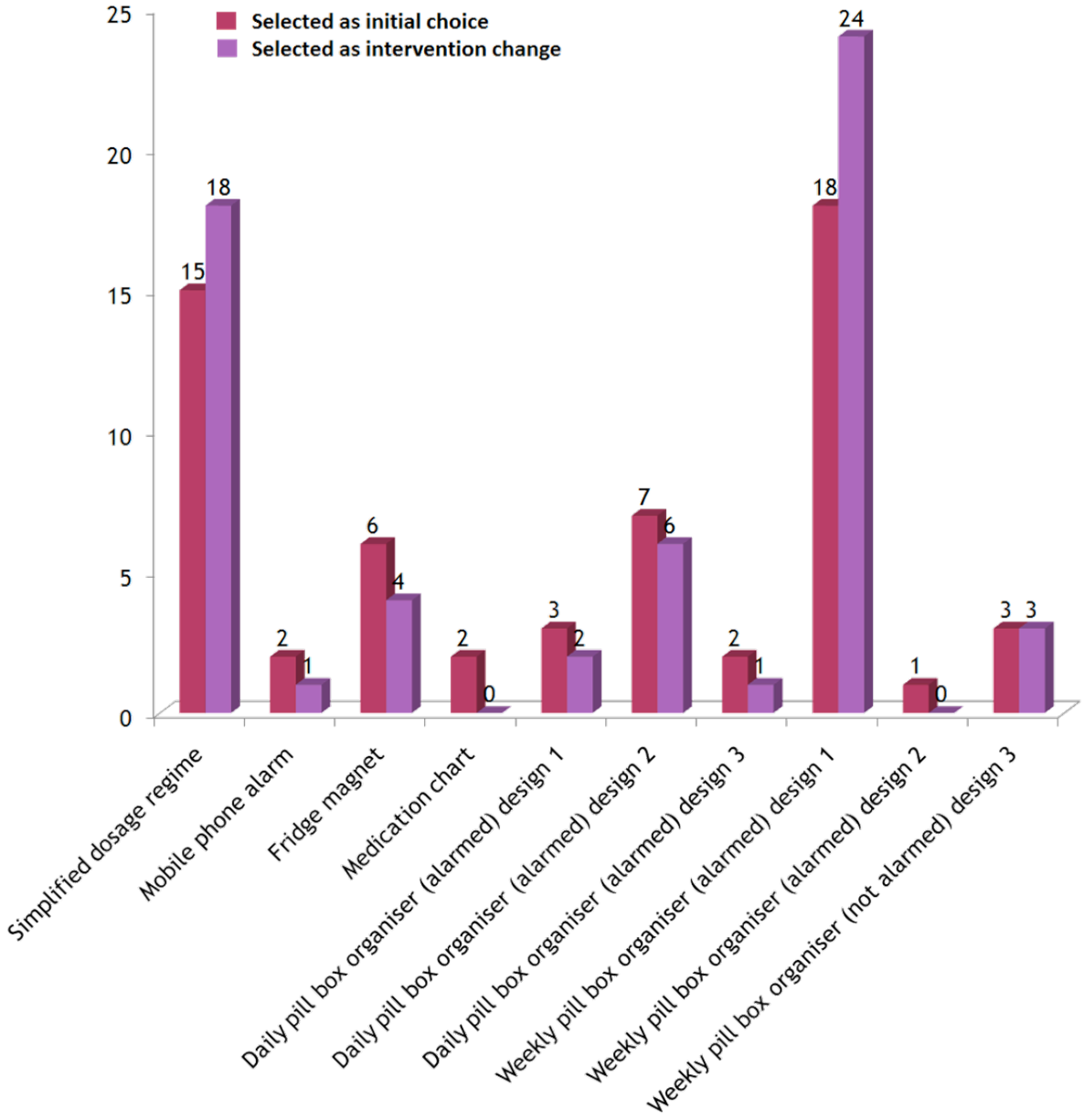


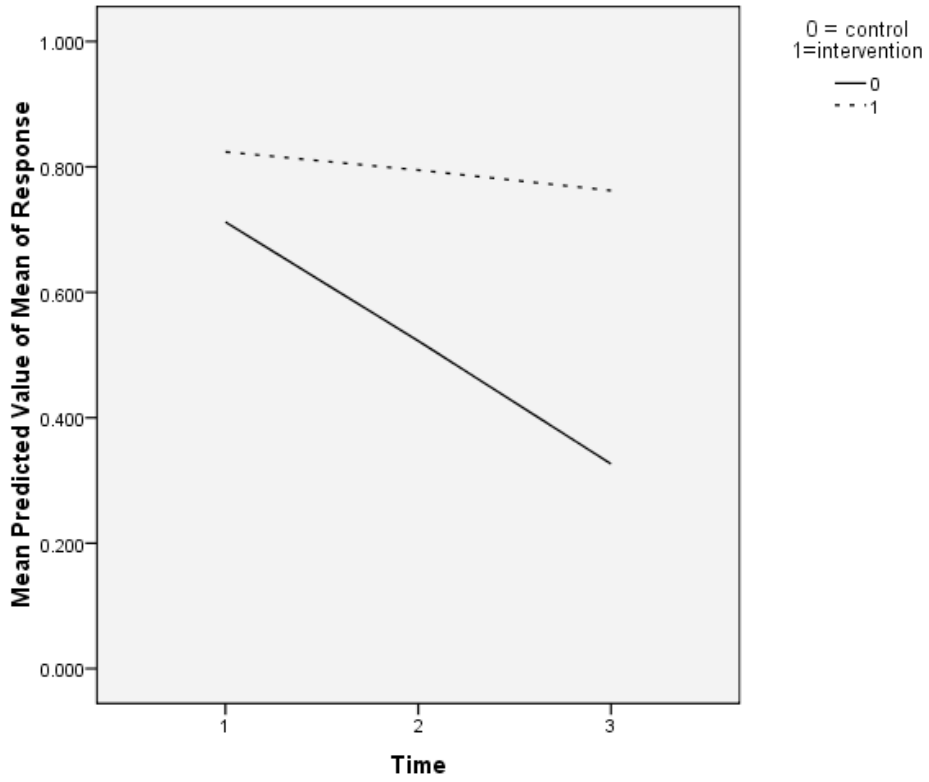
Figure 9.2: Interventions selected by patients

None of the study participants were taking once-daily mesalazine formulations. The dosing regime simplification offered was therefore restricted to a reduction in frequency from four or three times to twice-daily. Fifteen patients made this request and confirmed that the regime had been changed accordingly.

Twenty-two out of 37 participants (59%) chose a weekly pill box organiser and 12/37 patient (32%) chose a daily organiser. It was noted that 18/37 (49%) participants initially chose the same organiser design, a brightly coloured, tower shaped weekly organiser with multiple audio alarms (Appendix 21 top of page). It contained 7 separate compartments labelled Monday-Sunday, with each tablet compartment having 4 numbered sub-compartments for different times of the day. Additionally, 6 people changed their pill box after 5 months for this most popular format. When asked about their reasons for this choice, participants cited convenience, portability and helpfulness in identifying times when they had missed a dose and ensuring they remembered to fill prescriptions early. Patients' noted that the pill box organiser helped them establish good patterns of taking medication. Once this has been achieved over a period from one to three months the need for the pill box becomes less.

The control group had a higher overall decline in their 5-ASA medication adherence rate during the study period, with a decrease of 39% (from 71% to 32%), compared to a decline of only 5% (from 81% to 76%) in the

intervention group (Figure 9.3). There was no difference between the groups in terms of frequency of flare ups, 8/34 in the control and 9/37 people in the intervention group (24% in each group).



Additional data

Adherence rates depending on time point in each study group:

	Baseline	Mid-study	End of study
Intervention group	81% (30/37)	81% (30/37)	76% (28/37)
Control group	71% (24/34)	53% (18/34)	32% (11/34)

Difference between groups at each time point:

	OR	95% CI	p	%
1-Baseline	1.79	0.59 to 5.39	0.30	10
2-Mid-study	3.68	1.26 to 10.75	0.02	28
3-End of study	7.69	2.34 to 25.29	0.001	44

Figure 9.3: Change in adherence over time by groups

9.4.1 Summary of main findings and comparison with other studies

In spite of a relatively small sample size, this study was able to demonstrate positive benefits in the intervention group, in which the lower rate of decline in levels of adherence was highly statistically significant. A general decline in rates of adherence was also observed by Kane *et al*, who studied persistence at 3 and 18 months after first prescription (290).

Our finding of a positive impact on satisfaction with information is consistent with the results of a previous study of 69 patients with IBD. This study demonstrated improved knowledge, patient satisfaction, and a positive trend towards greater adherence in patients who had undertaken an IBD educational programme consisting of pamphlets and *ad hoc* physician education (211). Studies across a wide range of disciplines have shown that patients who are more satisfied and informed about their care are more likely to be adherent to treatment regimes (291), (232). In inflammatory bowel disease, previous research has shown that the degree of information received from clinicians, comprehension of instructions for appropriate use of medication, understanding of the potential consequences of non-adherence and the extent of self-management skills all significantly influence patient medication adherence (236).

The most common reason (68%) for non-adherence identified in our patient sample was difficulties in remembering to take prescribed 5-ASA medication.

Therefore, the use of practical interventions was justified in the study with the aim of improving medication adherence. Our findings also suggest that pill box organisers make an important contribution to improving adherence and that this type of practical reminder could be beneficial for patients with UC to ensure better 5-ASA medication adherence. In a recent questionnaire study (258) of 1194 hypertensive patients and their physicians in Denmark 73% of patients stated that they always or mostly used the device. Overall 78% of patients and 83% of physicians assessed the device positively. The majority of respondents in the study in Denmark, and also participants of my study, wanted to continue using the device. Research in HIV (259), (260) and elderly patients (261) has also suggested that pill box organisers are simple and effective in helping patients to take their medications as prescribed. The fact that a high proportion of participants in this study independently selected the same pill box organiser suggests that the specific design of the product may be an important consideration.

9.4.2 Limitations of the study

It is acknowledged that there are a number of potential limitations to this study. Only 42% of those approached agreed to take part in the study and, for ethical reasons, it is not possible to record data about those who declined. Anecdotally, however, the main reasons given for not participating were reluctance to provide urine samples, make additional visits to the hospital, or complete questionnaires. There is no reason to believe that differences

between those who agreed or did not agree to take part resulted in recruitment bias due to patient characteristics.

This was an exploratory study for which the sample size was not powered to detect a clinical difference relating to flare-ups. It is acknowledged that the definition of a flare-up in this study is based on an unscheduled hospital appointment or admission, and that this definition is open to challenge. In addition, the sample recruited contained a low proportion of people assessed as non-adherent at baseline. However, the findings suggest a useful area for future research involving a larger sample size of people with lower baseline adherence levels and collection of more detailed data relating to flare-ups, in order to further investigate the question of clinical impact.

Additionally, a general problem with evaluating complex interventions is that it is difficult to accurately assess the contribution made by the various components. Nevertheless, the study findings suggested that combining adherence enhancing interventions tailored to individual patients was an effective way of improving persistence with 5-ASA medication. The difficulty of accurately measuring adherence to 5-ASA medication has been previously confirmed in Chapter 7.3 of this thesis; however, the objective measure used was probably the most appropriate method available for evaluating the intervention. It is not possible to confirm whether the positive trend, but lack of significance, for results relating to changes in health beliefs was due to the small sample size or to the limited effectiveness of those aspects of the

intervention aimed at addressing patient perceptions; further studies exploring methods of modifying health beliefs are therefore required.

It could be suggested that this study does not take account of the potential impact of once-daily dosing regimes for patients with UC. Simplification of treatment can lead to improved patient adherence in a variety of disorders, and similar results have been reported in the treatment of UC. Whilst it is acknowledged that once daily regimes were not available to patients in this study, I do not believe that this reduces the validity of the study findings. A range of factors influence the prescribing decisions made by clinicians, including national and local guidelines, cost and availability. Moreover, a survey of 100 Canadian patients with UC revealed that factors such as medication efficacy and safety were rated as being more important than those related to the dosing regime or cost. In this survey, speed of symptom relief and infrequency of side effects were rated as the most important factors when considering UC medication (292). It may also be pertinent to note that changing to a once-daily dosing schedule could potentially lead to an actual decrease in adherence, as a single missed dose would equate to a full 24 hours of missed therapy.

Finally, the need to consider cost-effectiveness in the evaluation of adherence interventions has been suggested (215). Whilst formal assessment of cost-effectiveness was not within the scope of the present study, the actual costs could be described as relatively low since the

intervention involved only a brief educational session and provision of inexpensive leaflets and practical reminders. It would therefore seem reasonable to suggest that the intervention could be implemented in routine clinical care at relatively low cost.

9.4.3 Conclusions and implications of the findings

In spite of some limitations, this exploratory study has highlighted areas for further study and has provided data for future power calculations based on changes in adherence rates resulting from the type of intervention studied. Further studies are needed to confirm an impact on clinical outcomes such as rates of flare-ups, but these findings suggest that maintaining levels of medication adherence can be improved using a multi-faceted intervention that is tailored to the needs of individual patients and which addresses barriers related to both intentional and non-intentional non-adherence. This study has identified a practical way in which gastroenterologists, together with specialist inflammatory bowel disease nurses, can enhance persistence with 5-ASA amongst patients under their care and thus lead to improved clinical and quality of life outcomes for these patients.

Chapter 10

Summary of conclusions and recommendations

"Increasing the effectiveness of adherence interventions may have a far greater impact on the health of population than any improvement in specific medical treatments"

Haynes RB. Cochrane Database of Systematic Reviews 2001.

10 Chapter 10: Summary of conclusions and recommendations

10.1 Introduction

In this final chapter I will summarise the main conclusions of this thesis and relate them to the original hypothesis and aims outlined in Chapter 1. Key topics covered in the thesis are discussed, particularly in terms of the implications of my findings. The strengths and limitations of the study are reviewed, including identification of potential future research, and I reflect on what I have learnt from undertaking the PhD described in this thesis. I outline some overall recommendations relating to the implementation of my findings and present a summarised final conclusion.

10.2 Summary

The overall research programme addressed primarily the hypothesis that if the factors responsible for poor adherence can be identified, then adequate interventions, based on the reasons for non-adherence, specifically tailored to the needs of individual patients, could be developed to address specific barriers relating to individual patients.

Non-adherence to treatment in UC has a significant impact on the course of the disease and on patients' quality of life, and it can also lead to significantly

higher costs for the health care provider. A successful intervention to improve medication adherence is, therefore, needed.

Qualitative and quantitative studies undertaken as part of this overall programme have confirmed that adherence is a complex, multifactorial issue. It is unlikely, therefore, that there will be a simple, standardised “cure” for non-adherence. These studies provided a useful framework for development of a complex intervention with individualised approaches to target perceptual and practical barriers. The exploratory RCT demonstrated that a complex intervention addressing both practical and perceptual barriers of individuals could be successful. Based on my findings, I would suggest that a complex intervention of this type should combine educational and behavioural strategies (and optimally, include some elements of affective strategy such as an increase in social support). In addition, results might suggest that patients who were actively involved in the decision-making process of their treatment (intervention group), showed higher levels of adherence than patients who did not participate in this process (control group).

Adherence is a dynamic process, with factors varying between patients and changing over time, which requires ongoing monitoring and follow-up. All adherence improvement strategies tend to lose their effectiveness over time irrespective of how acceptable they may be to the patient initially. Health care professionals should assess the effectiveness of current interventions and

adjust them as needed to accommodate changes in the patient's life, such as different work or school schedules, or increasing age.

The approaches discussed and utilised in the programme of study and presented in this thesis, bring the patient into the centre of his or her care. The research findings provide practical ways in which gastroenterologists, together with specialist IBD nurses, can optimise adherence to treatment.

10.2.1 Enhancing adherence

The adherence-enhancement model resulting from this thesis suggests that health care professionals operating the model should:

1. identify instances of non-adherence through discussion with patients within the clinical consultation and make the evaluation of adherence part of any routine consultation;
2. impart appropriate knowledge related to the effects and efficacy of, and the rationale for, all medications prescribed to an individual patient;
3. identify patient beliefs and practical barriers regarding treatment, as this can provide valuable insight into the causes of non-adherence and thus provide opportunities for modifying behaviour;

4. actively involve patients in the decision-making process of their care.

10.2.2 Assessment of adherence

If a healthcare professional is unable to detect non-adherence, it is impossible to correct the problem. Hence, it becomes imperative to measure and evaluate patient adherence reliably. The quantitative survey suggests that, in the absence of a reliable gold standard, caution is needed in terms of reliance on the available measures. Potential poor sensitivity of patient self-report has also been highlighted by this survey, together with the limitations associated with use of urinary mesalazine measurements. Moreover it is unfortunate that the dipstick development project did not prove successful in terms of identifying a practical tool which could be used within the clinical setting. Improvements in the reliability of methods of measurement based on self-reporting are needed, as self-report has been shown to be the most practical and widely used tool in clinical practice. In the meantime, a simple series of questions such as the Morisky Self-Reported Measure of Medication Adherence (293) could be administered quickly to most patients. However, my research (Chapter 6) suggested that a single question such as: “People often have difficulty taking their pills for one reason or another. Have you missed any pills in the past two weeks?” might suffice. Accurate self reporting regarding adherence to treatment regimens can potentially be achieved if patients are asked simply and directly. This is likely to be particularly true if the possibility or likelihood of non-adherence is raised by

the clinician during the consultation. Assessment of adherence should form a key element of consultations especially with relapsing patients, in order to ensure that the prescribed regime is adhered to.

10.2.3 Imparting appropriate knowledge

As a trusted information source, gastroenterologist, other physicians and nurses managing patients have an important opportunity to enhance patient adherence through education. Many of the techniques and interventions described in this thesis could be incorporated into even the busiest health care settings. Effective patient education could be provided by:

- limiting instructions to 2 or 3 major points during each discussion;
- using simple, everyday language, especially when explaining the diagnosis and giving instructions;
- supplementing verbal information with written materials;
- involving the patient's family and friends (with the patient's agreement);
- reinforcing the concepts discussed.

Interactions that require more time may well be more appropriately undertaken by the physician scheduling time with a specialist nurse practitioner.

10.2.4 Addressing perceptual and practical barriers

Knowledge alone is not sufficient to enhance medication adherence; therefore, it is worthwhile to address patients' beliefs, intentions and preferences. The results of the survey and RCT have confirmed that patients' beliefs about treatment (necessity beliefs and concerns) have an important influence on adherence. It is important that the physician's understanding of what a patient values in his/her therapy correlates with what the patient is seeking. Health care professionals can optimise behaviour change within the consultation by ensuring that patients:

- perceive their medical conditions to be serious;
- believe in the positive effects of the suggested treatment (for example, patients should be reminded of the evidence that there is a far higher risk of relapse if they do not adhere to their medication; in addition, it may be beneficial to discuss the potential chemoprotective effects of 5-ASA).

Health care professionals should keep in mind that the patients' opinions about the best practical strategies for improving their medication-taking behaviour are probably more important than their own views. Instead of designing interventions unilaterally, health care professionals should offer patients a range of possible solutions, as described in this thesis, and work with patients to determine which options are most likely to be successful.

10.3 Strengths and limitations of the research

The main strength of the thesis is the originality in the conception of the programme of work and the multi-methods used. This thesis includes some elements of creativity and novelty, as there are no published reports on RCTs using complex adherence-enhance interventions in UC or more generally in IBD. This exploratory RCT is the first “real life” study of a complex adherence-enhancing intervention in UC. Novel aspects of this intervention were patients’ involvement in the development of interventions and their selection. In addition, this thesis developed practical algorithms to facilitate medication adherence in IBD in everyday clinical practice. These strategies may be transferable to the management of other chronic conditions.

The main limitations include the high levels of adherence at baseline in the study sample and an inability to demonstrate improved clinical outcomes in terms of a reduction in flare-ups. Despite some limitations, this research has highlighted areas for further study and has provided data for future power calculations based on changes in adherence rates resulting from the type of intervention studied. Future research could usefully involve a larger sample size of people with lower baseline adherence levels and collection of more detailed data related to flare-ups. This would allow further investigation of the clinical impact of adherence related interventions.

The RCT was unable to confirm whether the positive trend, but lack of significance, for results relating to changes in health beliefs was due to the

small sample size or limited effectiveness of aspects of the intervention aimed at addressing patient perceptions; further studies exploring methods which modify health beliefs and optimise the application of the necessity-concerns framework are therefore required.

Finally, a formal assessment of cost-effectiveness of the complex intervention was not undertaken in this programme of study and should be considered in future studies.

10.4 Overall recommendations

Non-adherence should not be viewed as a patient problem but rather as a health system challenge. Adherence should become a clinical objective equal to the prescription of the most appropriate medication.

It is essential that health care professionals receive specific training in adherence management. Medical students should be encouraged to understand and value the concordance model in order to translate concordance principles into practice once qualified. With leadership from physicians, an innovative therapeutic partnership between the patient and the health care team should be developed. In such a therapeutic relationship, the health care team and patient agree to work together to achieve the best possible results from the medication identified by the clinician as most appropriate for the treatment of the patient's condition.

The results contained in this thesis provide promising practical ways in which patient's health care practitioners can facilitate adherence to treatment. Although these results are encouraging, the challenge still remains as to how to implement complex adherence-enhancing interventions in a modern-day busy practice with the constraints of limited time and funding. I would suggest that IBD nurse specialists would be key agents in the application of this model, aimed at enhancing patient adherence and thus increasing patient benefit from the therapy. Patients view nurses as caring, compassionate health care providers and are usually willing to share sensitive information with them (294), (295). IBD nurses have longer consultation times than physicians and enhanced use of their time is likely to deliver clinical benefit and prove highly cost-effective. Therefore, nurse specialists are in an excellent position to help improve patient adherence with medication regimes, especially with long-term therapy such as 5-ASA.

As a consequence of this research I have been able to suggest that the development of a specific educational programme for specialist IBD nurses is needed. This programme would aim to ensure that proven adherence enhancing strategies can be embedded in nursing practice in order to encourage and facilitate patient adherence to prescribed 5-ASA medication and, therefore, to improve UC management and reduce healthcare costs. This proposal is currently receiving funding consideration by a major pharmaceutical company.

10.5 Reflective learning

The programme of study that ultimately led to the delivery of my thesis took me on a challenging learning journey that would have been very difficult to predict in full from the start. I significantly increased my knowledge of planning, designing and undertaking qualitative and quantitative research in an academic setting. I learned of the prejudice in favour of quantitative research and the challenge of achieving publication of qualitative research. I also realised the importance of qualitative research in order to better understand the patient perspective and incorporate this into the design of interventions.

I encountered a number of challenges whilst undertaking this programme of research. The first of these was the process of obtaining ethics committee approval. Recruitment of patients was a significant early challenge following on from this approval. Even the issue of where and how to undertake the urinary analysis was ultimately a challenge, and obtaining this at little or no cost took considerable negotiation and good fortune. During this process, I learned the benefit of collaborative study together with the application of lateral thinking. I was ultimately able to collaborate with Loughborough University and create a learning opportunity for chemistry students from my study requirements. A by-product of this collaboration was also my own experience as an MSc student study supervisor. I truly enjoyed and benefited

from this collaboration, whilst at the same time my research benefited greatly from the focus, resources and academic time that were afforded to it by the collaborative approach.

I believe that my learning can truly benefit patients both in the application of the model by other clinicians and also in the changes that I know have already occurred in the way in which I interact with patients. I feel that my work has led to a real increase in my personal effectiveness in communicating, planning and positively intervening in treatment approaches with patients.

As a speaker of English as a second language (my first language being Russian) this level of study has also increased my written and spoken English language abilities immeasurably. My ability to organise time, work and study has improved significantly through undertaking the type of effort necessary to complete my thesis and I developed a strong appreciation of the value of good support.

10.6 Conclusion

In conclusion, the results contained in this thesis demonstrate that a multi-faceted complex intervention tailored to the needs of individual patients can lead to improved adherence and persistence to prescribed medication regimes in UC. Healthcare professionals can play a key role in addressing perceptual and practical barriers to non-adherence in individuals, potentially facilitating sustained patient adherence to medication.

APPENDICES

Appendix 1: Patient information sheet (PIS) for qualitative study

This will be printed on University Hospitals NHS Trust headed paper

PATIENT INFORMATION SHEET, stage 1
(Qualitative study)

Research Study:

1. Study title: An investigation into adherence with prescribed therapy in ulcerative colitis, its limiting factors and how to improve it.

2. Invitation

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

3. What is the purpose of the study?

The aim of this study is to establish what helps you remember to take the medication that has been prescribed by your doctor for the treatment of ulcerative colitis. We would like to ask your opinion about the reasons some people sometimes do not take 5ASA medication for ulcerative colitis and also look at ways you think would encourage them to take the medication that has been prescribed by your doctors to prevent a flare-up of your condition. Research also shows that continuing the treatment reduces the risk of cancer of the colon.

4. Why have I been chosen?

We are looking at 3 areas of the UK to be involved in this study – Leicester, Cardiff and Norwich. As you are at least 18 years old, have a diagnosis of ulcerative colitis, are prescribed regular 5ASA medication and are living in one of these areas we would like to invite you to take part in this study.

5. Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you have this information sheet to keep. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision not to take part, or a decision to withdraw at any time, will not affect the standard of care you receive.

6. What will happen to me if I take part?
If you agree to take part in the study you will be offered the opportunity of being interviewed about 5ASA medication already prescribed by your doctor. This interview will be recorded on audio-tape.

You will be offered the opportunity of being interviewed, at your convenience, either on the day you are approached in clinic or at some time during the week after you were told of the study. The interview will take place in a confidential setting- namely a private room separate from clinic areas. The interview will last a maximum of 20 minutes. If you agree to be interviewed on the day, you will be contacted by telephone during the following week to confirm that you are happy for your interview to be used as part of the research project. If you do not agree the audiotape will be destroyed.

The anonymous audiotapes will be stored in a locked cabinet within a locked office within Leicester General Hospital. The audiotapes will be transcribed and destroyed.

7. What do I have to do?
You will be asked to answer some questions about 5ASA compounds, such as mesalazine, sulphalazine or balsalazide already prescribed by your doctor. This will only take about 20 minutes of your time. You will be asked about reasons why patients, including yourself, sometimes may not take their medication and what you think would be the best way to remind you to continue your course of treatment.

8. What are the possible disadvantages of taking part?
The study will not change your treatment at all. We are only looking the reason of poor adherence to 5ASA therapy and how to encourage and remind you to follow the treatment that has been prescribed by your

doctor. There are no disadvantages to your treatment by taking part in this study.

9. What are the possible benefits of taking part?
One major benefit of taking part in this study is that you will be more aware of your disease. Secondly, you will help us to identified factors responsible for compliance (or non-compliance) and adequate interventions for patients with ulcerative colitis which could be developed. In addition, you will be helping to increase knowledge into the treatment of ulcerative colitis.

10. What if something goes wrong?
This study does not change your treatment but only looking the reason of poor adherence to 5ASA therapy. It will also try to identify at the best ways to encourage or remind you to follow this treatment and therefore it is very unlikely that this study will cause any problem with your treatment. In fact it is designed to be helpful to you. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you.

11. Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves Leicester General Hospital, where this study is being conducted, will have your name and address removed so that you cannot be recognised from it. Your identity will remain confidential and only your study doctor will be able to subsequently identify the participants.

12. What will happen to the results of the research study?
This study will begin in March 2006 and continue until June 2007. The results of the study will then be published in medical Journals so that what we have learned can be passed on to other doctors so that treatment for ulcerative colitis can be improved.

13. Who is organising and funding the research?
Dr Tanya Moshkovska is conducting this research with Dr John Mayberry and the study is being funded by GEAR (Gastroenterology Education and Research).

14. Who has reviewed the study?
All research that involves NHS patients or staff, information from NHS medical records or that uses NHS premises or facilities must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

Please Contact for Further Information:

Dr Tanya Moshkovska or
Dr John Mayberry

Department of Gastroenterology
Leicester General hospital
Gwendolen Road

Leicester
LE5 4PW
Tel: 0116 258 8869
Email: john.mayberry@uhl-tr.nhs.uk

Thank you for taking the time to read this document.
You will be given a copy of this information sheet and a signed consent form to keep

Appendix 2: Consent form for qualitative study

This will be printed on University Hospitals NHS Trust headed paper

Consent Form for stage 1.
(qualitative study)

Investigations how to improve adherence with therapy in Ulcerative Colitis

		Please initial box
1	I confirm that I have read and understand the information sheet v.3 dated 14/03/06 for the above study and have had the opportunity to ask questions and I agree interview will be recorded on audio-tape	☐
2	I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason and without my medical care or legal rights being affected	☐
3	I understand that sections of any of my medical notes may be looked at by Dr J. Mayberry, Dr T. Moshkovska and any appropriately qualified individuals assigned by Dr Mayberry to monitor the quality of the study. I give permission for these individuals to have access to my records	☐
4	I agree to take part in the study	☐
5	I agree for my GP to be informed of my participation	☐

Name of Patient	Date	Signature
Name of Person taking consent (treating clinician)	Date	Signature
Researcher	Date	Signature

Appendix 3: Interview schedule for qualitative study

Interview schedule, stage 1 (qualitative study)

Study title: An investigation into adherence with prescribed therapy in ulcerative colitis, its limited factors and how to improve it.

1. How long you have been diagnosed with ulcerative colitis?
2. When regular 5ASA compound was prescribed by your doctor for your ulcerative colitis?
3. Do you take your 5ASA medication as prescribed?
4. Does this medication make you feel better?
5. How you can tell if it is working?
6. Have you been given enough information about this medication by your doctor or nurse?
7. Do you know about the benefits of continuing to take your 5ASA medication
   and the risks if you do not?
8. Do you get any unpleasant side-effects to your 5ASA medication?
   (If yes have you spoken to your Dr about this? If not, why?)
9. Do you concerned about the long-term effects of this medication?
10. Think about the last 2 weeks – have there been any times that you have missed taking your (5ASA) medication?
11. If not, what was the reason for not taking the medication?
12. Do you sometimes feel well and therefore think you don't need the medication any more?
13. Is there anything that you think would be helpful to encourage or remain you to take your medication?
14. Does your family remind you to take your 5ASA medication for ulcerative colitis?
15. Would you like to use any non-therapeutic interventions which could encourage or remind you to take your 5ASA medication.

Appendix 4: PIS for cross-sectional quantitative survey

This will be printed on University Hospitals NHS Trust headed paper

PATIENT INFORMATION SHEET, stage 2

(Quantitative study)

Study title: An investigation into adherence with prescribed therapy in ulcerative colitis, its limiting factors and how to improve it.

1. Invitation

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

2. What is the purpose of the study?

The aim of this study is to establish what helps you remember to take the medication that has been prescribed by your doctor for the treatment of ulcerative colitis. We would like to ask your opinion about the reasons some people sometimes do not take 5ASA medication for ulcerative colitis and also look at ways you think would encourage people to take the medication that has been prescribed by their doctor to prevent a flare-up of their condition. Research also shows that continuing the treatment reduces the risk of cancer of the colon.

Based on the observations of this study we will identify the factors that encourage or discourage patients in continuing to take the medication as prescribed. Once we have identified a range of interventions that appear to be helpful in this we will give the opportunity to try these and evaluate whether these interventions were helpful in assisting or reminding patients to take the medication.

3. Why have I been chosen?
We are looking at 3 areas of the UK to be involved in this study – Leicester, Cardiff and Norwich. As you are at least 18 years old, have a diagnosis of ulcerative colitis, are prescribed regular 5ASA medication and are living in one of these areas we would like to invite you to take part in this study.

4. Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you have this information sheet to keep. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision not to take part, or a decision to withdraw at any time, will not affect the standard of care you receive.

5. What will happen to me if I take part?
If you agree to take part in this study you will be given three questionnaires in the out-patients department and offered the choice of completing them on site or returning them by mail in a prepaid envelope.

The duration of the study is 28 days. You will be asked to complete three questionnaires and to provide details of your 5ASA medication consumption over 28 days. In addition you will be asked to provide two 20ml urine samples.

5ASA medication will be provided with your standard prescription for 28 days in a container or blister pack. (The number of 5ASA compounds tablets taken by most patients over 28 days period will be 4x28=112. This number can vary.

Some patients will be expected to take 56 tablets during this period. Some will be prescribed 168. You should continue to follow the prescription prescribed by your doctor!). At the end of 28 days you will be asked to return the container or blister pack with any remaining pills and to provide a 20ml sample of urine.

You will be offered the choice of returning to clinic to do this or to return the sample and pill container in a pre-paid envelope.

6. What do I have to do?
If you agree to take part in this study you will be asked to complete three questionnaires about 5ASA compounds, such as mesalazine, sulphasalazine or balsalazide already prescribed by your doctor and provide two 20 ml urine samples. You will be asked about reasons why patients, including yourself, sometimes may not take their medication and what you think would be the best way to encourage or remind you to continue your course of treatment.

You need to attend clinic one or two times, take your regular 5ASA medication and provide two 20 ml urine samples. It is also possible for your study doctor to make the assessment over the telephone and you can send urine samples by mail.

If in the unlikely event that a condition relating to your health is found during the study, the study doctor will discuss this with you. There are no lifestyle changes to be made during the duration of this trial.

7. What are the possible disadvantages of taking part?
Disadvantages include the possible occurrence of the side effects of medication and the inconvenience of collecting urine for testing.

The study will not change your treatment at all. We are only looking the reason of poor adherence to 5ASA therapy and how to encourage and remind you to follow the treatment that has been prescribed by your doctor.

8. What are the possible benefits of taking part?
One major benefit of taking part in this study is that you will be more aware of your disease. Secondly, perhaps you will be encouraged or reminded to follow the treatment prescribed by your doctor. Thirdly, you will help us to identified factors responsible for compliance (or non-compliance) and adequate interventions for patients with ulcerative colitis could be developed. In addition, you will be helping to increase knowledge into the treatment of ulcerative colitis.

9. What if something goes wrong?
This study does not change your treatment but only looks the reason for poor adherence to 5ASA therapy and finds the best ways to encourage or remind you to follow the treatment prescribed by your doctor.

Therefore it is very unlikely that this study will cause any problem with your treatment – in fact it is designed to be helpful to you.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you.

10. Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves Leicester General Hospital, where this study is being conducted, will have your name and address removed so that you cannot be recognised from it. Your identity will remain confidential and only your study doctor will be able to subsequently identify the participants. You GP will only be notified that you are taking part if you give permission on the consent form.

11. What will happen to the results of the research study?
This study will begin in February 2006 and continue until June 2007. The results of the study will then be published in medical Journals so that what we have learned can be passed on to other doctors so that treatment for ulcerative colitis can be improved.

12. Who is organising and funding the research?
Dr Tanya Moshkovska is conducting this research with Dr John Mayberry and the study is being funded by GEAR (Gastroenterology Education and Research).

13. Who has reviewed the study?
All research that involves NHS patients or staff, information from NHS medical records or that uses NHS premises or facilities must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

Please Contact for Further Information:

Dr Tanya Moshkovska or
Dr John Mayberry

Department of Gastroenterology
Leicester General hospital
Gwendolen Road

Leicester
LE5 4PW
Tel: 0116 258 8869
Email: john.mayberry@uhl-tr.nhs.uk

Thank you for taking the time to read this document.
You will be given a copy of this information sheet and a signed consent form to keep

Appendix 5: Consent form for cross-sectional quantitative survey

This will be printed on University Hospitals NHS Trust headed paper

Consent Form for stage 2.
(quantitative study)

Study title:

Investigation how to improve adherence with therapy in ulcerative colitis

		Please initial box
1	I confirm that I have read and understand the information sheet v.3 dated 14/03/06 for the above study and have had the opportunity to ask questions	☐
2	I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason and without my medical care or legal rights being affected	☐
3	I understand that sections of any of my medical notes may be looked at by Dr J. Mayberry, Dr T. Moshkovska and any appropriately qualified individuals assigned by Dr Mayberry to monitor the quality of the study. I give permission for these individuals to have access to my records	☐
4	I agree to take part in the study	☐
5	I agree for my GP to be informed of my participation	☐

Name of Patient	Date	Signature
Name of Person taking consent (treating clinician)	Date	Signature
Researcher	Date	Signature

Appendix 6: Study developed questionnaire (cross-sectional quantitative survey)

Study Developed Questionnaire, stage 2

Study title: An investigation into adherence with prescribed therapy in ulcerative colitis, its limited factors and how to improve it.

Date questionnaire completed:	
Patient name:	
Centre (Leicester, Norwich or Cardiff):	
Hospital Number:	
Length of UC diagnosis:	
How long have you been taking 5ASA medication?	

1

Being absolutely honest – How would you describe your attitude to taking your (5ASA) medication? (Please choose the one answer that best describes you)	
I take my medication as prescribed	☐
I don't think it is important so I don't take it	☐
I don't take my medication when I feel well	☐
I forget to take it	☐
Having to take this medication worries me	☐
Missing this medication for a day won't matter in the long run	☐
Taking this medication has been much worse than expected	☐
I sometimes worry about long-term effects of this medication	☐

2

How important do you feel it is for your condition to take 5ASA medication as prescribed?

☐ Very important
☐ Helpful but not so important
☐ Not at all important

3

Do you think that you have been given sufficient information about your 5ASA medication by your Doctor or Nurse?

Yes ☐ No ☐

4

Think about the last 2 weeks – have there been *any* times that you have missed taking your (5ASA) medication?

Yes ☐ No ☐
If yes, how many times?

5

What was the reason for not taking the medication?

6

Do you currently use any methods of reminding or encouraging your self to take your (5ASA) medication? If so, what are they?

Yes ☐ No ☐

7

Are these methods helpful?

Yes ☐ No ☐

8

Is there anything that you think would be helpful to ensure you take your medication (give some examples of what might be possible)

9

Would you like to use any non-therapeutic interventions which could encourage or remind you to take your 5ASA medication?
Yes ☐ No ☐

10

Do you get any side-effects to your medication? (If yes have you spoken to your Dr about this? If not why?)
Yes ☐ No ☐

11

Do your family remind you to take your medication?
Yes ☐ No ☐

12

Do you know about the benefits of continuing to take your (5ASA) medication and the risks if you do not?
Yes ☐ No ☐

Appendix 7: BMQ version used in cross-sectional quantitative survey

Your Personal Views about your Medicines for Maintenance Treatment of Ulcerative Colitis

We would like to ask you about your personal views about the maintenance medicines prescribed for regular treatment of your ulcerative colitis (UC). These are statements other people have made about their medicines. Please show how much you agree or disagree with them by ticking the appropriate box.

There are no right or wrong answers. We are interested in your personal views

		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
N1	My health at present depends on these medicines					
C1	Having to take these medicines worries me					
A1	I sometimes decide to miss a dose of these medicines					
N2	My life would be impossible without these medicines					
N3	Without these medicines I would be very ill					
A2	I sometimes forget to take these medicines					
N4	My future health depends on these medicines					
C2	These medicines disrupt my life					
C3	I sometimes worry about becoming too dependent on these medicines					
N5	These medicines protect me from becoming worse					
N6R	I can cope without these medicines					
N7	Whether my condition gets worse or better depends on these medicines					
C4	These medicines do me more harm than good					
N8	These medicines are the most important part of my UC treatment					
C5	People who are on these medicines should stop their treatment every now and then					
C6R	I have been given enough information about these medicines					
E1	These medicines make me feel better					
C7	These medicines cause unpleasant side effects					
C8	I am concerned about the long-term effects of these medicines					
C9	I am concerned that taking these medicines regularly will make them less effective in the future					

Appendix 8: Validated questionnaire (SIMS)

Satisfaction with Information about Medicines Scale (SIMS)

We would like to ask you about the information you have received about your medicines.

Please rate the information you have received about each of the following aspects of your 5-ASA medicines.

Rated: too much, about right, too little, none received, none needed.

Please, circle only one answer.

- What your medicine is called.

Too much, about right, too little, none received, none needed

- What your medicine is for.

Too much, about right, too little, none received, none needed

- What it does.

Too much, about right, too little, none received, none needed

- How it works.

Too much, about right, too little, none received, none needed

- How long it will take to act.

Too much, about right, too little, none received, none needed

- How you can tell if it is working.

Too much, about right, too little, none received, none needed

- How long you will need to be on your medicine.

Too much, about right, too little, none received, none needed

- How to use your medicine.

Too much, about right, too little, none received, none needed

- How to get a further supply.

Too much, about right, too little, none received, none needed

- Whether the medicine has any unwanted effects (side effects).

Too much, about right, too little, none received, none needed

- What are the risks of you getting side effects.

Too much, about right, too little, none received, none needed.

- What you should do if you experience unwanted side effects.

Too much, about right, too little, none received, none needed

- Whether you can drink alcohol whilst taking this medicine.

Too much, about right, too little, none received, none needed

- Whether the medicine interferes with other medicines.

Too much, about right, too little, none received, none needed

- Whether the medication will make you feel drowsy.

Too much, about right, too little, none received, none needed

- Whether the medication will affect your sex life.

Too much, about right, too little, none received, none needed

- What you should do if you forget to take a dose.

Too much, about right, too little, none received, none needed

- Other information (please specify below)

Appendix 9: PIS for participation in supplementary pharmacokinetics sampling

This will be printed on Hospital headed paper

PATIENT INFORMATION SHEET
For participation in supplementary pharmacokinetics sampling

Study title: Patient adherence with prescribed therapy in ulcerative colitis: an investigation of barriers & methods of improvement.

You have already agreed to take part in the main study for adherence with prescribed therapy in ulcerative colitis mentioned above. There are some additional, optional tests that we would like to offer you as part of the study, and you may choose to participate. Please read the information carefully and do not hesitate to ask any questions you may have. If you do decide to take part in this additional part of study, you will be given a copy of this information sheet to keep.

What is the purpose of the study?
Ulcerative colitis is a disease that causes inflammation of the large bowel, causing fever, diarrhoea, dehydration and other symptoms. Standard treatment for ulcerative colitis includes general medical treatment such as fluids and salt replacement and attention to diet. One of the usual medical treatments for this condition is a type of tablet known as "5-ASA" compounds (Mesalazine, Sulphasalazine, Olsalazine or Balsalazide).

5-ASA compounds are effective in reducing inflammation in ulcerative colitis and are specifically designed to deliver the drug to the colon. It is useful to gather information on how different 5-ASA formulations act within the body. Therefore we would like to perform urine test after 5-ASA medication are taken.

These tests measure the amount of 5-ASA medication excreted in the urine at specific times after the tablets are taken. The information can

be used to find out whether there are any differences of 5-ASA absorption and urinary excretion between different drug formulations and from one person compared to another.

Why have I been chosen?
You have been invited because you are at least 18 years old; you have a diagnosis of ulcerative colitis and you are prescribed regular 5-ASA tablets.

Do I have to take part?
It is up to you to decide about this. If you do decide to take part you will have this information sheet to keep and you would still be free to withdraw at any time and without giving a reason. A decision not to take part, or a decision to withdraw at any time, will not affect the standard of care you receive.

What will happen to me if I take part?
We will ask you to take your 5-ASA medication as prescribed by your doctor. On an agreed day you will continue to take your 5-ASA medication as normal and we will ask that you provide a urine sample at two hourly intervals during the day (09.00, 11.00, 13.00, 15.00, 17.00, 19.00). The time of taking your 5-ASA will also be recorded. This study will not influence the decision to prescribe 5-ASA medication or its dosage and would not affect your treatment plan.

What are the possible disadvantages of taking part?
There should not be any disadvantages but some people may also find it inconvenient having to collect urine samples. We will try to fit in research visits with your usual clinic appointments, but it is possible that some people may have to make extra visits to the hospital. However, we will be able to pay for extra travel costs by public transport or the cost of travelling by car at the usual NHS rate.

What are the possible benefits of taking part?
There are no benefits to you if you take part in this pharmacokinetics urine sampling. However, you will be helping us to learn more about how different formulations and dosages of 5-ASA compounds are works and this might help other people in the future.

What if something goes wrong?
It is unlikely that this study will cause any problem with your treatment. This study will not influence the decision to prescribe 5-ASA medications or its dosage and would not change any plan for you. However, if you wish to complain, or have any concerns about the way you have been approached or treated during the course of this research, the normal National Health Service complaints mechanisms would be available to you.

Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the main research site will have your name and address removed so that you cannot be recognised from it. Your identity will remain confidential and only your study doctor will be able to identify who took part. Your GP will be notified that you are taking part only if you give permission on the consent form.

Who is organising and funding the research?
Dr Tanya Moshkovska is conducting this research with Dr John Mayberry and the study is being funded by GEAR (Gastroenterology Education and Research).

Who has reviewed the study?
All research that involves NHS patients or staff or information from NHS medical records, or that uses NHS premises or facilities, must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

For Further Information Please Contact:

Dr Tanya Moshkovska or
Dr John Mayberry

Department of Gastroenterology
Leicester General hospital
Gwendolen Road
Leicester
LE5 4PW

Tel: 0116 258 8869

Email:john.mayberry@uhl-tr.nhs.uk

Thank you for taking the time to read this document. If you decide to take part, you will be given a copy of this information sheet and a signed consent form to keep

Appendix 10: Consent form for participation in supplementary pharmacokinetics sampling

This will be printed on University Hospitals NHS Trust headed paper

Informed Consent Form

For optional, supplementary pharmacokinetic sampling

Study title: Patient adherence to prescribed therapy in ulcerative colitis: an investigation of barriers & methods of improvement.

		Please initial box
1	I confirm that I have read and understand the information sheet v 2.1 dated 25/04/08 relating to the collection of optional, additional pharmacokinetic urine samples and have had the opportunity to ask questions.	☐
2	I understand that my participation is voluntary and that I am free to withdraw from the study at any time, without giving a reason and without my medical care or legal rights being affected.	☐
3	I understand that sections of any of my medical notes may be looked at by Dr J. Mayberry, Dr T. Moshkovska and any appropriately qualified individuals assigned by Dr Mayberry to monitor the quality of the study. I give permission for these individuals to have access to my records.	☐
4	I agree to take part in the additional pharmacokinetic urine sampling.	☐

Name of Patient	Date	Signature
Name of Person taking consent (treating clinician)	Date	Signature
Researcher	Date	Signature

Appendix 11: PIS for RCT

This will be printed on Hospital headed paper

PATIENT INFORMATION SHEET

Patient adherence with prescribed therapy in ulcerative colitis: an investigation of barriers & methods of improvement: stage 3

You are being invited to take part in a research study. Before you decide about this it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

Thank you for reading this.

What is the purpose of the study?
You have been invited to take part because you have ulcerative colitis. One of the usual treatments for this condition is a type of tablet known as "5ASA" (Mesalazine, Sulphasalazine, Olsalazine or Balsalazide). However, sometimes these tablets don't work as well as they might because patients don't always take them regularly. Some research that we have already done has helped to give us some ideas about things that might encourage or remind people to take their tablets as prescribed. To find out whether these ideas will work, we need to compare "usual care" with "usual care plus some extra things". These "extras" will be things that we hope will encourage or remind patients to follow their treatment. In research we call these extra things "interventions".

Why have I been chosen?
For this research we are looking at patients from 3 areas of the UK – Leicester, Cardiff and Norwich. You have been invited because you live in one of these areas; you are at least 18 years old; you have a diagnosis of ulcerative colitis and you are being prescribed regular 5ASA tablets.

Do I have to take part?
It is up to you to decide about this. If you do decide to take part you will have this information sheet to keep and you would still be free to withdraw at any time and without giving a reason. A decision not to take part, or a decision to withdraw at any time, will not affect the standard of care you receive.

What will happen to me if I take part?
If you decide to take part you will be in the research study for 48 weeks. There are two groups of patients in the trial. To try to make sure that the groups have similar people in them, each patient will be put into one of the two groups by chance using a computer. Whichever group you are in, taking part in this research will not change your prescribed treatment at all. People in one group will continue to receive their usual care and people in the second group will also be offered a number of different interventions to help them to take their tablets as prescribed.

The chance of being in the group that is offered the interventions is 1 in 2 but you must decide if you want to take part in the research before we tell you which group you will be in. At the end of the research results for the two groups will be compared to see whether the interventions worked for helping or reminding patients to take their tablets.

Group one: People in this group will just be asked to provide three 20 ml urine samples at 0, 24 and 48 weeks and "pill counts" for the previous 4 weeks at weeks 4, 24 and 48 in the study. People in this group will continue to receive their usual care and their treatment will not be changed because they are taking part in the research. This is what we call the "control group".

Group two: This will be our "intervention group". People in this group will be asked to provide urine samples and pill counts just like people in the control group but they will also be offered some "interventions". These will be things that may help to remind or encourage them to take their tablets for their ulcerative colitis. One of these interventions will be a short one-to-one education and motivation session with a trained person. We will ask everyone in group two to agree to attend one of these sessions. People in group two will also be asked to fill in three

questionnaires about their 5ASA tablets and tell us what they thought of the interventions.

If you agree to take part and are put in group two, during the first research visit you will fill in a questionnaire about your 5ASA tablets and you will attend the one-to-one education and motivation session or arrange to attend on another day. This session will be used to discuss things that may stop people taking their tablets and possible ways of getting round any difficulties. You will be able to choose to bring a relative or friend to this session if you wish.

During the educational session, you will be offered a choice of up to three extra things that might help you with taking your tablets. You will also be given a telephone number on which you can obtain advice at specified times or leave a message for a return telephone call. After 24 weeks you will be asked if you wish to change any of the extra things you have chosen to help you with taking your tablets. You will be asked to fill in a questionnaire to tell us what you thought of the things you have tried out. We will also need to collect a urine sample and pill count.

Groups one and two: During the research visit at 48 weeks we will need urine samples and pill counts for patients in both groups. All patients in both groups will need to return to the clinic at this point. We may be able to give you the choice of a home visit to collect your urine sample and pill count at week 24 if you do not have a clinic appointment near that time.

What do I have to do?

If you decide to take part you will be asked to sign a consent form. Whichever group you are in, you will not be asked to take any different medicines as part of this research. If you agree to take part you will be asked to give three 20 ml urine samples, provide pill counts and come to a follow up visit at the end of the 48 weeks. If you are the intervention group you will also be asked to fill in some questionnaires and attend an educational session.

What are the possible disadvantages of taking part?

There should not be any disadvantages but if the "interventions" help people to take their usual tablets then it is possible that this could

result in them getting side effects. Some people may also find it inconvenient having to collect urine samples. We will try to fit in research visits with your usual clinic appointments, but it is possible that some people may have to make extra visits to the hospital. However, we will be able to pay for extra travel costs by public transport or the cost of travelling by car at the usual NHS rate

What are the possible benefits of taking part?
If you are in the intervention group we hope that the study may help you to take your 5ASA tablets regularly. In addition, you will be helping us to learn more about ways of helping people with ulcerative colitis and this might help other people in the future.

What if something goes wrong?
It is unlikely that this study will cause any problem with your treatment – in fact it is designed to be helpful to you. However, if you wish to complain, or have any concerns about the way you have been approached or treated during the course of this research, the normal National Health Service complaints mechanisms would be available to you.

Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the main research site will have your name and address removed so that you cannot be recognised from it. Your identity will remain confidential and only your study doctor in Leicester, Cardiff or Norwich will be able to identify who took part. Your GP will be notified that you are taking part only if you give permission on the consent form.

Who is organising and funding the research?
Dr Tanya Moshkovska is conducting this research with Dr John Mayberry and the study is being funded by GEAR (Gastroenterology Education and Research).

Who has reviewed the study?
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take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

For Further Information Please Contact:

Dr Tanya Moshkovska or
Dr John Mayberry

Tel: 0116 258 8869
Email:john.mayberry@uhl-tr.nhs.uk

Department of Gastroenterology
Leicester General hospital

Gwendolen Road
Leicester
LE5 4PW

Thank you for taking the time to read this document.
If you decide to take part, you will be given a copy of this information sheet and a signed consent form to keep

Appendix 12: Consent form for RCT

Study title: Patient adherence to prescribed therapy in ulcerative colitis: an investigation of barriers & methods of improvement.

		Please initial box
1	I confirm that I have read and understand the information sheet v.1.0 dated 16/10/06 for the above study and have had the opportunity to ask questions	☐
2	I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason and without my medical care or legal rights being affected	☐
3	I understand that sections of any of my medical notes may be looked at by Dr J. Mayberry, Dr T. Moshkovska and any appropriately qualified individuals assigned by Dr Mayberry to monitor the quality of the study. I give permission for these individuals to have access to my records	☐
4	I agree to take part in the study	☐
5	I agree for my GP to be informed of my participation	☐

Name of Patient	Date	Signature
Name of Person taking consent (treating clinician)	Date	Signature
Researcher	Date	Signature

Appendix 13: Questionnaires for RCT: 1st- study commencement; 2nd-mid-study review; 3d-end of study review)

This will be printed on University Hospitals NHS Trust headed paper

Questionnaire 1 (Study commencement)
(Randomised controlled trial)

Study title: Patient adherence to prescribed therapy in ulcerative colitis: an investigation of barriers & methods of improvement.

Date questionnaire completed:	
Patient name:	
Centre (Leicester, Norwich or Cardiff):	
Hospital Number:	
Length of UC diagnosis:	
How long have you been taking 5ASA medication?	

1

Being absolutely honest – How would you describe your attitude to taking your (5ASA) medication? (Please choose the one answer that best describes you)	
I take my medication as prescribed	☐
I don't think it is important so I don't take it	☐
I don't take my medication when I feel well	☐
I forget to take it	☐
Having to take this medication worries me	☐
Missing this medication for a day won't matter in the long run	☐
Taking this medication has been much worse than expected	☐
I sometimes worry about long-term effects of this medication	☐
I sometimes feel well and therefore think I don't need the medication any more.	☐

2

How important do you feel it is for your condition to take 5ASA medication as prescribed?

☐ Very important
☐ Helpful but not so important
☐ Not at all important

3

Do you think that you have been given sufficient information about your 5ASA medication by your Doctor or Nurse?

Yes ☐ No ☐

4

Think about the last 2 weeks – have there been *any* times that you have missed taking your (5ASA) medication?

Yes ☐ No ☐
If yes, how many times?

5

What was the reason for not taking the medication?

6

Do you currently use any methods of reminding or encouraging your self to take your (5ASA) medication? If so, what are they?

7

Are these methods helpful?

Yes ☐ No ☐

8

Is there anything that you think would be helpful to ensure you take your medication (give some examples of what might be possible)

9

Do you get any side-effects to your medication? (If yes have you spoken to your Dr about this? If not why?)
Yes ☐ No ☐

10

Do your family remind you to take your medication?
Yes ☐ No ☐

11

Do you know about the benefits of continuing to take your (5ASA) medication and the risks if you do not?
Yes ☐ No ☐

This will be printed on Hospital headed paper

Questionnaire 2 (Mid-study review)
(Randomised controlled trial)

1
What method of encouragement or reminder did you use?

2					
Would you say that the encouragement/reminder method you used worked – rank it out of 5 (0 = no help at all, 5 = extremely helpful) Please circle the relevant number below:					
0	1	2	3	4	5

3
Think about the last 2 weeks – have there been *any* times that you have missed taking your (5ASA) medication?

4
Why do you think your reminder/encouragement method did or didn't work?

5
Could we change the method of reminder/encouragement to make it more effective? – How?

6
If you are still tempted to not take your (5ASA) medication – what is the reason for this?

7
Do you get any side-effects to your medication? (If yes have you spoken to your Dr about this? If not why?)

8
Have your family been helpful in reminding/encouraging you to take the (5ASA) medication during this study?

This will be printed on Hospital headed paper

Questionnaire 3 (End of study review)
(Randomised controlled trial)

1
What method of encouragement or reminder did you use?

2					
Would you say that the encouragement/reminder method you used worked – rank it out of 5 (0 = no help at all, 5 = extremely helpful) Please circle the relevant number below:					
0	1	2	3	4	5

3
Throughout this study – have there been *any* times that you have missed taking your (5ASA) medication?

4
Why do you think your reminder/encouragement method did or didn't work?

5
Did you change the method of reminder/encouragement during the study period? What method did you find more effective and why?

6
Do you think that changing reminder was helpful? If yes, tell us how often and why.

7
If you are still tempted to not take your (5ASA) medication – what is the biggest reason for this?

8
Have your family been helpful in reminding/encouraging you to take the (5ASA) medication during this study?

Appendix 14: BMQ Specific & General (version used in RCT)

YOUR VIEWS ABOUT MEDICINES PRESCRIBED FOR MAINTENANCE TREATMENT OF ULCERATIVE COLITIS

We would like to ask you about your personal views about medicines prescribed for maintenance treatment of your ulcerative colitis. These are statements other people have made about their medicines.
Please show how much you agree or disagree with them by ticking the appropriate box. There are no right or wrong answers – we are interested in your personal views

		Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
N1	My health, at present, depends on my medicines					
C1	Having to take medicines worries me					
N2	My life would be impossible without my medicines					
C2	I sometimes worry about long-term effects of my medicines					
N3	Without my medicines I would be very ill					
C3	My medicines are a mystery to me					
N4	My health in the future will depend on my medicines					
C4	My medicines disrupt my life					
C5	I sometimes worry about becoming too dependent on my medicines					
N5	My medicines protect me from becoming worse					
C6	These medicine give me unpleasant side effects					
E1	I sometimes decide to miss a dose of these medicines					
E2	I sometimes forget to take these medicines					
E3	I can cope without these medicines					
E4	Whether my condition gets better or worse depends on these medicines					
E5	These medicines are the most important part of my UC treatment					
E6	I have been given enough information about these medicines					
E7	These medicines make me feel better					
E8	I am concerned that taking these medicines regularly will make them less effective in the future					

YOUR VIEWS ABOUT MEDICINES IN GENERAL

These are statements that other people have made about medicines in general.
Please show how much you agree or disagree with them by ticking the appropriate box.

	Views about MEDICINES IN GENERAL	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
O1	Doctors use too many medicines					
H1	People who take medicines should stop their treatment for a while every now and again					
H2	Most medicines are addictive					
O2	Natural remedies are safer than medicines					
H3	Medicines do more harm than good					
H4	Most medicines are poisons					
O3	Doctors place too much trust on medicines					
O4	If doctors had more time with patients they would prescribe fewer medicines					

Appendix 15: Education and motivation session – draft guidance for content

The content and conduct of the session will be flexible to the needs of the individual patient but the style will be based on an empathic and non-judgemental approach. It is envisaged that the following topics will be covered:

The patient experience
Tell me about your experience of being prescribed and taking 5-ASA medication
Would you say you generally take this medicine as prescribed? We know that lots of people find this difficult.
Information given here can be drawn on for discussion of goals and barriers later in the session

Knowledge
What do you know about the benefits of taking this medication?
Discussion and information-giving relating to the role of 5-ASA medication in preventing flare-ups and reducing colorectal cancer risk

Motivation
How ready do you feel to try and take your medicine as prescribed?

Barriers
What things do you think might stop you?
What might help you to overcome these barriers?

Facilitation
Telephone and e-mail contact service to be mentioned
Discussion of specific optional 'aids' which are available as part of the intervention:
'Mechanical aids' such as pill dispensers
Contract signing (emphasise that this is optional)
Engaging help – discussion of whether family/friends might help

Take-aways
Patients to be given patient information leaflet (and information leaflet for relatives and friends if appropriate) and telephone/ e-mail contact details. Also to be informed about when and how they will receive any 'aids' they have selected.

Tips for remembering

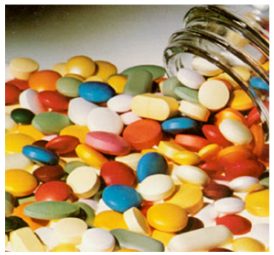
If your doctor has prescribed a 5-ASA medication these tips can help you remember to take your medication:

- Place your medication with something you use every day, like your toothbrush, spectacles or deodorant.
- Take you medication at the same time(s) every day.
- Set your watch, alarm clock or mobile phone to remind you when it's time to take your medication.
- Carry your medication in your purse, briefcase or pocket.
- Keep medication locked in your office drawer or locker at work.
- Post reminder notes somewhere you often look, like the fridge at home or on a locker or desk at work.
- Ask a family member or friend to remind you to take your medication.
- Take your medication with you when you are travelling and keep

University Hospitals of Leicester NHS
NHS Trust

This leaflet was developed as a result of interviewing a number of patients with UC in Leicester General Hospital and is designed to provide the information that these patients identified as either missing or that patients found difficult to ask.

If any of this information causes you concern or if you want additional information about your medicine and its use, please check with your doctor or pharmacist. Don't be afraid to ask questions about your treatment, especially if you are unsure how to take the medication or what to expect from it. You can also contact us



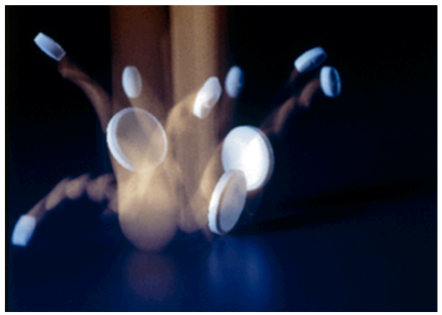
Dr Tetyana Moshkovska
Research Associate

Dr John Mayberry
Consultant Gastroenterologist

Leicester General Hospital
Department of
Gastroenterology
Gwendolen Road
Leicester
LE5 4PW
Tel: 0116 2588869

Version 1.0 16/10/2006

You and your oral 5-ASA medication



"To wish to be well is a part of becoming well"

Seneca

Many patients are not as well-informed about prescription medication as they ought to be. We believe that the more you know about medication, the better.

Therefore this leaflet explains more about 5-ASA compounds & the importance and benefits of taking them properly.

Taking your medication regularly and correctly can really help manage your ulcerative colitis (UC) and will therefore help you to feel better and improve your quality of life.

University Hospitals of Leicester NHS
NHS Trust

What are 5-ASA compounds?

5-ASA (5-aminosalicylic acid) is an anti-inflammatory medication chemically similar to aspirin. Aspirin has been used for many years to reduce tissue inflammation. Aspirin, however, is not effective in UC. Modern 5-ASA compounds are very effective in reducing inflammation in UC. They are modified either chemically or by special coating to prevent absorption by the stomach and upper intestines and deliver the active ingredient to the inflamed colon.

These modified oral 5-ASA compounds are:

ASACOL, PENTASA, IPOCOL, MESREN, SALOFALK, COLAZIDE, SALAZOPYRIN, DIPENTUM.

5-ASA compounds are safe and effective drugs that can be of tremendous benefit to you as they help with keeping UC in remission. Millions of prescriptions have been written for 5-ASA compounds in the USA, Europe and Canada. They are generally well tolerated and there is no evidence that long-term use is harmful.

As with all medications, however, side effects are possible and we encourage you to read the information supplied with your medication.

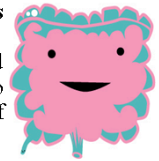
You should not take 5-ASA compounds if you are allergic to aspirin or have untreated peptic ulcer disease. Inform your doctor if you are pregnant, planning to become pregnant soon, or breast-feeding.

There is no medication that can cure UC. The goals of treatment with 5-ASA medication are to induce remissions, maintain remissions, minimize side effects of treatment, and ultimately improve quality of life.

How I can help myself?

Take the dose as prescribed. Your doctor will determine what 5-ASA compound and dose is best for you on the basis of your age, weight, the activity of your disease, and any other medical condition that you have.

Always remember UC requires lifelong management.



Taking your tablets as prescribed is really important if you want to give yourself the best chance of staying well.

Try not to miss doses.

Don't deliberately miss doses. However, if you forget a dose occasionally there is no harm. Just carry on with the next dose when it is due. Never intentionally take a double dose.

Do not stop taking prescribed medication on your own. Typically, 5-ASA compounds are prescribed for long-term treatment of ulcerative colitis. They help reduce the symptoms of an acute attack and also help to reduce the risk of future attacks. Stopping this medication may trigger another flare up.

Don't be tempted to stop the medication when you feel better.

This means the medication is working, ***not*** that your UC is cured. Often the better you feel, the more tempted you are to cut back the dose or stop taking the medication.

Taking multiple pills, several times a day may be an inconvenience. However, when you start self-adjusting your dose or forget to take your medication, you don't get the full benefit of your tablets. This will you put you at increased risk of a flare-up.

Did you know…?

Research suggested that people who have had UC for longer than 10 years have a greater risk of getting colon cancer compared to similar people without UC. There may be a 5-10% risk 10 years after getting UC. Figures from different research studies vary, but after 30 years of getting UC the risk may increase to between 15% and 40%.

Good news!

There has been some good news from recent research. This has confirmed that 5-ASA helps patients to feel and function better, by controlling symptoms of colitis. In addition, there has been promising evidence that long-term treatment with 5-ASA may protect people with UC against colon cancer. For example, a new UK primary care survey of 19,000 patients with IBD published in a professional journal called "Gut" in 2005 showed that the incidence of colorectal cancer was significantly reduced by use of 5-ASA

Indeed, if 5-ASA medication is taken regularly it is possible that the extra risk of colon cancer is removed!

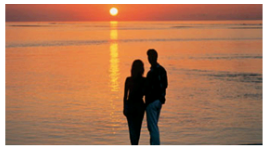
Living with someone with UC

It is hard to see someone you love suffering. Your natural reaction will be to try to help, but you may not always know how or when to give your support. Here are some tips to help you:

- **Be available and listen**. Listen to what he/she says about the problems and the anxieties they have. Try to be non-judgemental and look at things from their point of view.
- **Accept** that the chronic illness will not go away.
- **Don't underestimate** how powerful simple words of encouragement can be - even your smallest attempts at support can have a major impact.
- **Focus on** positive aspects of living. Support them in the choice they make and encourage them to continue doing the things they enjoy.
- **Eat together** a nutritionally balance diet. It is important to maintain a healthy diet together,
- **Encourage** your friend or relative to set goals for his/her future life and appreciate what you achieve together. People with ulcerative colitis want the hope that the future will be better than the present.

University Hospitals of Leicester NHS
NHS Trust

This leaflet was developed as a result of interviewing a number of patients with UC in Leicester General Hospital. Patients indicated that support family and friends is important.



They really need your support and understanding!

Having to ask for help from friends and family is hard for many UC patients. Patients usually don't want to inconvenience others, but they often need your help.

If any of this information causes you concern or if you want additional information about this medicine and its use, please check with the doctor or pharmacist. You can also contact us:

Dr Tetyana Moshkovska
Research Associate
Dr John Mayberry
Consultant Gastroenterologist
Leicester General Hospital
Department of Gastroenterology
Gwendolen Road
Leicester
LE5 4PW
Tel: 0116 2588869

Version 1.0 16/10/2006

Supporting someone with ulcerative colitis (UC).

Information for family and friends who support someone with ulcerative colitis

Ulcerative colitis is a lifelong condition with considerable impact on patient quality of life.

The effects of this long-term illness can be emotionally and physically draining. Living with UC is difficult for the person who suffers from it. Life can also be difficult for family members and friends who live with and care for people with UC.

Together you can find a way around temporary difficulties, perhaps through a combination of your support and mutual understanding.

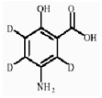
University Hospitals of Leicester NHS
NHS Trust

What are 5-ASA compounds?

5-ASA (5-aminosalicylic acid) is an anti-inflammatory medication chemically similar to aspirin. Aspirin has been used for many years to reduce tissue inflammation. Aspirin, however, is not effective in treating UC.

Modern 5-ASA compounds are very effective in reducing inflammation in UC and are modified either chemically or by special coating to prevent absorption by the stomach and upper intestines and deliver the active ingredient onto the inflamed colon.

These modified oral 5-ASA compounds are:



ASACOL, PENTASA, IPOCOL, MESREN, SALOFALK, COLAZIDE, SALAZOPYRIN, DIPENTUM.

5-ASA compounds are safe and effective drugs that can be of tremendous benefit to you as they help with keeping UC in remission. Millions of prescriptions have been written for 5-ASA compounds in the USA, Europe and Canada and they are generally well tolerated. There is no evidence that this long-term use is harmful.

As with all medications, however, side effects are possible and we encourage you to read the information supplied with the medication.

Patients should not take 5-ASA compounds if they are allergic to aspirin or have untreated peptic ulcer disease. The doctor should be informed if a female patient is pregnant, planning to become pregnant soon, or breast-feeding.

There is no medication that can cure UC. The goals of treatment with 5-ASA medication are to induce remissions, maintain remissions, minimize side effects of treatment, and ultimately improve quality of life.

How can I help my relative to take his/her medication as prescribed?

Try to involve yourself in his/her treatment - offer to accompany them to their next appointment and be supportive if they are having problems complying with the treatment the doctor has prescribed.

Always remember UC requires life long management. Work with your friend or relative to develop a reminder system for daily medication to help him/her treat active ulcerative colitis and stay in remission. Your support may encourage them to persevere with a treatment that he/she may otherwise have given up on.

It's important that patients comply fully with the doctor's prescribed regime. One of the biggest challenges is convincing patients with UC that once their symptoms are gone, continued therapy is necessary to control their disease long-term. 5-ASA remission therapy can help reduce the risk of future flare-ups and may help improve your time spent together. Make sure when you are travelling he/she stays on their regular dosing regime.

Together find out more information about ulcerative colitis. Information and knowledge will very often help you both to overcome difficulties with UC. Researching the subject together is also demonstration of your support and involvement in his/her treatment.

Useful websites:
www.ibdclub.org.uk
www.livingwithuc.com/voices/index.jsp
www.digestive.healthcentersonline.com/
www.patient.co.uk/showdoc/23068968/

Did you know?...

Research suggested that people who have had UC for longer than 10 years have a greater risk of getting colon cancer compared to similar people without UC. There may be a 5-10% risk 10 years after getting UC. Figures from different research studies vary, but after 30 years of having UC the risk may increase to between 15% and 40%.

Good news!

There has been some good news from recent research. This has confirmed that 5-ASA helps patients to feel and function better, by controlling symptoms of colitis. In addition, there has been promising evidence that long-term treatment with 5-ASA may protect people with UC against colon cancer. For example, a new UK primary care survey of 19,000 patients with IBD published in a professional journal called "Gut" in 2005 showed that the incidence of colorectal cancer was significantly reduced by use of 5-ASA.

Don't forget...

Your support is really necessary to ensure that your friend or relative takes their medication as prescribed because successful treatment with 5-ASA can greatly reduce cancer risk.

Appendix 18: Sample medication reminder chart

			How much to take & when			
What the Doctor gave me (Name of medication	What I call it	What it is for	Breakfast	Midday meal	Evening meal	Bedtime

Appendix 19: Visual medication reminders for fridges and bedside cabinets

Appendix 20: Daily electronic pill box organisers with alarms

Appendix 21: Weekly electronic pill box organisers

Appendix 22: Weekly non- electronic pill box organisers

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