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PRELIMINARY ANALYSIS OF DRUG ADHERENCE OF PATIENTS SUFFERING WITH ULCERATIVE COLITIS

(Diploma thesis)

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CONTENTS

INTRODUCTION AND AIM OF DIPLOMA THESIS

It is common sense that patient compliance to their medication plays a significant role to the treatment and the medication efficacy. Typically, about 50% of patients present low adherence to the prescribed treatment. Several clinical studies show that non-adherence to the medication increase danger for reoccurrence, affect the quality of life of patient, as well as enlarge the costs of treatment.

The diploma thesis aims to investigate the role of the beliefs of patients about medicines and their adherence of patient to the prescribed medication according to age group (young: age between 20-45 years old versus old: age between 46-65 years old). The study employs the Belief about Medicine Questionnaire to measure the adherence of patients with Ulcerative Colitis in Greece. A previous experience of the Greek version of questionnaire provided guidelines for this purpose. A statistical analysis is attempted, in order to estimate relations between patient adherence with his age and the number of the prescribed drugs per day.

STATEMENT

I declare that this thesis is my original authorial work, which I wrote alone. All literature and other sources which I used, are listed in the reference and are not previously published

10/5/2016 Konstantina Tsianou

LIST OF ABBREVIATIONS

BMQ	Beliefs about Medicine Questionnaire
BSQ	Beliefs about Surgery Questionnaire
CCKNOW	Crohn Colitis Knowledge Score
CD	Crohn ‘s Disease
DAI	Drug Attitude Inventory
GI	Gastrointestinal
GORD	Gastro-oesophageal reflux disease
HAART	Highly Active Antiretroviral Therapy
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-related quality of life
IBD	Inflammatory Bowel Diseases
KMO	Kaiser-Meyer Olkin (factor)
MAQ	Medication Adherence Questionnaire
MARS	Medication Adherence Report Scale
MPR	Medication Possession Ratio
PDC	Proportion of Days Covered
QoL	Quality of Life
sIBDQ	Short Inflammatory Bowel Disease Questionnaire
UC	Ulcerative Colitis
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI:GH	Work Productivity and Activity Impairment Questionnaire in General Health
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire in Specific Health Problem

Chapter 1

Ulcerative Colitis

Ulcerative Colitis (UC) are chronic Inflammatory Bowel Diseases that affect primary young adults worldwide. This chapter focuses on the etiopathology of the disease, the clinical condition, the diagnosis and the treatments.

1.1 Etiopathology

The etiology of UC is currently unknown but is likely multifactorial. The currently held paradigm involves a complex interaction of three elements: genetic susceptibility, host immunity, and environmental factors. Dysregulation of the enteric immune response in genetically predisposed persons leads to the development of acute and chronic inflammation and the pathologic feature of mucosal damage. The specific inciting antigens for the inflammatory process have yet to be identified, but several sources have been suggested, including pathogenic and commensal microorganisms, metabolic byproducts of these agents, and normal epithelial structures.

1.1.1 Etiology

a. Genetics

Genetic factors have been linked to the development of UC, supported largely by the observation that family history is one of the most important risk factors for developing the disease. A familial incidence of UC has been recognized for many years, and although figures vary widely in different studies, about 10% to 20% of patients have at least one other affected family member. [1] Familial associations generally occur in first-degree relatives. The relative risk of the same disease in a sibling of a person with UC has been estimated to be between 7% and 17% based on North American and European studies. Parents, offspring, and second- degree relatives appear to be at a lower risk for developing UC than are first-degree relatives. Data from the United States suggest a preponderance

of parent-sibling combinations, but in the United Kingdom, the disease is shared more commonly by siblings. Indeed, the strongest evidence of a genetic influence for UC is derived from twin studies. In three large European twin pair studies, approximately 6% to 16% of monozygotic twin pairs had concordant UC com- pared with 0% to 5% of dizygotic twin pairs. [2] These concordance rates are substantially lower than those for Crohn's disease, suggesting that genetic determinants, although important, play a less-significant role for UC than for Crohn's disease. No twin pair demonstrated both UC and Crohn's disease, further supporting the genetic basis of these disorders.

The inheritance of UC cannot be described by a simple mendelian genetics model. It is likely that multiple genes are involved and that different genes confer susceptibility, disease specificity, and phenotype. Linkage studies have suggested that there are susceptibility genes for UC on chromosomes 1, 2, 3, 5, 6, 7, 10, 12, and 17. The IBD2 locus on chromosome 12 appears to have strong linkage demonstrated in studies involving large numbers of families with UC. The NOD2/CARD15 gene mutations located on chromosome 16 associated with Crohn's disease have not been associated with UC, although UC patients from families with a history of Crohn's disease and UC might possess NOD2 variants. In contrast, the C3435T polymorphism for the human multidrug resistance 1 (MDR1) gene is linked to susceptibility for UC but not Crohn's disease. The MDR1 gene product, P-glycoprotein, is highly expressed in intestinal epithelial cells and serves an important barrier function against xenobiotics. In contrast to NOD2/CARD15, the frequency of this polymorphism in patients with Crohn's disease is similar to that in control subjects. There also are genes that appear to influence disease behavior independently of susceptibility genes. The best studied of these genes are the human leukocyte antigen (HLA) alleles. One allele of HLA-DR2 (DRB1*1502) appears to be involved in disease susceptibility in Japanese and Jewish populations. [3]

b. Environmental Factors

It is now almost universally accepted that the pathogenesis of IBD is a result of continuous antigenic stimulation by commensal enteric bacteria, fungi, or viruses, which leads to chronic inflammation in genetically susceptible hosts who have defects in mucosal barrier function, microbial killing, or immunoregulation. Several infectious organisms, including mycobacteria and viruses, have been implicated in the pathogenesis of IBD. No specific infective organism, however, has been isolated consistently from patients with UC, and therefore it is unlikely that the disease is caused by a single common infectious agent.

Numerous clinical and experimental observations have suggested involvement of intestinal bacterial microbiota in the pathogenesis of IBD. The most obvious observation perhaps is that Crohn's disease and UC preferentially occur in regions of the bowel that contain the highest concentration of bacteria, namely, the terminal ileum and the colon, where bacterial concentrations approach 1012 organisms per gram of luminal contents. Interestingly, diverting the fecal stream in patients with Crohn's disease can treat and even prevent disease, whereas reinfusion of ileostomy contents leads to new inflammatory changes within only one week. Other human data have shown that antibiotics are useful in the treatment or postoperative prevention of Crohn's disease and pouchitis. Finally, probiotics have been shown to have efficacy in the primary and secondary prevention of pouchitis. The most glaring evidence of the necessary role of bacteria in the pathogenesis of IBD from rodent data is that genetically susceptible mice or rats in a gnotobiotic (germ-free) environment do not have intestinal inflammation; however, these same rodents rapidly develop intestinal inflammation after bacterial colonization. Just as in humans, rodent gut inflammation can be treated and prevented with antibiotics and probiotics. [4, 5]

Four general mechanisms have been postulated to explain how components of the normal intestinal microbiome might initiate or contribute to the development of the chronic inflammatory state.44 First, microbes can induce intestinal inflammation, either by adhering to or invading intestinal epithelial cells, thereby causing downstream proinflammatory cytokine production or by producing enterotoxins.

Second, a breakdown in the balance between protective and harmful intestinal bacteria, termed dysbiosis, can lead to disease. [6]

The third and fourth ways bacteria could play a role in the pathogenesis of IBD deal with the host itself. Genetic defects in host microbial killing or impaired mucosal barrier function can lead to immune hyper-responsiveness to intestinal bacteria, as the microbes have more exposure to epithelial cells and can trigger the production of high levels of proinflammatory cytokines. Finally, genetic defects in host immunoregulation can lead to a heightened immune response to even nonpathogenic bacteria, such as abnormal antigen processing or presentation, loss of tolerance, or overly aggressive T-cell responses.

In addition to infectious agents, several other environ- mental factors have been proposed as contributing etiologic factors of UC. The best characterized environmental factor associated with UC

is cigarette smoking. Numerous studies have consistently shown that UC is more common among nonsmokers than among current smokers, with the relative risk of UC in nonsmokers ranging from two to six; this association is independent of genetic background and gender. Furthermore, there may be a dose-response relation- ship, with the disease more common in current light smokers than in heavy smokers. This risk of developing UC with smoking is particularly high for former smokers, especially within the first two years of smoking cessation. [7]

Several mechanisms have been postulated to account for the apparent protective effect of active smoking on UC. These include modulation of cellular and humoral immunity, changes in cytokine levels, increased generation of free oxygen radicals, and modification of eicosanoid-mediated inflammation. Other environmental risk factors that have been suggested to influence the development of UC include diet (wheat, maize, cow's milk, refined sugar, fruits and vegetables, alcohol), oral contraceptives, food additives (silicon dioxide), toothpaste, and breast-feeding7; none, however, has been shown conclusively to be associated with UC.

c. Immune Factors

The prevailing theory of the pathogenesis of UC emphasizes the role of the enteric immune response. The physiologic state of the intestine is one of constant low-grade inflammation in response to environmental stimuli such as bacterial products or endogenous factors. Breaches in this well-regulated mucosal immune system lead to the chronic, uncontrolled mucosal inflammation observed in UC. In this regard, immunologic mechanisms in the pathogenesis of UC involve both humoral and cell-mediated responses.

Histologic examination of the inflamed colon indicates a marked increase in the number of plasma cells. This increase is not uniform among cells producing different classes of immunoglobulins. The largest proportional increase occurs in immunoglobulin (Ig)G synthesis, which has the highest pathogenic potential among antibody classes. The increase in IgG synthesis in UC is most pronounced in the IgG1 and IgG3 subclasses, in contrast to Crohn's disease, in which the increase in IgG2 synthesis is more prominent. This disparity in the local IgG subclass response likely reflects differences in antigenic stimuli or host immunoregulatory responses between the two groups of IBD patients. The increased IgG synthesis in IBD may represent polyclonal stimulation; patients with UC often have circulating anti- bodies to dietary, bacterial, and self antigens that are mostly of the IgG isotype, usually the IgG1 subclass. Many of these antibodies are thought to be epiphenomena because the serum antibody titers do not correlate with clinical features. Nevertheless, the known

crossreaction between enterobacterial antigens and colonic epithelial epitopes may be an important triggering event, even though, later in the course of the disease, the serum antibody titer to either the bacterial or the colonic antigen may be unimportant. [8]

The concept that UC is an autoimmune disease is supported by its increased association with other autoimmune disorders, including thyroid disease, diabetes mellitus, and pernicious anemia. Patients with UC have varying levels of autoantibodies to lymphocytes, ribonucleic acid, smooth muscle, gastric parietal cell, and thyroid; these are specific for neither tissue nor disease. Antibodies to epithelial cell-associated components, which specifically recognize intestinal antigen, also have been described.

Immune dysregulation in UC also involves cell-mediated immunity. Cell-mediated immunity consists of two components, innate immunity and adaptive immunity. The innate immune system, which involves largely monocyte macrophages and dendritic cells, is nonspecific and untrained and acts as the first line of defense against foreign antigens, particularly bacterial antigens. Bacteria prompt immune responses largely through pattern-recognition receptors (PRRs), which include the 11 Toll-like receptors (TLRs) and 23 nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) that have been identified to date.

Activation of the TLRs and NLRs results in downstream activation of nuclear factor-κB (NF-κB), which then stimulates the transcription of genes coding for various proinflammatory cytokines (including TNF, IL-1, IL-6, and IL-8), chemokines, adhesion molecules, and costimulatory molecules. In addition, activation of NF-κB stimulates the maturation of dendritic cells, which are involved in antigen presentation. Defects in any of the PRR pathways can lead to abnormal bacterial processing and possibly IBD.

Intestinal epithelial cells serve barrier functions and play a role in enteric immunity. Colonocytes express class II major histocompatibility complex (MHC) antigens and can function as antigen-presenting cells. In addition, they also express cytokine receptors, secrete various cytokines and chemokines, and express leukocyte adhesion molecules. Thus, abnormalities in colonic epithelial cells can contribute to the development of UC. [9]

d. Psychogenic Factors

Psychosomatic factors first were implicated in the pathogenesis of UC in the 1930s, but there is no good direct evidence to support this concept. Since the introduction of glucocorticoids for the treatment of patients with UC and the focus on immunologic aspects of the pathogenesis of the disease in the 1950s, this previously widely held notion has diminished in popularity.

Experimental studies have helped identify mechanisms of the proinflammatory potential of stress in animal models of colitis. When rats are exposed to stress before proinflammatory stimuli are introduced, the severity of colonic inflammation is increased. This particular response has been shown not to be mediated by either vasopressin or corticotropin-releasing factor. In addition, stress has been shown to directly increase intestinal permeability in rats, an action mediated by cholinergic nerves, and to potentiate intestinal inflammation in this particular situation. There are indeed studies reporting that psychosocial stress increases the risk of relapse in patients with quiescent UC. Conversely, many of the psychological features observed in patients with UC are likely secondary to this chronic disease process, a phenomenon physicians must be aware of when managing these patients. [10]

1.1.2 Pathology

At the time of initial presentation, approximately 45% of patients with UC have disease limited to the rectosigmoid, 35% have disease extending beyond the sigmoid but not involving the entire colon, and 20% of patients have pancolitis. The disease typically is most severe distally and progressively less severe more proximally. In contrast to Crohn's disease, continuous and symmetrical involvement is the hallmark of UC, with a sharp transition between diseased and uninvolved segments of the colon. [11]

There are a few exceptions to this general rule. First, medical therapy can result in areas of sparing. For example, topical enema therapy can lead to near-complete mucosal healing in the rectum and distal sigmoid colon. Second, up to 75% of patients with left-sided UC have periappendiceal inflammation in the colon and patchy inflammation in the cecum,99 resembling the skip pattern characteristic of Crohn's disease. These patterns of rectal sparing and skip lesions can lead to a misdiagnosis of Crohn's disease. [12]

Macroscopically, the mucosa in UC appears hyperemic, edematous, and granular in mild disease. As disease progresses, the mucosa becomes hemorrhagic, with visible punctate ulcers. These ulcers can enlarge and extend into the lamina propria. They often are irregular in shape with overhanging edges or may be linear along the line of the teniae coli. Epithelial regeneration with recurrent attacks results in the formation of pseudopolyps, which is typical of long-standing UC but which also may be seen in acute disease. Another characteristic appearance of long-standing disease is atrophic and featureless colonic mucosa, associated with shortening and narrowing of the colon. Patients with severe disease can develop acute dilatation of the colon, also characterized by thin bowel wall and grossly ulcerated mucosa with only small fragments or islands of mucosa remaining. With perforation of the colon, a fibrinopurulent exudate may be seen on the serosal surface of the bowel.
Microscopically, the early stage of UC is marked by edema of the lamina propria and congestion of capillaries and venules, often with extravasation of red blood cells. This is followed by an acute inflammatory cell infiltrate of neutrophils, lymphocytes, plasma cells, and macrophages, often accompanied by increased numbers of eosinophils and mast cells. Neutrophilic infiltration of colonic crypts gives rise to cryptitis and ultimately to crypt abscesses with neutrophilic accumulations in crypt lumens. This migration of neutrophils from the circulation into the lamina propria occurs in response to a variety of chemoattractants, including chemo- tactic peptides of colonic bacteria, IL-8, activated complement, platelet-activating factor, and leukotriene B4. The cryptitis is associated with discharge of mucus from goblet cells and increased epithelial cell turnover. Thus, the acute inflammatory infiltration results in the characteristic histopathology of goblet cell mucin depletion, formation of exudates, and epithelial cell necrosis. None of these histologic findings, however, is specific for UC.

Inflammation in UC characteristically is confined to the mucosa, in contrast to the transmural involvement of Crohn's disease. The inflammatory changes typically end at the luminal aspect of the muscularis mucosa. With increasing inflammation, however, the surface epithelial cells become flattened, eventually ulcerate, and can become undermined if the ulcers are deep. At this stage of the disease, some inflammation and vascular congestion may be present in the submucosa, and ulceration can extend into the muscularis mucosa. This deeper involvement may be confused with Crohn's disease, but it usually presents diffusely rather than with the segmental fissuring pattern of transmural inflammation that characterizes Crohn's disease.

During the healing phase of UC, the inflammatory infiltrate subsides and epithelial regeneration takes place. Epithelial cells undergoing regenerative changes become cuboidal with eccentric, large

nuclei, and prominent nucleoli. These features may be confused with dysplasia. Thus, a diagnosis of dysplasia in UC should be made with caution in the presence of acute inflammation. Accordingly, surveillance colonoscopy should be performed during a period of remission.

A classic histologic feature of chronic quiescent UC is crypt architectural distortion or actual dropout of glands. Architectural changes include branching or bifid glands, wide separation among glands, and shortened glands that do not extend down to the muscularis mucosa. Architectural alteration is a prominent feature of chronic quiescent UC, but the histologic abnormalities can revert to normal after mild flares early in the course of disease. Another characteristic feature of chronic quiescent UC is Paneth cell metaplasia, with Paneth cells located distal to the hepatic flexure, where they normally are absent. Other nonspecific chronic changes seen in UC include neuronal hypertrophy and fibromuscular hyperplasia of the muscularis mucosa. Varying degrees of acute or chronic inflammation of the lamina propria may be present in chronic quiescent disease. A thin band of predominantly lymphocytic inflammation occasionally may be seen deep to the muscularis mucosa, presenting diagnostic challenges.

Most of these pathologic findings are not specific for UC. Features that reflect chronicity and thus argue against a diagnosis of infectious or acute self-limited colitis include distorted crypt architecture, crypt atrophy, increased inter- crypt spacing to fewer than six crypts per millimeter, an irregular mucosal surface, basal lymphoid aggregates, and a chronic inflammatory infiltrate. The histologic severity of inflammation does not necessarily correlate with clinical disease activity in patients with UC, because patients may be relatively symptom free although histology reveals significant inflammation.

1.2. Clinical Features

Patients with UC can present with a variety of symptoms. Common symptoms include diarrhea, rectal bleeding, passage of mucus, tenesmus, urgency, and abdominal pain. In more severe cases, fever and weight loss may be prominent. The symptom complex tends to differ according to the extent of disease. Patients with proctitis often have local symptoms of tenesmus, urgency, mucus, and bleeding, whereas patients with extensive colitis usually have more diarrhea, weight loss, fever, clinically significant blood loss, and abdominal pain. In general, the severity of the symptoms correlates with the severity of the disease; however, active disease may be found at colonoscopy in

patients who are otherwise asymptomatic. Additionally, patients with known UC can have severe symptoms that are not necessarily due to UC, such as those caused by bacterial (e.g., Clostridium difficile) or viral (e.g., cytomegalovirus) infections or a host of other similar disorders. The onset of UC typically is slow and insidious. Symptoms usually have been present for weeks or months by the time the typical patient seeks medical attention. The median interval between the onset of symptoms and diagnosis of UC is approximately nine months. Some patients with UC present much more acutely, with symptoms mimicking acute infectious colitis. Indeed, it is not uncommon to find a patient whose UC began after a documented gastrointestinal infection, such as Salmonella or C. difficile. This observation raises the question whether the infection revealed preexisting but silent disease or whether it was actually the initiating factor.[13]

1.2.1 Symptoms

a. Rectal Bleeding

Rectal bleeding is common in UC, its characteristics determined by the distribution of disease. Patients with proctitis usually complain of passing fresh blood, either separately from the stool or streaked on the surface of a normal or hard stool. This symptom often is mistaken for bleeding from hemorrhoids. In contrast to hemorrhoidal bleeding, however, patients with ulcerative proctitis often pass a mixture of blood and mucus and might even be incontinent. Patients with proctitis also often complain of the frequent and urgent need to defecate, only to pass small quantities of blood and mucus without fecal matter. When the disease extends proximal to the rectum, blood usually is mixed with stool or there may be grossly bloody diarrhea. When disease activity is severe, patients typically pass liquid stool containing blood, pus, and fecal matter. This stool often is likened to anchovy sauce, and some patients with this symptom do not actually recognize that they are passing blood. Unless the patient has severe disease, passage of blood clots is unusual and suggests other diagnoses such as a tumor. Active UC that is sufficient to cause diarrhea almost always is associated with macroscopically evident blood. The diagnosis needs to be questioned if visible blood is absent.[14]

b. Diarrhea

Diarrhea is common but not always present in patients with UC. Up to 30% of patients with proctitis or proctosigmoiditis complain of constipation and hard stools. Most patients with active disease complain of frequent passage of loose or liquid stools and may have nocturnal diarrhea. Fecal urgency, a sensation of incomplete fecal evacuation, and fecal incontinence also are common,

especially when the rectum is severely inflamed. Diarrhea in this setting often is accompanied by passage of large quantities of mucus, blood, and pus. The pathophysiology of diarrhea in UC involves several mechanisms, but failure to absorb salt and water is the predominant factor and results from reduced Na+,K+- ATPase (adenosine triphosphatase) pump activity, increased mucosal permeability, and altered membrane phospholipids. High mucosal concentrations of lipid inflammatory mediators, which are detected in UC, have been shown to stimulate chloride secretion in normal colon, and it is possible that these mediators also contribute to diarrhea by increasing mucosal permeability. Urgency and tenesmus, which are common symptoms when the rectum is inflamed, are caused by decreased rectal compliance and loss of the reservoir capacity of the inflamed rectum. With severe inflammation, the urgency can be sufficiently acute to cause incontinence. Colonic motility is altered by inflammation, and there is rapid transit through the inflamed colon. With left-sided disease, distal colonic transit is rapid, but there is actual slowing of proximal transit, which might help explain the constipation that is commonly seen in patients with distal colitis. Prolonged transit in the small intestine also occurs in the presence of active colonic inflammation. [14]

c. Abdominal Pain

Many patients with UC complain of abdominal pain with active disease, although pain generally is not a prominent symptom unless disease activity is severe. Patients can experience vague lower abdominal discomfort, an ache in the left iliac fossa, or intermittent abdominal cramping that precedes bowel movements and often persists transiently after defecation. Severe cramping and abdominal pain can occur in association with severe attacks of the disease. The cause of the pain is unclear but might relate to increased tension within the inflamed colonic wall during muscular contraction. Patients with active proctitis also often complain of tenesmus and urgency associated with painful straining and passage of mucus and blood with only scanty stools.

d. Others

Disease of moderate or severe activity often may be associated with systemic symptoms. Patients can develop anorexia and nausea and, in severe attacks, might actually vomit. These symptoms, as well as protein loss through inflamed mucosa, hypercatabolism, and down-regulation of albumin synthesis caused by the inflammation, account for weight loss and hypoalbuminemia that may be profound. Fever, an added catabolic factor, usually accompanies severe attacks but is typically moderate. Patients also might complain of symptoms from anemia and hypoalbuminemia, including fatigue, dyspnea, and peripheral edema. Patients can present with extraintestinal manifestations,

including acute arthropathy, episcleritis, and erythema nodosum, that typically parallel the activity of colitis.

1.2.2 Signs

Patients with mild or even moderately severe disease exhibit few abnormal physical signs. These patients are usually well nourished and well appearing and show no signs of chronic disease. Caution should be exercised because these patients can appear deceptively well. Weight always should be recorded and, for children and adolescents, both height and weight should be plotted on developmental growth charts. The affected portion of the colon may be tender on abdominal palpation, but tenderness usually is mild and not associated with rebound or guarding. Bowel sounds are normal. Digital rectal examination also is often normal, but the rectal mucosa might feel velvety and edematous; the anal canal may be tender; and blood may be seen on withdrawal of the examining finger.

Patients with severe attacks also might appear well, but most are ill with tachycardia, fever, orthostasis, and weight loss. The abdomen typically is soft, with only mild tenderness over the diseased segment. Abdominal tenderness may become diffuse and moderate with more severe disease. Bowel sounds may be normal or hyperactive but diminish with disease progression. In fulminant colitis, the abdomen often becomes distended and firm, with absent bowel sounds and signs of peritoneal inflammation. There may be aphthoid ulceration of the oral mucosa. Clubbing of the fingernails is a manifestation of chronic disease. Peripheral edema can occur secondary to hypoalbuminemia. Minor perianal disease may be present but is never as severe as is seen in patients with Crohn's disease. Signs of extraintestinal manifestations also may be present.

1.2.2 Laboratory Findings

Laboratory findings in UC are nonspecific and reflect the severity of the underlying disease. Patients with active proctitis and proctosigmoiditis often have normal laboratory test results. Patients with limited distal disease often pass visible blood in the stool, but the amount of blood loss typically is small and anemia, if present, is mild. Patients with active extensive disease or severe distal disease can demonstrate laboratory abnormalities. Hematologic changes, including anemia, leukocytosis, and thrombocytosis, reflect active disease. In contrast, patients with quiescent UC typically manifest no laboratory abnormalities. Iron deficiency anemia may be present because of chronic blood loss.

Anemia also may be present secondary to bone marrow suppression resulting from chronic inflammation or medications, including azathioprine, 6-mercaptopurine (6-MP), and sulfasalazine. Mild or moderate attacks rarely are associated with any biochemical disturbance. Hypokalemia, metabolic alkalosis, and elevated serum levels of blood urea nitrogen and creatinine may be present in severe flares of UC, reflecting volume depletion. Hypoalbuminemia may be seen with acute and chronic disease. Minor elevations in serum levels of aspartate aminotransferase or alkaline phosphatase also are commonly associated with severe disease, but these changes are transient and return to normal when the disease enters remission; these abnormalities probably reflect a combination of fatty liver, sepsis, and poor nutrition. Persistently elevated liver biochemical tests, especially serum alkaline phosphatase, are seen in about 3% of patients with UC and should lead to further investigation, particularly to exclude primary sclerosing cholangitis (PSC).

Serum inflammatory markers including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be elevated in active disease. These abnormalities are typically absent or minimal in patients with mildly to moderately active disease. Elevation in these inflammatory parameters is neither sensitive nor specific for UC; measuring them, however, may be useful in clinical practice to assess disease activity in individual patients, particularly if these values are normal during periods of inactive disease. For following clinical changes, CRP is more sensitive than ESR because of the shorter half-life of CRP.

1.3 Diagnosis

Currently, there is no single test that allows the diagnosis of UC with acceptable sensitivity and specificity. Thus, diagnosis relies on a combination of compatible clinical features, endoscopic appearances, and histologic findings. Stool cultures should be obtained to exclude infection with routine bacterial pathogenic organisms; assay for toxins A and B of C. difficile, and examinations for ova and parasites also should be performed. Infection with E. coli O157:H7 should be considered and requires special stool cultures (or molecular probes). Similarly, special cultures for gonococcus or Chlamydia may be necessary in selected cases. In immunosuppressed patients, the possibility of opportunistic infection of the colon must be excluded. The diagnosis of UC should be questioned if there is only a single episode of acute illness or if the histopathology findings are nonspecific and lack signs of chronicity.

1.3.1 Diagnostic Methods

a. Endoscopy

The diagnosis of UC can be strongly suggested by sigmoidoscopy in most cases. In patients presenting with their first attack of UC, sigmoidoscopy with biopsies usually is sufficient to confirm the diagnosis, thereby allowing initiation of therapy. In patients with active flares, sigmoidoscopy is best performed in unprepared bowel so the earliest signs of UC can be detected without the hyperemia that is often present because of preparative enemas. Colonoscopy is not recommended in patients with severely active disease for fear of perforation; care must be taken to avoid excessive distention. After active disease has been controlled in a patient with newly diagnosed UC, colonoscopy should be performed to establish the extent of the disease and to exclude Crohn's disease or other disease states that can complicate UC.

Multiple biopsy specimens should be taken from through- out the colon to map the histologic extent of disease and to confirm the diagnosis if there is concern about Crohn's disease. In addition, intubation and biopsy of the terminal ileum should be attempted to exclude the presence of Crohn's disease or other disease states that can mimic IBD. [15]

In patients with an established diagnosis of UC who present with a typical flare, sigmoidoscopy usually is not necessary, although it may be indicated for the rapid diagnosis of pseudomembranous colitis. Sigmoidoscopy combined with histologic evaluation, however, may be useful for assessing disease severity, particularly when therapeutic response is in question. Colonoscopy may be similarly useful, especially in patients whose symptoms seem out of proportion to the known extent of disease. Additionally, colonoscopy is essential for colorectal cancer surveillance (see below).

The hallmark of UC is symmetrical and continuous inflammation that begins in the rectum and extends proximally without interruption for the entire extent of disease. The earliest endoscopic sign of UC is a decrease or loss of the normal vascular pattern, with mucosal erythema and edema; distortion or loss of vascular markings may be the only endoscopic evidence of UC in patients with quiescent disease. As disease progresses, the mucosa becomes granular and friable. With more-severe inflammation, the mucosa may be covered by yellow-brown mucopurulent exudates associated with mucosal ulcerations. In UC, mucosal ulcerations occur in areas of inflammation, vary in size from a few millimeters to several centimeters, and may be punctate, annular, linear, or serpiginous. Finally, severe UC is associated with mucosa that bleeds spontaneously, and, with

diffuse colitis, there may be extensive areas of denuded mucosa from severe mucosal ulcerations. Marked edema can at times lead to narrowing of the lumen.

In patients with long-standing UC, pseudopolyps may be present. Inflammatory pseudopolyps develop in active disease and result from inflamed, regenerating epithelium that is interposed among ulcerations. These inflammatory pseudopolyps may give the colonic mucosa a cobblestoned appearance. With repeated inflammation that is followed by healing, these pseudopolyps remain during the quiescent phase of disease and usually do not regress with treatment. Endoscopically, pseudopolyps typically are small, soft, pale, fleshy, and glistening; however, they may be large, sessile, or pedunculated and may have surface ulcerations. Differentiation of these benign pseudopolyps from neo- plastic polyps may be difficult and require histologic confirmation.

There is a loss of normal colonic architecture with long- standing inflammation that is characterized by muscular hypertrophy, loss of the normal haustral fold pattern, decreased luminal diameter, and shortening of the colon; a resultant featureless appearance of the colon in chronic UC gives rise to the lead pipe appearance seen on barium enema. Strictures can occur in patients with chronic UC and result from focal muscular hypertrophy associated with inflammation. Malignancy must be excluded in patients with UC who have strictures, particularly long strictures without associated inflammation and strictures proximal to the splenic flexure.

b. Plain Films

Patients with a severe attack of UC should have a supine plain film of the abdomen. The presence of intraperitoneal air may be missed on plain abdominal films, however, and CT has demonstrated a better diagnostic yield than plain abdominal radiography for detecting disease complications and extent. In the presence of severe disease, the luminal margin of the colon—the interface between the colonic mucosa and the luminal gas—becomes edematous and irregular. Thickening of the colonic wall often is apparent on a plain film, and prognostic signs such as islands of residual mucosa surrounded by extensive deep ulcerations, distention of the small bowel, and dilatation of the colon can be detected.

Plain films also are useful for detecting the presence of fecal material. Inflamed colons seldom contains feces, and no fecal material is present when the whole colon is involved. It is common, however, for a patient with left- sided disease to have proximal constipation. Thus, a plain film can give considerable information with respect to the extent of disease. The presence of marked colonic

dilatation suggests fulminant colitis or toxic mega- colon. A plain abdominal film also can detect unsuspected free air and is especially useful in following the daily progress of a patient on high-dose glucocorticoid therapy in whom such a complication may be masked.

c. Barium Enema

With the advent of endoscopy, barium studies have been used less often in the care of patients with UC. Barium studies of the colon remain important, however, and may be superior to colonoscopy for certain specific scenarios, such as evaluation of colonic strictures; barium enema pro- vides information on their location, length, and diameter and allows visualization of the entire colon when the presence of strictures precludes advancement of the colonoscope. Upper gastrointestinal barium study and small bowel follow-through with air-contrast visualization of the terminal ileum should be performed to exclude Crohn's disease.

The earliest radiologic change of UC seen on barium studies is fine mucosal granularity. The mucosal line becomes irregular and is not as sharp as that of a normal colon. With increasing severity, the mucosal line becomes thickened and irregular, and superficial ulcers are well shown en face. Deep ulceration can appear as collar-stud or collar-button ulcers in tangent, which indicates that the ulceration has extended through the mucosa to the muscularis propria. Haustral folds may be normal in mild disease but become edematous and thickened as disease progresses. Loss of haustrations also can occur, especially in patients with long-standing disease. Because the left colon may normally lack haustration, this sign is relevant for only the ascending and transverse colon. With long-standing disease, loss of haustration can lead to a featureless and tubular appearance of the colon. Other chronic changes are shortening of the colon and widening of the presacral (retrorectal) space as seen on a lateral film of the rectum. Pseudopolyps may be present and often are filiform. In the presence of active changes, these pseudopolypoid changes can resemble a cobblestone pattern.

1.3.2 Diagnostic Factors

The diagnosis of ulcerative colitis is based on the presence of chronic diarrhea for more than four weeks and evidence of active inflammation on endoscopy and chronic changes on biopsy. Since these features are not specific for ulcerative colitis, establishing the diagnosis also requires the exclusion of other causes of colitis by history, laboratory studies, and by biopsies of the colon obtained on endoscopy.

a. History

A history of risk factors for other causes of colitis should be sought. This includes a history of recent travel to areas endemic for parasitic infections including amebiasis, recent antibiotic use that might predispose to an infection with Clostridium difficile, a history of or risk factors for sexually transmitted diseases (eg, Neisseria gonorrhea and herpes simplex virus (HSV)) that are associated with proctitis. Atherosclerotic disease or prior ischemic episodes are suggestive of chronic colonic ischemia. A history of abdominal/pelvic radiation and NSAID/medication exposure should be sought as these may also be associated with colitis. In an immunocompromised patient, cytomegalovirus (CMV) can mimic ulcerative colitis.

b. Laboratory studies

Stool studies should include stool Clostridium difficile toxin, routine stool cultures (Salmonella, Shigella, Campylobacter, Yersinia), and specific testing for E. coli O157:H7. Microscopy for ova and parasites (three samples) and a Giardia stool antigen test should also be performed, particularly if the patient has risk factors such as recent travel to endemic areas. In addition, specific serologic testing for sexually transmitted diseases including Neisseria gonorrhea, HSV, and Treponema pallidum should be considered, particularly in patients with severe rectal symptoms including urgency and tenesmus.

In addition, a complete blood count, electrolytes, albumin, and markers of inflammation erythrocyte sedimentation rate and C-reactive protein (CRP) should be obtained to assess disease severity. A number of autoantibodies have been detected in patients with inflammatory bowel disease (IBD). Perinuclear antineutrophil cytoplasmic antibody (pANCA) may be elevated in patients with ulcerative colitis. However, the accuracy of antibody tests in differentiating ulcerative colitis from Crohn disease in patients with “indeterminate colitis” on biopsy, is uncertain. Antibody testing is therefore not part of the diagnostic evaluation of patients with suspected IBD. [16]

c. Endoscopy and biopsy

Endoscopic findings in patients with ulcerative colitis are nonspecific. Biopsies of the colon obtained on endoscopy are necessary to establish the chronicity of inflammation and to exclude other causes of colitis. An ileocolonoscopy allows for evaluation of the terminal ileum for inflammation that would be suggestive of Crohn disease and to determine the endoscopic extent and severity of colonic disease. However, a colonoscopy should be avoided in hospitalized patients with severe colitis

because of the potential to precipitate toxic megacolon. In such patients, a flexible sigmoidoscopy should be performed and evaluation limited to the rectum and distal sigmoid colon. [17]

The endoscopic findings in patients with ulcerative colitis include loss of vascular markings due to engorgement of the mucosa, giving it an erythematous appearance. In addition, granularity of the mucosa, petechiae, exudates, edema, erosions, touch friability, and spontaneous bleeding may be present. More severe cases may be associated with macroulcerations, profuse bleeding, and copious exudates. Nonneoplastic pseudopolyps may be present in areas of disease involvement due to prior inflammation.

The biopsy features suggestive of ulcerative colitis include crypt abscesses, crypt branching, shortening and disarray, and crypt atrophy. Epithelial cell abnormalities including mucin depletion and Paneth cell metaplasia may be seen. Inflammatory features of ulcerative colitis include increased lamina propria cellularity, basal plasmacytosis, basal lymphoid aggregates, and lamina propria eosinophils. Although none of these features are specific for ulcerative colitis, the presence of two or more histologic features is highly suggestive of ulcerative colitis. Basal plasmacytosis may also be a predictor of relapse in patients with seemingly well-controlled ulcerative colitis with complete mucosal healing.

The inflammation usually involves the rectum and extends proximally in a continuous and circumferential pattern. The initial episode of ulcerative colitis is limited to the rectum or sigmoid colon in 30 to 50 percent of patients, 20 to 30 percent have left-sided colitis, and only approximately 20 percent of patients have pancolitis with disease extending proximal to the splenic flexure and involving the cecum. Occasionally a subset of patients with ulcerative colitis have focal inflammation around the appendiceal orifice that is not contiguous with disease elsewhere in the colon (a "cecal patch"). Ileal inflammation (“backwash” ileitis) may occasionally be seen in patients with ulcerative colitis with active right-sided colitis. Unlike the ileitis associated with Crohn disease which is patchy, backwash ileitis associated with ulcerative colitis is diffuse. [18]

In patients with CMV colitis, conventional hematoxylin and eosin stains reveal enlarged (cytomegalic) cells that are often two- to fourfold larger than surrounding cells, usually with large eosinophilic intranuclear inclusions, sometimes surrounded by a clear halo, and smaller cytoplasmic inclusions. Immunoperoxidase staining should be done to confirm suspected CMV. Cultures for

Neisseria gonorrhea and HSV should be performed in patients with severe rectal symptoms of urgency and tenesmus. [19]

1.3.3 Differential Diagnosis

The differential diagnosis of ulcerative colitis includes other causes of chronic diarrhea:

- **Crohn disease**: Crohn disease that involves the colon may have a similar clinical presentation to ulcerative colitis. [20] However, features that are suggestive of Crohn disease include absence of gross bleeding, presence of perianal disease (eg, anal fissures, anorectal abscess), and fistulas. The absence of rectal inflammation and the presence of ileitis, focal inflammation, and granulomas on endoscopy and biopsy are also suggestive of Crohn disease. Although ileal inflammation ("backwash" ileitis) may occasionally be seen in ulcerative colitis, these patients have active right-sided colitis. In addition, backwash ileitis associated with ulcerative colitis is diffuse and not patchy as seen in Crohn disease.
- **Infectious colitis**: Infectious colitis may have a similar clinical presentation and endoscopic appearance to ulcerative colitis. Infectious colitis must be excluded with stool and tissue cultures, stool studies, and on biopsies of the colon.
- **Radiation colitis**: Radiation colitis may be seen weeks to years after abdominal or pelvic irradiation. Radiation colitis involving the rectum or sigmoid colon has a similar appearance to ulcerative colitis on endoscopy. Although not specific for radiation colitis, histologic findings suggestive of radiation colitis include eosinophilic infiltrates, epithelial atypia, fibrosis, and capillary telangiectasia.
- **Diversion colitis**: Individuals with diversion colitis have a history of a surgically excluded bowel loop and prominent lymphoid hyperplasia on histology.
- **Solitary rectal ulcer syndrome:** Patients with solitary rectal ulcer syndrome may have bleeding, abdominal pain, and altered bowel habits. Mucosal ulceration may be seen on endoscopy similar to ulcerative colitis but solitary rectal ulcer syndrome has a characteristic appearance on histology with a thickened mucosal layer and distortion of crypt architecture. The lamina propria is replaced with smooth muscle and collagen leading to hypertrophy and disorganization of the muscularis mucosa.
- **Graft versus host disease:** Graft versus host disease (GVHD) of the colon can cause chronic diarrhea in patients with a history of bone marrow transplantation. Patients may have symptoms due to involvement of the proximal gastrointestinal tract (eg, dysphagia, painful

ulcers) or other organs (eg, liver involvement as suggested by elevated liver tests, skin involvement resembling lichen planus or scleroderma). There are no endoscopic features of chronic GVHD of the colon that distinguish it from ulcerative colitis. However, histologic examination in chronic GVHD is characterized by the presence of crypt cell necrosis with the accumulation of degenerative material in the dead crypts [21]

- **Diverticular colitis:** Diverticular colitis is characterized by inflammation in the interdiverticular mucosa without involvement of the diverticular orifices. In contrast, in patients with IBD and diverticulosis, the inflammation involves the colonic area harboring diverticula, as well as the diverticular orifices. In addition, the distribution of the colitis in patients with diverticular colitis (ie, limitation to a segment of diverticular disease, sparing the rectum, terminal ileum, and other portions of the colon) also assist in differentiating it from ulcerative colitis [22]
- **Medication associated colitis:** Nonsteroidal antiinflammatory drugs (NSAIDs) can cause chronic diarrhea and bleeding. Other drugs that may cause a similar clinical presentation include retinoic acid, ipilimumab, and gold. The diagnosis is established by a history of medication use and the presence of non specific mucosal inflammation or mucosal erosions on biopsy that resemble ischemic changes. [23]

1.4. Treatment

1.4.1 Medical Treatment

The goals of therapy of UC are to induce remission, to maintain remission, to maintain adequate nutrition, to minimize disease and treatment-related complications, and to improve the patient's quality of life. Current management strategy focuses on using appropriate medical therapy and optimizing timing of surgery.

Several factors should be considered in determining optimal therapy for patients with UC. Current therapeutic strategies can be classified broadly, based on disease activity, into those that treat active disease (induction therapy) and those that prevent recurrence of disease once remission is achieved (maintenance therapy). This concept of induction and maintenance of remission forms the basis of our evaluation of the efficacy of a specific therapy. The extent of disease is an important consideration that helps determine the route of administration of medication. Thus, for example, proctitis may be treated with suppositories or foam preparations as well as with oral therapy, and enema preparations may be used alone or in combination with systemic therapy for patients with left-

sided disease. Other important factors to consider are a patient's prior response to or side effects from a specific medication and compliance with medication. These factors might favor or preclude the use of a specific agent. Given the chronic nature of UC, medications need to be efficacious and well accepted by patients from the standpoints of safety and ease of administration. The mainstay of medical therapy focuses on regimens that alter host response to decrease mucosal inflammation. Therapies that target other aspects of the systemic inflammatory process or manipulate the enteric flora also have been developed to treat UC.

1.4.2 Surgical Treatment

Removal of the colon and rectum cures UC. Common indications for surgical therapy of UC are medically refractory disease, intractable disease with impaired quality of life, and unacceptable side effects from medical therapy e.g. colonic dysplasia or carcinoma, uncontrollable colonic hemorrhage, colonic perforation, growth retardation, toxic megacolon, systemic complications that are recurrent or unmanageable.

a. Toxic megacolon

Toxic megacolon is defined as acute colonic dilatation with a transverse colon diameter of greater than 6 cm (on radio- logic examination) and loss of haustration in a patient with a severe attack of colitis. This complication of UC results from extension of colonic inflammation beyond the mucosa to the underlying tissues, including the muscularis propria. Loss of contractility from the inflammatory reaction leads to the accumulation of gas and fluid within the lumen and subsequent colonic dilatation. [24]

b. Strictures

Colonic strictures complicate UC in approximately 5% of patients, most commonly in those with extensive and long- standing colitis. Patients with colonic strictures usually present with alterations in bowel habits, both constipation and diarrhea. Clinically significant obstruction is rare. Colonic strictures complicating UC typically are short (2 to 3 cm), occur distal to the splenic flexure, and represent hypertrophy and thickening of muscularis mucosa rather than fibrosis. There needs to be a high index of suspicion of malignancy in patients with colonic strictures associated with UC. [25]

c. Colorectal cancer

Patients with UC have an increased risk of colorectal cancer. This risk depends on several factors, the most important being the duration and extent of the disease. Other risk factors include PSC, family history of colon cancer, age at diagnosis of disease, severity of inflammation, presence of pseudopolyps, and possibly backwash ileitis. The incidence of colon cancer in UC varies depending primarily on the duration and extent of the disease, but it has been estimated at approximately 7% to 10% at 20 years of disease and as high as 30% after 35 years of disease. [26]

1.5 Assessment of clinical severity

Patients can present with mild, moderate, or severe disease. Stratification based on clinical severity is important in guiding management. [27])

- **Mild:** Patients with mild clinical disease have four or fewer stools per day with or without blood, no signs of systemic toxicity, and a normal erythrocyte sedimentation rate (ESR). Mild crampy pain, tenesmus, and periods of constipation are also common, but severe abdominal pain, profuse bleeding, fever, and weight loss are not part of the spectrum of mild disease.
- **Moderate:** Patients with moderate clinical disease have frequent loose, bloody stools (>4 per day), mild anemia not requiring blood transfusions, and abdominal pain that is not severe. Patients have minimal signs of systemic toxicity, including a low grade fever. Adequate nutrition is usually maintained and weight loss is not associated with moderate clinical disease.
- **Severe:** Patients with a severe clinical presentation typically have frequent loose bloody stools (≥6 per day) with severe cramps and evidence of systemic toxicity as demonstrated by a fever (temperature ≥37.5ºC), tachycardia (HR ≥90 beats/minute), anemia (hemoglobin <10.5 g/dL), or an elevated ESR (≥30 mm/hour). Patients may have rapid weight loss. The management of severe ulcerative colitis is discussed separately.

1.6 Management according to clinical severity

1.6.1 Management of mild to moderate ulcerative colitis

Initial treatment of ulcerative colitis is based upon disease severity and extent. Topical 5-aminosalicylic acid (5-ASA) medications are first-line treatment in those who are willing to use rectal therapy. Topical therapies also provide a quicker response time than oral preparations and

typically require less frequent dosing Topical 5-ASA medications are preferred over topical steroids in those who are willing to use topical therapy Maintenance therapy is **not** recommended in patients with a first episode of mild ulcerative **proctitis** that has responded promptly to treatment. Maintenance therapy is recommended in patients with ulcerative proctitis who have more than one relapse a year and in all patients with proctosigmoiditis Patients with mildly or moderately active left-sided colitis and pancolitis benefit most from combination therapy with oral 5-ASA medications, 5-ASA or steroid suppositories, and 5-ASA or steroid enemas or foam. [28, 29]

Despite the approaches described above, some patients continue to have severe gastrointestinal symptoms. Patients with continued symptoms should be carefully reassessed, paying specific attention to the type of ongoing symptoms, the degree to which symptoms have improved or worsened, and compliance with medications. Reassessment of the extent of disease is indicated if a patient has a recurrence of symptoms after initial improvement that does not mimic the initial presentation.

1.6.2 Management of severe ulcerative colitis

Patients with a severe ulcerative colitis have frequent loose bloody stools (≥6 per day) with severe cramps and evidence of systemic toxicity as demonstrated by a fever (temperature ≥37.5°C), tachycardia (heart rate [HR] ≥90 beats/minute), anemia (hemoglobin <10.5 g/dL), or an elevated erythrocyte sedimentation rate (ESR) (≥30 mm/hour). Patients may have rapid weight loss.

Patients with severe ulcerative colitis should be treated with oral glucocorticoids and combination therapy with high dose oral 5-aminosalicylic acid (5-ASA) (eg, mesalamine 4.8 grams/day), 5-ASA or steroid suppository, and 5-ASA, steroid enema, or foam. Some patients should also receive antibiotics. Initiation of oral glucocorticoids should not be delayed until the results of stool studies and cultures are available. Nutritional support should be considered in patients who are malnourished. [30]

Chapter 2

Medical Treatment of Ulcerative Colitis

One important consideration when evaluating the efficacy of a particular medication (e.g., in a RCT that compares a novel therapy to placebo) is the placebo response rate. Even though placebos often are thought of as inert agents, they have been noted to lead to improvement in a variety of both subjective and objective outcome measures in a number of different medical conditions, such as anxiety, depression, insomnia, pain, asthma, obesity, hypertension, and even myocardial infarction. [31]

2.1 Aminosalicylates

2.1.1 Oral

Sulfasalazine consists of an antibacterial component, sulfapyridine, bonded by an azo bond to a salicylate, 5-aminosalicylic acid (5-ASA, mesalamine). The drug was synthesized by Nana Svartz in 1938-1939 and its benefit for the treatment of IBD was discovered seren-dipitously in 1941-1942 by her when patients with UC receiving this medication for a presumed diagnosis of rheumatoid arthritis noted improvement in colitis symptoms; in retrospect, these patients had peripheral arthropathy associated with their IBD. Research subsequently established that 5-ASA is the principal therapeutic moiety of sulfasalazine in IBD and that the sulfapyridine component of the parent drug serves as an inactive carrier, largely preventing absorption of 5-ASA in the small intestine and allowing it to be released in the colon.Approximately 90% of sulfasalazine reaches the colon, and only a small amount is absorbed in the small intestine. On reaching the colon, the enzyme azoreductase, which is elaborated by colonic bacteria, cleaves the azo bond to release the active constituent moiety, 5-ASA. After 5-ASA is absorbed from the colon, 20% of the compound undergoes hepatic acetylation, forming N-acetyl 5-ASA, and is excreted in the urine. Sulfasalazine is one of several agents in the class of 5-ASA compounds that is considered to be the first line of therapy for inducing remission in

patients with mild to moderate UC. Mesalamine derivatives have not been evaluated in a randomized, controlled fashion in patients with severely active disease. At a dose of 3 to 6 g/day, sulfasalazine induces remission in 39% to 62% of patients with mild to moderate UC, about twice the remission rate of placebo- treated patients. [32, 33]

Various formulations and controlled-release systems have been developed to deliver 5-ASA to specific sites of the gastrointestinal tract without the sulfapyridine moiety, which is thought to be responsible for most of the side effects. Olsalazine (Dipen- tum) is a 5-ASA dimer linked by an azo bond and is formulated in gelatin capsules. Balsalazide (Colazal) consists of a 5-ASA monomer linked to a biologically inactive carrier molecule, 4-aminobenzoyl-β-alanine. Similar to sulfasalazine, 5-ASA is released from olsalazine and balsalazide in the colon upon cleavage of the azo bond via the bacterial enzyme azoreductase. Approximately 99% of the drug is delivered intact to the colon, and its metabolites are cleared rapidly in the urine.

Three commonly used mesalamine preparations allow delivery of 5-ASA before the drug reaches the colon: Pentasa, Asacol, and Lialda. Pentasa uses ethyl cellulose-coated microgranules that release mesalamine from the duodenum throughout the small bowel and the colon; about 50% of 5-ASA is released in the small intestine, and the remainder is released in the colon. Asacol is a Eudragit-S-100–coated mesalamine tablet that is released at a pH greater than 7, usually in the distal ileum and the colon. With Asacol, about 15% to 30% of mesalamine is released in the small intestine. Lialda (MMx mesalamine) is a novel mesalamine formulation that uses a multimatrix structure composed of an inner lipophilic matrix and an outer hydrophilic matrix. It is coated with a pH-dependent polymethacrylate film to allow the delayed release of mesalamine in the terminal ileum and colon at a pH greater than 7. This technology also allows mesalamine to be released slowly and in close proximity to the colonic mucosa.

These oral 5-ASA derivatives (mesalamines) have been shown to be superior to placebo for mildly to moderately active UC. Meta-analyses have demonstrated that the mesalamines are as efficacious as sulfasalazine, and the various mesalamine preparations appear to be comparable in efficacy. Balsalazide has been shown to have superior efficacy and a more rapid response compared with traditional mesalamine agents. In a RCT, balsalazide 6.75 g/day, a dose equivalent to mesalamine 2.4 g daily, achieved higher rates of remission and had better tolerance compared with pH-dependent mesalamine 2.4 g/day. It has been suggested that the greatest benefit of balsalazide is in patients with newly diagnosed left-sided UC.

More important than the specific 5-ASA preparation is the dose-dependent response when 5-ASA is used as an induction therapy for active UC. For this indication, mesalamine is not effective at doses lower than 2 g daily, and there is an increased response at doses of 4 to 4.8 g daily. The ASCEND I and II trials showed that mesalamine at doses of 2.4 and 4.8 g/day have similar efficacy for patients with mildly active disease, but the higher dose (4.8 g/day) was more efficacious in patients with moderately active disease. This dose of mesalamine is comparable to 12 g/day of sulfasalazine, which is impractical in clinical practice because of the high probability of intolerance. No RCT has evaluated the use of aminosalicylates for severely active UC, but these agents are generally thought not to be effective in severely active disease. [34]

Once remission is achieved, sulfasalazine and other 5-aminosalicylates are effective in maintaining it. This benefit appears to be dose dependent for sulfasalazine, with a dose of 2 g/day often used to balance efficacy and adverse side effects. Such a dose-dependent response, however, has not been found with the other 5-ASA preparations, and at doses of 1.5 to 4.8 g/day, remission can be maintained in more than 50% of patients. One meta-analysis has suggested that sulfasalazine might have a slight but statistically significant therapeutic superiority relative to the newer 5-ASAs in maintaining remission when considering trials of six months' duration; however, when these trials were combined with those of 12 months' duration, this statistically significant benefit was lost. A double-blind RCT comparing two doses of balsalazide (1.5 g twice daily and 3 g twice daily) with mesalamine 0.5 g three times daily for six months reported a remission rate of 77.5% with the higher dose of balsalazide compared with remission rates of 56.8% and 43.8% with mesalamine and the lower dose of balsalazide, respectively. In general, the same dose of 5-ASA derivative that induces remission is recommended for maintenance therapy, although this recommendation has not been formally tested in a randomized, placebo- controlled fashion. [35]

Common side effects of sulfasalazine include fever, rash, nausea, vomiting, and headache. Other, less-common but important side effects of sulfasalazine include hypersensitivity reactions, reversible sperm abnormalities, and impairment of folate absorption. Approximately 15% of patients taking sulfasalazine develop significant side effects that require discontinuing the medication. Up to 90% of patients who are intolerant to sulfasalazine, however, can tolerate mesalamine. In clinical trials, the newer 5-ASA preparations and balsalazide have been shown to be better tolerated than sulfasalazine, although the adverse event profiles during maintenance therapy appear to be similar for 5-ASA preparations and sulfasalazine. Sulfasalazine can impair folate absorption (by competitively

inhibiting the jejunal enzyme, folate conjugase) thereby contributing to anemia, and folate supplementation should be prescribed to patients receiving sulfasalazine. Olsalazine is associated with drug-induced diarrhea in up to 10% of patients, which often limits its use. It has been noted that if olsalazine is ingested with meals and is continued despite the diarrhea, the incidence of this side effect can be lessened substantially to 3%. A systematic review of oral 5-ASA for maintenance of remission in UC found olsalazine to be significantly inferior to sulfasalazine, and this reduced efficacy was related mostly to a significantly higher rate of withdrawals because of adverse events. Oral mesalamine preparations do not appear to have significant dose- dependent toxicity. [34]

2.1.2 Topical

Topical aminosalicylates can be administered in the form of 5-ASA enemas, 5-ASA suppositories, and, in Europe, 5-ASA foam. The use of enemas allows the medication to be delivered up to the level of the splenic flexure in about 95% of patients, and suppositories can be used to treat disease up to 15 to 20 cm from the anal verge.

Topical mesalamine derivatives may be used as an alternative monotherapy or as an adjunctive therapy to oral agents in patients with left-sided colitis or pancolitis. They are effective for inducing remission in patients with mildly to moderately active distal UC, without a clear dose-response effect in non refractory patients. The standard dosing regimens used to induce remission are 1 to 4 g of 5-ASA in the form of an enema nightly, or mesalamine suppositories 1 to 1.5 g either nightly or in divided doses throughout the day. Mesalamine enemas have been shown to be comparable to oral sulfasalazine in the treatment of active distal UC, with fewer side effects. Similar efficacies have been demonstrated for mesalamine enemas regardless of whether the 1-, 2-, or 4-g formulation is used for inducing remission in patients with mild to moderate left-sided UC not requiring concurrent glucocorticoids or immunomodulators. In fact, mesalamine enemas are perceived to be even more effective than topical glucocorticoid enemas in this setting. A combination of topical and oral mesalamine also may be more effective than either agent alone in patients with left-sided colitis or pancolitis, suggesting a dose-response effect. In patients with proctitis, mesalamine suppositories, 500 mg administered twice daily, have been shown to be beneficial for treating active disease. Mesalamine foam has a more uniform distribution and longer persistence in the distal colon compared with mesalamine enemas. The foam preparation has been shown to have better patient acceptance than the enema preparation, but mesalamine foams currently are not available in the United States. [36, 37]

Topical mesalamine preparations also are effective for maintaining remission in left-sided UC or proctitis. The effective maintenance dosing interval ranges from nightly to every three days. Topical mesalamine is as effective as oral mesalamine, and the combination of topical and oral mesalamine may be more effective than oral mesalamine alone as a maintenance regimen.

2.2 Glucocorticoids

2.2.1 Systemic

At doses equivalent to 40 to 60 mg/day of oral prednisone, glucocorticoids are effective first-line therapy for moderate or severe flares of UC. The use of doses higher than 60 mg/day is associated with increased side effects without appreciable clinical benefit and thus should be avoided. The addition of sulfasalazine to corticosteroids in moderately to severely active UC does not offer any incremental benefit. Although no study has directly compared the efficacy of oral and parenteral glucocorticoids, the latter commonly are used in severe disease. No adequately designed controlled study has been performed to confirm the clinical impression that continuous infusion of parenteral glucocorticoids is superior to pulse therapy. [38]

The use of adrenocorticotropin (ACTH) has been suggested as an alternative to conventional glucocorticoid therapy of active UC in small studies. Because most patients with severely active flares have been treated previously with glucocorticoids, ACTH rarely is used in clinical practice. A noteworthy complication of ACTH therapy is bilateral adrenal hemorrhage.

Glucocorticoids have no maintenance benefits in patients with UC. Steroid-dependent patients, or patients who are unable to taper off glucocorticoids without experiencing disease exacerbation, benefit from the addition of steroid sparing agents. There has been no trial to date assessing mesalamine therapy and its efficacy in maintaining remission induced with glucocorticoids. The long-term remission rate in patients who require parenteral glucocorticoids for severe UC is approximately 50%. Immunomodulatory agents, as discussed, should be considered in patients who are dependent on steroids, who require two courses of glucocorticoids for induction of clinical response or remission within one year, or who require parenteral glucocorticoids to induce remission. In addition to the use of immunomodulatory agents, one should consider using infliximab for steroid-dependent patients. [39]

Glucocorticoids are associated with many mild and serious side effects in patients with IBD (cutaneous, endocrine, gastrointestinal, infectious, metabolic, musculoskeletal, neuropsychiatric, and ocular). These side effects occur commonly and involve nearly every organ system. Every effort should be made to minimize glucocorticoid use and exposure.

Budesonide is a glucocorticoid preparation that is structurally different from prednisone. The presence of 16α,17α- acetyl side chains allows enhanced topical anti-inflammatory activity and affinity for glucocorticoid receptors compared with prednisone. In addition, budesonide has an approximately 90% first-pass metabolism in the liver and erythrocytes and is converted to metabolites that have little or no biological activity. The resultant low systemic bioavailability translates to significantly less toxicity compared with traditional glucocorticoids. Entocort is a controlled-ileal-release oral budesonide preparation consisting of Eudragit- L-100–coated microgranules with an internal ethyl cellulose component; it releases budesonide at pH greater than 5.5, and about 50% to 80% of budesonide is absorbed in the ileocecal region. There currently is no oral formulation of budesonide that provides optimal release characteristics for the entire length of the colon. A small uncontrolled study has suggested that Budenofalk, which is not available in the United States, may be effective for prednisone-dependent UC. Controlled studies have not shown the benefit of oral budesonide for the treatment of active UC. [40]

2.2.2 Topical

Topical glucocorticoids in liquid and foam formulations are effective short-term therapy for active UC distal to the splenic flexure. Foam preparations often are tolerated better by patients and may be easier to retain than liquid preparations. Topical glucocorticoids have been found to be less effective than topical mesalamine for inducing remission of distal UC; however, the combination of topical corticosteroids and topical mesalamine has been more efficacious than either alone in the short-term treatment of distal UC.

Whereas systemic absorption of glucocorticoids with topical therapy is significantly less than that with oral administration, prolonged treatment with topical glucocorticoids still may be associated with steroid-related side effects and should be avoided. As mentioned previously, budesonide is a potent corticosteroid with a rapid first-pass metabolism. Budesonide enemas, which currently are neither available nor approved in the United States, have been shown to be effective for the treatment of active distal UC in several controlled trials. Subsequent trials have shown budesonide enema to be

as efficacious as or even superior to prednisolone enema without resultant depression of endogenous cortisol levels.

Budesonide enema perhaps is inferior in efficacy to mesalamine enema, but it clearly presents an alternative topical glucocorticoid for treatment of distal UC. The optimal dose for budesonide enema consistently has been shown to be 2 mg/100 mL once daily. Budesonide in foam preparation also has been shown to have comparable efficacy with traditional hydrocortisone foam for the treatment of active proctosigmoiditis. Additional studies are needed to determine the effect of longer-term topical budesonide use. As with other glucocorticoid preparations, budesonide enema is not effective for maintaining remission in UC. [41]

2.3 Immunomodulators

2.3.1 Azathioprine and 6-Mercaptopurine

Of the various immunomodulatory agents, the most widely used are azathioprine and 6-MP. These two agents are purine analogs that interfere with nucleic acid metabolism and cell growth and exert cytotoxic effects on lymphoid cells. They are inactive prodrugs with subtle structural differences. Azathioprine is nonenzymatically converted to 6-MP, which is then metabolized through a series of enzymatic pathways to active and inactive metabolites. The two primary metabolites of 6-MP are 6-thioguanine nucleotides (6-TGNs) and 6-methylmercapto- purine (6-MMP). The 6-TGN metabolites are thought be responsible for the immunomodulatory action of azathioprine and 6-MP and their bone marrow suppression property, whereas hepatotoxicity is thought to be related to 6-MMP. One key enzyme involved in the biotransformation of 6-MP is thiopurine methyl transferase (TPMT), which converts 6-MP to its inactive metabolites, 6-MMP and 6-methylmercaptopurine ribonucleotides.

There is a population polymorphism in the TPMT gene: 89% of the population have homozygous wild-type TPMT, and 11% and 0.3% of the population have heterozygous and homozygous mutations, respectively. Persons with heterozygous and homozygous TPMT mutations have decreased to absent enzyme activity. The clinical significance of this genetic polymorphism is that inherited differences in TPMT may be responsible for most of the variability in drug response observed among individual patients. [42]

The efficacy of azathioprine in the treatment of UC is a matter of debate. Four RCTs have evaluated azathioprine for inducting remission in active UC. These four studies were small, heterogeneous in design, used different outcome definitions for response, and reached different conclusions. Two of the studies involved steroid- dependent patients, one other study used steroids for induction, and two studies used 5-ASAs as a comparator group rather than placebo. Only one study showed a significant benefit with azathioprine compared with 5-ASA for induction therapy in steroid-dependent disease.
With respect to the use of azathioprine for maintenance of remission in UC, four RCTs have been performed. Just as with studies of induction therapy, these four studies also had small sample sizes, used heterogeneous designs with different outcome definitions of response, allowed for various cotherapies, and again reached different conclusions. One of the studies was in steroid- dependent disease, another allowed the use of steroids for relapse, one study used 5-ASA as a comparator group rather than placebo and another included patients who were mostly taking 5-ASAs and was actually a study of azathioprine withdrawal. Only this withdrawal study showed a benefit with continued azathioprine. [43]

Thus, for the purpose of induction or maintenance therapy for UC, our use of azathioprine is largely based on its established efficacy in Crohn's disease rather than any proven benefit in UC. One subset of patients, however, has been shown to obtain benefit with the use of azathioprine, specifically patients who have severely active UC and who are able to attain induction of remission with intravenous followed by oral cyclosporine. In these patients, maintenance therapy with azathioprine has been reported to decrease colectomy rates.

The optimal dose of azathioprine or 6-MP for treating UC is unclear, and no formal dose-ranging study has been reported in the literature. The effective doses for 6-MP and azathioprine generally are 1 to 1.5 mg/kg/day and 2 to 3 mg/ kg/day, respectively. At these doses, however, there still may be non responders and, for them, higher doses may be necessary. Induction of leukopenia had been advocated for dose optimization, but this practice was not supported by subsequent studies. Monitoring metabolite levels may be beneficial in determining the optimal dose of azathioprine or 6-MP.

To date, at least 13 studies examining response in IBD with respect to 6-TGN level have been published. A meta- analysis of the first 12 of these studies found that the studies were similar in that they were retrospective and the majority of patients were adults with Crohn's disease, but they were heterogeneous with respect to sample size, the proportion of patients in remission, and the activity

indices used to assess response. Of the seven studies that reported data on 6-TGN threshold levels, a pooled analysis of the first six studies showed a three-fold significantly higher rate of remission among patients with a 6-TGN level of greater than 230 to 260 pmol/8 × 108 red blood cells. Incorporation of 6-TGN metabolite measurement into the management regimen of patients receiving azathioprine or 6-MP therapy for IBD is not mandatory and it is a subject of continuing controversy. Currently, 6-TGN measurement appears to be most useful for identifying reasons for nonresponse to therapy and for suspected noncompliance. If used, metabolite levels should be determined at least two weeks following any dose adjustment to allow sufficient time for the metabolites to reach steady-state. [44]

Currently, it is recommended in the package insert and by the U.S. Food and Drug Administration (FDA) to determine TPMT genotype or phenotype before initiating therapy. The active metabolites, 6-TGNs, also are responsible for myelosuppression with therapy, and patients with TPMT mutation or decreased TPMT enzyme activity are more likely to experience this toxicity because of preferential shunting of 6-MP metabolism toward the excessive production of 6-TGN.201 Thus, identifying TPMT polymorphism before initiating azathioprine or 6-MP therapy can decrease the risk of myelotoxicity. Patients with homozygous wild- type TPMT or normal (to high) TPMT enzyme activity level may receive these agents starting at the weight-based optimal dose of 2.5 mg/kg/day for azathioprine or 1.5 mg/kg/day for 6-MP. It has been suggested by some investigators that in patients with heterozygous TPMT mutation or intermediate enzyme activity level, 6-MP or azathioprine should be started at 50% of the weight-based optimal dose. Alternative therapy should be considered in patients with homozygous mutations for TPMT. Regardless of whether a patient's TMPT genotype or phenotype is known, continued frequent monitoring of complete blood counts remains necessary, because only 27% of all patients with leukopenia have TPMT mutations. In addition, two studies have reported that TPMT testing may be cost effective.

Azathioprine and 6-MP therapy have a delayed onset of action. The mean time to clinical response with azathioprine or 6-MP therapy in patients with UC has been reported to be three to four months in uncontrolled studies, a figure that is similar to the 17 weeks' response time to clinical benefit in placebo-controlled trials of azathioprine or 6-MP therapy for active Crohn's disease. Intravenous loading of azathioprine at 40 mg/kg for 36 hours does not shorten the time required for a therapeutic response in patients with Crohn's disease. Such practice presumably would have the same results if attempted in patients with UC. [45, 46]

Because azathioprine or 6-MP therapy is associated with a number of potentially significant toxicities, its duration of therapy should be determined by weighing clinical benefit against these potential toxicities. The optimal duration of maintenance therapy with azathioprine or 6-MP currently is unknown in patients with UC. In patients with Crohn's disease, the maintenance benefit of azathioprine or 6-MP can be observed for at least five years. Based on these data in Crohn's disease and the paucity of alternative maintenance therapies, in patients with UC in whom remission is maintained with azathioprine or 6-MP, treatment generally is continued indefinitely as long as there is no significant adverse side effect.

Common side effects of azathioprine and 6-MP therapy include nausea, vomiting, bone marrow suppression, pancreatitis, allergic reactions, and infections. Bone marrow suppression occurs in 2% to 5% of patients. It is dose dependent and manifests primarily as leukopenia, although all three cell lines may be affected. This hematologic toxicity can increase with concurrent use of sulfasalazine or mesalamine compounds. It is known that mesalamine can interact with the enzyme TPMT, leading to increased levels of 6-TGN, and that this interaction has been associated with leukopenia. Bone marrow suppression is managed by reducing the dosage of immunomodulator or withdrawing the medication. Routine monitoring of complete blood count with differentials is necessary for patients receiving azathioprine or 6-MP and should be continued for the entire duration of therapy. Allergic reactions to azathioprine or 6-MP usually manifest as fever, rash, and arthralgia and resolve following discontinuation of these medications. Recurrence of similar reactions occurs with medication challenge, although patients who develop allergic reactions to one agent may be able to tolerate subsequent challenge with the other. Pancreatitis also is idiosyncratic and independent of dosage. It usually occurs during the first month of therapy and is reversible upon withdrawal of the drug. [47]

Patients using azathioprine or 6-MP therapy can have abnormal liver biochemical tests, but these usually resolve following drug withdrawal. Because liver biopsy is not performed routinely in these patients, their pattern of hepatic injury, if any, is unknown. Cholestasis with inflammation, nodular regenerative hyperplasia, and peliosis hepatis have been reported with azathioprine and 6-MP therapy. As is the case for complete blood counts, routine monitoring of liver biochemical tests is recommended. An increased risk of malignancy, primarily lymphoma, has been reported, but not consistently. A meta- analysis of six studies examining this risk reported a four- fold elevated risk of lymphoma with 6-MP/azathioprine. The lymphoma that develops in patients who have IBD and receive these immunomodulatory agents appears to be associated with Epstein-Barr virus. [48]

2.3.2 Cyclosporine

Cyclosporine A is a potent inhibitor of cell-mediated immunity. Its use in UC is primarily in patients with severe, steroid-refractory disease. There has only been one randomized, placebo-controlled trial evaluating the efficacy of intravenous cyclosporine in severe UC. In this study of 20 patients who did not respond to at least seven days of intravenous hydrocortisone, nine (82%) of the 11 patients receiving continuous intravenous infusion of cyclosporine at 4 mg/kg/day responded, compared with none of the nine patients receiving placebo therapy. The time to clinical response was rapid, at a mean of seven days. After the intravenous route of therapy was converted to oral cyclosporine, 44% of those patients who responded initially required colectomy during the six- month follow-up period. Intravenous cyclosporine monotherapy may be as effective as intravenous glucocorticoids in patients with severely active UC; its use thus potentially minimizes the toxicities of combination therapy. The addition of azathioprine or 6-MP in patients who have responded to intravenous cyclosporine has been shown in other studies to reduce the rate of relapse or colectomy. Thus, cyclosporine can be considered a bridge therapy to control active disease in patients with steroid-refractory UC while waiting for elective surgery or the onset of action of azathioprine or 6-MP. [49]

With the addition of azathioprine, long-term remission at one year may be more likely in patients who initially respond to intravenous cyclosporine monotherapy than in those who respond to intravenous glucocorticoids. A European retrospective cohort study of 142 patients who were treated with cyclosporine, of whom responded initially, reported the probability of avoiding colectomy to be 63% at one year, 41% at four years, and 12% at seven years; overall, 54% of patients required colectomy at some point. Patients who were already taking 6-MP or azathioprine at the time cyclosporine was initiated continued taking their current dose, and those who were naïve to 6-MP or azathioprine were started at target doses at the time of response to cyclosporine during their hospitalization. The authors found that 59% of patients previously taking 6-MP or azathioprine required eventual colectomy, compared with 31% for patients naïve to these drugs ($P < 0.05$).

Because most of the serious adverse effects associated with the use of cyclosporine are dose-dependent, intravenous doses lower than 4 mg/kg that still can achieve efficacy are desirable. One RCT has shown that a dose of 2 mg/kg is as effective as 4 mg/kg given intravenously in patients with severely active UC, judged by clinical response rates, time to response, and short-term colectomy rates. The mean plasma cyclosporine levels were 237 ng/mL in patients receiving the 2 mg/kg dose

and 332 ng/mL in patients receiving the 4 mg/kg dose. Thus, initiating therapy at 2 mg/kg may be reasonable, but regardless of the dose used, careful monitoring of plasma cyclosporine trough levels is necessary.

Cyclosporine has been associated with many adverse effects, including paresthesias, tremors, headache, hypertrichosis, and gingival hyperplasia. Other potentially serious toxicities include hypertension, seizures, electrolyte and liver biochemistry abnormalities, nephrotoxicity, anaphylaxis, and opportunistic infections. These complications are mostly dose-dependent. Severe complications have been reported with cyclosporine in up to 12% of patients with UC, and two large series have reported death rates of 1.8% to 2.8% with cyclosporine, more than half of which were due to infections acquired while taking the drug. [50, 51]

Careful monitoring for adverse effects is critical during cyclosporine therapy. Baseline serum electrolytes, creatinine, cholesterol, and liver biochemical values should be measured. Cyclosporine therapy should be avoided in patients with an impaired creatinine clearance to minimize the risk of severe nephrotoxicity. Patients with serum cholesterol lower than 120 mg/dL should receive nutritional support to improve the level before initiating cyclosporine therapy, because a low cholesterol level is associated with an increased risk of seizures. During intravenous therapy, cyclosporine levels should be monitored daily, and the dose should be adjusted to achieve a trough concentration (measured one hour before dosing) between 200 and 400 ng/mL, determined by high-pressure liquid chromatography. Serum electrolytes and serum creatinine levels should be monitored daily or every other day. The dose of cyclosporine also should be decreased when the serum creatinine increases by 20% to 30% over baseline.

If patients respond to intravenous cyclosporine, the route of administration can be changed to oral therapy with 2 mg of oral agent for each 1 mg of intravenous cyclosporine. The drug can be administered in two divided doses daily. Drug monitoring during oral cyclosporine therapy includes weekly trough cyclosporine levels and weekly to biweekly electrolyte and creatinine levels. Oral cyclosporine should be continued for three to six months, while waiting for surgery or for azathioprine or 6-MP to take effect. Patients on long-term cyclosporine therapy should receive Pneumocystis carinii pneumonia prophylaxis with trimethoprim- sulfamethoxazole.

2.3.3 Methotrexate

Methotrexate is a folic acid antagonist and has antimetabolite and anti-inflammatory properties. Although early reports suggested potential benefit of methotrexate administered intramuscularly or orally in UC, the only randomized, placebo-controlled trial failed to demonstrate its efficacy for the treatment of active UC. In this study of 67 patients with chronic active UC, oral methotrexate at 12.5 mg/wk for nine months was comparable to placebo therapy in the rate of achieving first remission, time to first remission, relapse following remission, and the mean glucocorticoid dose. It is unknown if methotrexate at higher doses administered intramuscularly or subcutaneously may be beneficial in inducing or maintaining remission in UC. Given the absence of data supporting its efficacy, methotrexate cannot at this time be considered a standard therapy for UC. [52]

2.3.4 Other Immunomodulators

Alternative immunomodulators have been explored for patients who do not tolerate or have not responded to the previously mentioned immunosuppressants. Mycophenolate mofetil has pharmacodynamic properties similar to those of azathioprine and 6-MP but a more rapid onset of action. A pilot study of patients with chronic active UC receiving concomitant prednisolone found azathioprine to be superior to mycophenolate mofetil throughout the one- year study period, with remission rates at one year of 100% and 88%, respectively. Uncontrolled studies reported less than 50% remission rates with mycophenolate mofetil therapy in patients with steroid-dependent UC and the intolerance rate was high. A substantial number of patients developed adverse effects necessitating drug withdrawal, including recurrent upper respiratory tract infection, bacterial meningitis, depression, and migraine headache. Tacrolimus is another immunosuppressant with actions similar to those of cyclosporine. In contrast to cyclosporine, it has a 100-fold greater potency and a more rapid onset of action. A number of small uncontrolled studies have suggested benefit of oral or intravenous tacrolimus for the treatment of patients with refractory UC. The only randomized, placebo-controlled trial of tacrolimus in UC involved 63 Japanese patients with either steroid-dependent or steroid-refractory disease who were randomized to receive either initial oral tacrolimus at 0.05 mg/kg or placebo twice daily. Patients in the high-trough concentration (10 to 15 ng/mL) tacrolimus group had a significantly higher rate of response and nonsignificantly higher rate of remission than those in the placebo group at week two, and a number of patients demonstrated response or remission (or both) after an additional 10 weeks of open label therapy. As with cyclosporine, tacrolimus can result in a number of toxicities including nephrotoxicity, electrolyte abnormalities, nausea, diarrhea, headache, tremors, paresthesias, insomnia, alopecia, hirsutism, and

gingival hyperplasia. Thus, given the limited data and potential for harmful adverse events, the use of these alternative immunomodulators currently is not incorporated into standard practice.

2.4 Antibiotics

Antibiotics have a limited role in the management of UC, and most controlled studies have not demonstrated their benefit either in active disease or maintenance of remission. The most commonly used antibiotics in this setting are metronidazole and ciprofloxacin. One RCT found oral tobramycin to be superior to placebo as a short-term adjunctive therapy to glucocorticoids for active UC. Another RCT reported a modest benefit for the addition of ciprofloxacin for six months in patients with UC refractory to mesalamine and corticosteroids. At present, the data showing efficacy of antibiotics for treatment of patients with UC are not as convincing as are the data for antibiotic treatment of Crohn's disease. Thus, at present the primary role of antibiotics in the treatment of UC is in the management of its suppurative complications. [53]

2.5 Probiotics, Prebiotics, and Synbiotics

Probiotics are living organisms in foods and dietary supplements that might beneficially affect the host in a number of ways, including improving its intestinal microbial balance, blocking adhesion sites on colonocytes (which might improve mucosal barrier function), and enhancing local immune response. A probiotic can be a specific non- pathogenic strain of a bacterial species or a mixture of multiple species and strains, most commonly including Lactobacillus or Bifidobacterium species; sometimes they contain fungal antigens as well. An example of a common probiotic is VSL#3, which contains four strains of Lactobacillus (Lactobacillus acidophilus, Lactobacillus delbrueckii subspecies bulgaricus, Lactobacillus plantarium, and Lactobacillus casei), three strains of Bifidobacterium (Bifidobacterium infantis, Bifidobacterium longum, Bifido- bacterium breve), and one strain of Streptococcus (Strepto- coccus salivarius subspecies thermophilus).

Prebiotics are nondigestible food ingredients that selectively stimulate the growth or activity of one or more organisms of the intestinal microbiota, such as Lactobacillus or Bifidobacterium species, thereby potentially conferring beneficial effects to the host. The majority of prebiotics are nondigestible oligosaccharides, with galacto-oligosaccharide, fructo-oligosaccharide, lactulose, and inulin being the most commonly used agents. [54]

Because probiotics have the challenge of competing with indigenous microbiota for nutrients, scientists have developed synbiotics, which are combinations of probiotics and prebiotics, in the hope of facilitating the survival of probiotics in the intestines.

With respect to the use of these agents for inducing remission in mildly to moderately active UC, four RCTs have been performed using different agents. Two of three studies that measured rates of remission found no benefit of probiotics (VSL#3 in one study, fermented milk in the other) added to 5-aminosalicylates; the third study found that E. coli Nissle 1917 combined with glucocorticoids had efficacy similar to that of mesalazine com- bined with glucocorticoids. The fourth study, which used a synbiotic, reported a nonsignificant improvement in disease activity when the synbiotic was combined with standard therapy. With respect to the use of these agents for the maintenance of remission in mildly to moderately active UC, six RCTs have been published. Two of these studies reported significantly lower rates of relapse for patients receiving a probiotic (Bifidobacterium in one study, fermented milk in the other) after medically induced remission compared with those receiving placebo, and the other four studies (using E. coli Nissle in three studies and Lactobacillus rhamnosus strain GG in the fourth) found no difference in rates of relapse. [55]

Nontraditional probiotic therapies that also have been evaluated include Saccharomyces boulardii and Trichuris suis. A small, uncontrolled study of 24 patients with mild to moderate active UC suggested a potential benefit of Saccharomyces boulardii when used in addition to mesalamine. The use of helminths in active UC was investigated by Weinstock and colleagues, who randomized 54 patients with active disease to receive 2500 T. suis ova or placebo orally every 2 weeks for 12 weeks and reported that rates of improvement were significantly higher in the active treatment group at week 12 (43% vs. 17%, P = 0.04); significant improvement was seen as early as week six.

In summary, at present, there is no convincing evidence to support the use of probiotics, prebiotics, or synbiotics for the treatment of UC. However, future large well-designed RCTs are necessary to address this issue more definitively.

2.6 Biological Therapy

Recent advances in our understanding of the pathogenesis of IBD have resulted in the development of therapies targeted at specific molecules or mediators involved in the inflammatory processes of

these diseases. Most studies evaluating the efficacy of these agents have been performed in patients with Crohn's disease, and only limited data are available for patients with UC.

TNF is a key proinflammatory cytokine that has been demonstrated to play a role in several disease states, including IBD. Elevated TNF concentrations have been found in inflamed intestine in patients with Crohn's disease and UC, and stool and mucosal concentrations of TNF in patients with IBD have been shown to correlate with clinical disease activity. Infliximab (Remicade) is a chimeric monoclonal antibody of IgG1 subclass directed against human TNF-α. It consists of 75% human and 25% murine components. The efficacy of infliximab in Crohn's disease is well established, and it is approved by the FDA to treat Crohn's disease and UC. Infliximab is thought to operate in Crohn's disease via a multitude of mechanisms, including antagonizing the activity of TNF-α, initiating cytotoxicity on immune cells, and inducing T-cell apoptosis. [56]

Results from two large, multicenter, randomized, double- blind, placebo-controlled trials (ACT 1 and 2) showed efficacy of infliximab therapy in UC. In these two similarly designed trials, 728 patients with moderately to severely active UC who failed conventional therapy with glucocorticoids alone or in combination with thiopurines (ACT 1) or glucocorticoids alone or in combination with thiopurines and 5-aminosalicylates (ACT 2) were randomized to placebo, infliximab 5 mg/kg, or infliximab 10 mg/kg at weeks 0 and 2 and then every eight weeks through week 46 (ACT 1) or week 22 (ACT 2). With respect to clinical response at week 8, in ACT 1 69% and 61% of patients receiving infliximab at 5 and 10 mg/kg, respectively, had a clinical response, compared with 37% of patients receiving placebo ($P < 0.001$ for both comparisons). In ACT 2 at week 8, 64% and 69% of patients receiving infliximab at 5 mg/kg and 10 mg/kg, respectively, had a clinical response, compared with 29% of patients receiving placebo ($P < 0.001$ for both comparisons). With respect to clinical remission at week 8 in ACT 1, 39% and 32% of patients receiving infliximab at 5 mg/kg and 10 mg/kg, respectively, attained remission, compared with 15% of patients receiving placebo ($P < 0.003$ for both comparisons). In ACT 2 at week 8, 34% and 28% of patients receiving infliximab at 5 mg/kg and 10 mg/kg, respectively, attained remission, compared with 6% of patients receiving placebo ($P < 0.001$ for both comparisons). The results for clinical remission at week 30 (ACT 1 and 2) and week 54 (ACT 1) were very similar for all groups, with highly significant greater than two-fold higher remission rates for the infliximab-treated patients. The proportions of patients with a sustained clinical response or remission also were significantly higher in the infliximab groups. Treatment with infliximab also was shown to have steroid-sparing and mucosal healing properties.

These data have led to the approval of infliximab by the FDA for patients with moderately to severely active UC who have had an inadequate response to conventional therapy. Infliximab is now accepted as part of the standard treatment options in patients with UC. Two other anti-TNF agents, adalimumab and certolizumab pegol, have shown efficacy for the induction and maintenance of remission in Crohn's disease but have not yet been studied in patients with UC. [57]

Chapter 3

Adherence of drug compliance measurement

The significant role of the adherence of patients to their prescribed medication is extensively investigated, by recent research studies, regarding the lack of diseases control and the quality of life (QoL) of patients. In terms of heathcare, adherence represents the extent that patients follow the advice of healthcare professionals regarding their medication and disease management [58]. Typically, about 50% of patients present low adherence to the prescribed treatment [59-60]. The main aim of studies is the affect of the non-compliance of patients, who follows a specific drug medication for their diseases.

3.1 The multifactorial nature of adherence

The multifactorial nature of adherence in chronic disease patients, could explain a variety of reasons that patients fail to adhere to their maintenance medication [61]. The main factors that affect patient compliance include:

- **The disease extent and duration:** In most of the cases, the interest of patients for their disease decreasing during a long time medication, due to the constant situation of the disease.
- **The cost of medication:** One of the main reasons, which can affect the compliance of the patients, is the cost medication. If the patient can ‘t afford the cost of drug or health providers cannot provide the medication, there is high possibility to have an effect to the patient adherence.
- **The fear of adverse effects:** Generally**,** peoples belief that drug medication can be harmful for their health. It is a common sense that drugs can cause several adverse effects, which actually damage human organs.

- **Individual psychosocial variables:** The disease situation and quality of life of patients can cause several mental disorders, which can also affect the compliance of the patient to the prescribed medication.
- **Even the patient-physician relationship.** Physicians have to keep the patient informed and to provide Knowledge about the disease. Patients need to trust the physicians

Especially in chronic diseases, the consequences of non-compliance to the prescribed medication could affect the lack of disease control, as well as the QoL of patients. Most of the remission cases present clinical recurrence after several months, due to non-adherence of patient to the maintenance medication [62].

3.2 Strategies for adherence improvement

Several strategies have been proposed to improve the patient adherence. In practice, common approaches attempt to improve the dose regimen using reminders, specific pill-boxes or simplifying the dosing. Most of research studies for adherence improvement focus on the education of the patient for understanding:

- **The disease process:** It is important for patients to know exactly all the stages of the disease, in order to recognize the symptoms and signs. Symptoms and signs of the disease can feed patients with interest about the disease and the significance of medication.
- **The treatment plan:** The treatment plan is generated around the problems that the patient brings into treatment. According to the diagnostic summary, treatment plan the can provide the staff what the patient will do during the treatment. It is important to take into account all of the physical, emotional, and behavioral problems relevant to the patient's care, as well as the patient's strengths and weaknesses. All this issues have to be drawn with the patient contribution, in order to choose the optimal personalized treatment plan. This fact could help the patient to adhere the prescribed medication.
- **The efficacy of medicines:** Apart from side effects of medicines, patients have to focuses on their beneficial role. Sometimes the fear of adverse effects, as well as the fear of the disease itself, makes it difficult for the patients to emphasize how well medicines effect in practice. Physicians can discuss with patients several patients' examples to underline the efficacy of the medicine for the treatment of their disease.

Better understating and knowledge about the above factors could improve the compliance. For example, sessions between physicians and patient are proposed to address therapeutic goals, such as increasing the chance of disease regression or reducing the risk for the development of colorectal cancer. Even demonstration tools, which illustrate photographic documentation about the disease, could be also beneficial [63]. In this direction Elkjaer et al. [64-66] developed a web-based educational tool, where patients improve their ability to self-initiate treatment and increase the level of disease specific knowledge. Finally, Nigro et al. [67] shows correlation between non-adherence and psychiatric disorders, proposing preventive psychiatric interventions.

Apart from the important role of the compliance to the patient health, increasing the adherence could be beneficial for the costs of health providers. OLuga *et al.* [68] presents the most recent developments in the investigation of compliance with emphasizing to the impact of medication adherence or non-adherence on healthcare costs in the US health system. The study denotes the magnitude of the nonadherence problem and related costs, with an extensive discussion of the mechanisms underlying the impact of nonadherence on costs. Employing the Medication Possession Ratio (MPR) and the Proportion of Days Covered (PDC) metrics the authors estimate the impact of non-adherence on health care costs in several chronic diseases, such as diabetes and asthma. MPR is calculated as the total number of days supplied, divided by the number of days between the first and last refills; while PDC is calculated as the total number of days supplied during an interval, divided by the total number of days during that interval.

3.3 Methods for Adherence measurement

The quantification of patient adherence can be performed either directly or indirectly. There are two direct methods to measure the compliance of the patients to their medication [69]:

i) **Bioassays and Biomarkers:** Direct proof that medication has been taken is attempted via lab test of biologic fluid for evidence of drug. However there are several disadvantages of this approach. It cannot be employed for all the cases, due to the fact that there are not markers for all the drugs. Furthermore, this approach is potentially expensive.

ii) **Directly observed each dose:** This approach aims the direct observation of medication taking. This approach is impractical for outpatient setting, and especially for long-term treatment.

Apart from direct methods, four different indirect methods have been proposed and investigation in the literature:

i) **Pharmacy refill rates:** Health providers can capture the frequency and the amount of medications via their databases. They can easily observe the timelines that patient refill their medications. This fact directly reflects the decision of patient to continue the medication.

ii) **Pill counts:** Remaining medication counted and compare with amount that should remain at that time. This is a simple and inexpensive method, however requires the reliance of the patient, and may over estimate adherence due to pill dumping or sharing.

iii) **Electronic adherence monitoring:** For this method electronic devices are required, which is attached to the medication container. It provides information on daily intake and analysis of long-term patterns of medication. This method requires extra costs for the device, as well as there are several issues about its reliability.

iv) **Self report:** This method can be employed either via completion of questionnaire and diaries or via interviews between the patient and the physician. This is also a simple and inexpensive method which can provide the physician with several important data about the patient's situation.

Figure 3.1 present a summary of methods for the quantification of adherence.

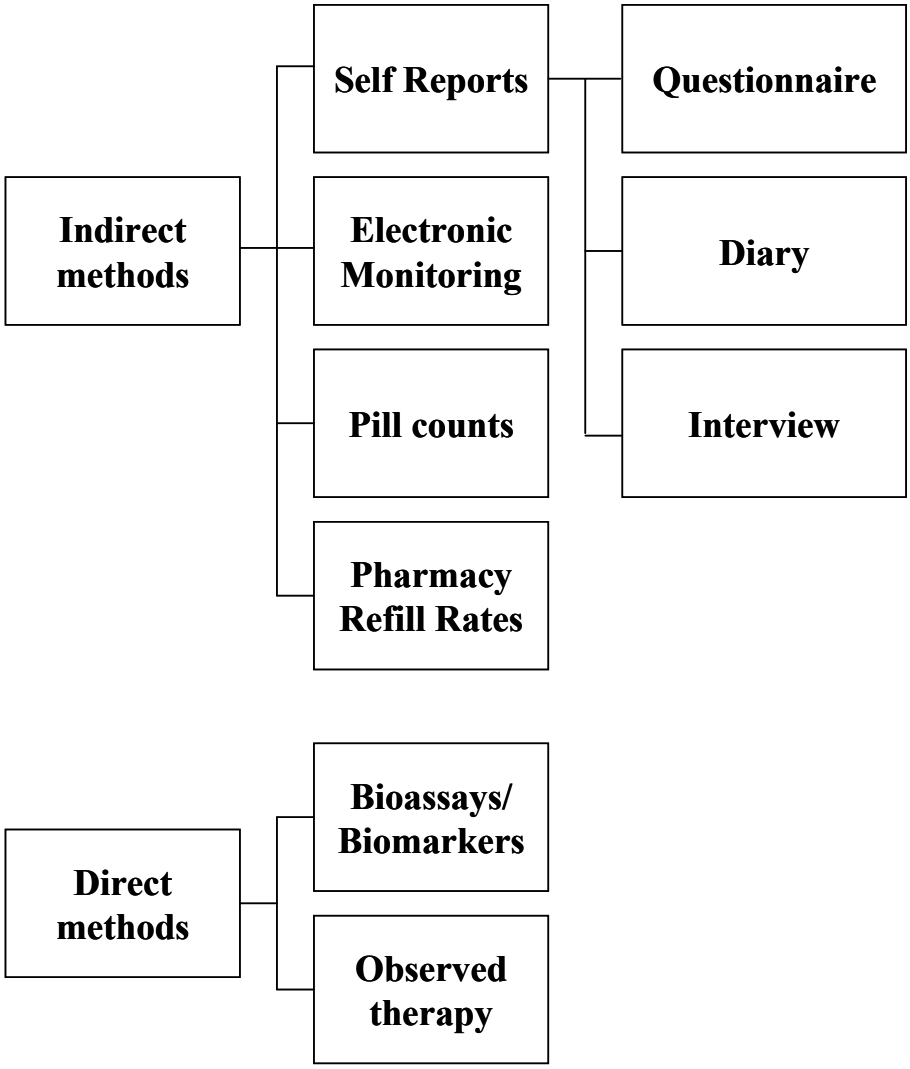

Figure 3.1: Categorization of the methods for adherence quantification

There are two significant reasons to employed simple and inexpensive methods to measure the patient compliance:

a) The need of measure the compliance in outpatient long-term medication.
b) The frequent contact between patients and health care providers for examination purposes increases the costs and discomfort the patients.

Thus, a number of self-administered questionnaires have been proposed for measuring the patient adherence, and statistical analysis is employed for the validation them [70].

3.4 Self-administered questionnaires for adherence measurement

Employing self-administered questionnaire for the clarification of several factor about disease process, beliefs and preferences of the patients, or QoL, is a common practice for the physicians. Extracted statistical findings highlight a number of physical aspects for the treatment progress regarding personal beliefs, concerns or lifestyle. The quantification of the compliance of patients to their prescribed medication also employs several self-administered questionnaires, as it is presented in the literature [70]. Each questionnaire attempts to measure patient adherence from different point of view. Most frequently used, focuses on the specific disease regarding its symptom, medication, psychological factor, QoL of the patient, and finally the knowledge of the patient about the disease. Below, a summary of the most well-known questionnaires for compliance quantification is presented. There are several general health scales and questionnaire to measure the adherence of patient regardless of the disease, as well as there are several specific questionnaire for specific diseases. We emphasize to general health scales, as well as to specific questionnaires presented in the literature for Inflammatory Bowel Diseases (IBDs).

A general health scale, which could be employed for the quantification of patient adherence is the by Medication Adherence Report Scale (MARS) [71]. MARS scale is a combination of two other scales, the Drug Attitude Inventory (DAI) [72] and the Medication Adherence Questionnaire (MAQ) [73], consisting of 10 selected items (Table I). Although, MARS scale has been employed mainly in the Psychiatric field, the findings of its analysis could be extremely useful to quantify patient compliance.

Table I: Medication Adherence Rating Scale (MARS)

MAQ 1	• Do you ever forget to take your medicine?
MAQ 2	• Are you careless at times about taking your medicine?
MAQ 3	• When you feel better, do you sometimes stop taking your medicine?
MAQ 4	• Sometimes if you feel worse when you take your medicine, do you stop taking it?
DAI 6	• I take my medication when I am sick
DAI 8	• It is unnatural for my mind and body to be controlled by medication
DAI 9	• My thoughts are clearer on medication
DAI 10	• By staying on medication I can prevent getting sick
DAI 2	• I feel weird, like a ‘zombie’, on medication
DAI 5	• Medication makes me feel tired and sluggish

MAQ: Medication Adherence Questionnaire; DAI: Drug Attitude Inventory; •

Another general scale is the Trust in Physician [74] scale which focuses on the relation between patient and physician. A five point response scale is employed in 11 items as it is shown in Table II.

Table II: Trust in Physician Scale

Item	*Score*
• I doubt that my doctor really cares about me as a person. †	1-5
• My doctor is usually considerate of my needs and puts them first.	1-5
• I trust my doctor so much that I always try to follow his/her advice.	1-5
• If my doctor tells me something is so, then it must be true.	1-5
• I sometimes distrust my doctor's opinion and would like a second one.†	1-5
• I trust my doctor's judgement about my medical care.	1-5
• I feel my doctor does not do everything he/she should for my medical care.†	1-5
• I trust my doctor to put my medical needs above all other considerations when treating my medical problems.	1-5
• My doctor is a real expert in taking care of medical problems like mine.	1-5
• I trust my doctor to tell me if a mistake was made about my treatment.	1-5
• I sometimes worry that my doctor may not keep the information we discuss totally private	1-5
Five-point response scale: 1 totally disagree; 2 disagree; 3 neutral; 4 agree; 5 totally agree •	
† Reverse-scored items	

Hospital Anxiety and Depression Scale (HADS) [75] consists of two sets of items, which are related to the anxiety and the depression of patient (Table III). Indirectly, the HADS scales could be employed to extract the compliant of patient to their medication.

Table III: Hospital Anxiety and Depression Scale (HADS)

Relate to anxiety	*Relate to depression*
• I feel tense or wound up (0-3)	• I still enjoy the things I used to enjoy (0-3)
• I get a sort of frightened feeling as if something bad is about to happen (0-3)	• I can laugh and see the funny side of things (0-3)
• Worrying thoughts go through my mind (0-3)	• I feel cheerful (0-3)
• I can sit at ease and feel relaxed (0-3)	• I feel as if I am slowed down (0-3)
• I get a sort of frightened feeling like butterflies in the stomach (0-3)	• I have lost interest in my appearance (0-3)
• I feel restless and have to be on the move (0-3)	• I look forward with enjoyment to things (0-3)
• I get sudden feelings of panic (0-3)	• I can enjoy a good book or radio or TV programme (0-3)

A general questionnaire is also the Beliefs about Medicine Questionnaire (BMQ) [76], which is extensively presented in the next section. BMQ can be employed in a variety of diseases, especially in choric diseases, to measure the adherence of patients. The main innovation of BMQ is the direct quantification of the beliefs of patients about the drugs and theirs use. This factor could be the most significant, that affect the compliance or not of the patients to their prescribed medication. The questions of BMQ is presented in Table IV.

Table IV: Belief about Medicine Questionnaire (BMQ)	
• **BMQ-Specific**	• **The BMQ-General**
• Without my medicines I would be very ill (1-5) • My life would be impossible without my medicines (1-5) • My health, at present, depends on my medicines (1-5) • My health in the future will depend on my medicines. (1-5) • My medicines protect me from becoming worse (1-5) • I sometimes worry about becoming too dependent on my medicines(1-5) • My medicines disrupt my life (1-5) • My medicines are a mystery to me (1-5) • Having to take medicines worries me (1-5) • I sometimes worry about long-term effects of my medicines (1-5) • These medicines give me unpleasant side effects (1-5)	• Medicines do more harm than good (1-5) • All medicines are poisons (1-5) • Most medicines are addictive (1-5) • People who take medicines should stop their treatment for a while every now and again (1-5) • Natural remedies are safer than medicines (1-5) • Doctors use too many medicines (1-5) • If doctors had more time with patients they would prescribe fewer medicines(1-5) • Doctors place too much trust on medicines(1-5)

The Work Productivity and Activity Impairment Questionnaire (WPAI) was created as a patient-reported quantitative assessment of the amount of absenteeism, presenteeism and daily activity impairment attributable to general health (WPAI:GH). Due to the fact that sometimes, it is more effective to employ specific questionnaires, regarding the disease WPAI has been modified for specific health problem (WPAI:SHP). The WPAI:GH and the WPAI:SHP were created simultaneously and use the same template, but in the GH version the subject is instructed to respond with reference to general health status while in the SHP version, the subject responds with reference to a specified health problem, disease or condition. The specific version of WPAI for Crohn's Disease is initially validated by Reilly et al. [77] in a total of 662 patients. The 6 items of the questionnaire is presented in Table V.

Table V: Work Productivity and Activity Impairment Questionnaire: Crohn's Disease (WPAI-CD)	
Item	***Question***
• Are you currently in paid employment? If NO, choose "NO" and skip to question 6.	_____NO _____YES
• During the past seven days, how many hours did you miss from work because of problems ASSOCIATED WITH YOUR CROHN'S DISEASE? Include hours you missed on sick days, times you went in late, left early, etc., because of your Crohn's disease. Do not include time you missed to participate in this study.	_____HOURS
• During the past seven days, how many hours did you miss from work because of any other reason, such as annual leave, holidays, time off to participate in this study?	_____HOURS
• During the past seven days, how many hours did you actually work? (If "0", skip to question 6)	_____HOURS
• During the past seven days, how much did your Crohn's disease affect your productivity WHILE YOU WERE WORKING? (Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If Crohn's disease affected your work only a little, choose a low number. Choose a high number if Crohn's disease affected your work a great deal.)	1-10 1-10

• During the past seven days, how much did your Crohn's disease affect your ability to perform your normal daily activities, excluding your job? (By normal activities, we mean the usual activities you perform, such as working around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could perform and times you accomplished less than you would like. If Crohn's disease affected your activities only a little, choose a low number. Choose a high number if Crohn's disease affected your activities a great deal.)

Another specific questionnaire for the measurement of Knowledge level of IBDs patients presented by Eaden *et al.* [70] called the Crohn Colitis Knowledge Score (CCKNOW). The aim of this study was to develop a valid and reliable self-administered questionnaire to assess patient knowledge of IBD and its treatment. 30 multiple-choice items focuses on specific details of symptoms and signs. The article reports the findings when the questionnaire was posted to patients with IBD from the Leicestershire IBD patient database. Table VI presents all the items of the CCKNOW questionnaire.

The Short Inflammatory Bowel Disease Questionnaire [78] (Short - IBDQ) is a health-related quality of life (HRQoL) tool measuring physical, social, and emotional status (score 10–70, poor to good HRQoL). The SIBDQ has been predominantly used in trials for Crohn's disease, and further validation of the SIBDQ is desirable in ulcerative colitis (UC) patients. Short – IBDQ consists of 10 multiple choice questions focuses on the difficulties of the patient which yield from the disease. Table VII presents the questions of the short IBDQ questionnaire.

Table VI: Crohn Colitis Knowledge Score

1. The intestines play an important role in the body but they only work during meal times:
   a) True b) False c) Don't know
2. People with inflammatory bowel disease are never allowed to eat dairy products:
   a) True b) False c) Don't know
3. Elemental feeds are sometimes used to treat Crohn's disease and ulcerative colitis. They:
   a) Always contain a lot of fibre b) Are very easy to digest
   c) Come in the form of tablets d) Don't know
4. Proctitis:
   a) Is a form of colitis that affects the rectum or back passage only
   b) Is a form of colitis that affects the whole of the large bowel
   c) Don't know
5. When a patient with inflammatory bowel disease passes blood in their stool it means:
   a) They definitely have bowel cancer b) They are having a flare
   c) Don't know
6. Patients with inflammatory bowel disease are probably cured if they have been symptom free for 3 years:
   a) True b) False c) Don't know
7. Inflammatory bowel disease runs in families:
   a) True b) False c) Don't know
8. If patients with inflammatory bowel disease are not careful with their personal hygiene they can pass on their disease to friends and members of the family:
   a) True b) False c) Don't know
9. Patients with inflammatory bowel disease can get inflammation in other parts of the body as well as the bowel:
   a) True b) False c) Don't know
10. A fistula:
   a) Is an abnormal track between 2 pieces of bowel or between the bowel and skin
   b) Is a narrowing of the bowel which may obstruct the passage of the contents
   c) Don't know
11. The terminal ileum:
   a) Is a section of the bowel just before the anus
   b) Is a section of the bowel just before the large intestine
   c) Don't know
12. During a flare up of inflammatory bowel disease:
   a) The platelet count in the blood rises
   b) The albumin level in the blood rises
   c) The white cell count in the blood falls
   d) Don't know
13. Steroids (such as prednisolone/udesonide/hydrocortisone):
   a) Can only be taken by mouth
   b) Can be given in the form of an enema into the back passage
   c) Cannot be given directly into the vein
   d) Don't know
14. Steroids usually cause side effects:
   a) only after they have been taken for a long time and in high doses
   b) Immediately and even after small doses
   c) Which are not permanent and all disappear after treatment is stopped
   d) Don't know
15. Immunosuppressive drugs are given to inflammatory bowel disease patients to:
   a) Prevent infection in the bowel by bacteria
   b) Reduce inflammation in the bowel c) Don't know
16. Sulphasalazine:
   a) Controls the level of sulphur in the bloodstream
   b) Can be used to reduce the frequency of flare ups
   c) Cannot be used to prevent flare ups
   d) Don't know
17. An example of an immunosuppresive drug used in inflammatory bowel disease is:
   a) Sulphasalazine b) Mesalazine c) Azathioprine d) Don't know
18. If a woman has Crohn's disease:
   a) She may find it more difficult to become pregnant
   b) She should not have children
   c) Her pregnancy will have complications
   d) She should stop all medication
   e) Don't know
19. Patients who smoke are more likely to have:
   a) Ulcerative colitis b) Crohn's disease c) Don't know
20. Which one of the following statements is false?
   a) Ulcerative colitis can occur at any age
   b) Stress and emotional events are linked with the onset of ulcerative colitis
   c) Ulcerative colitis is least common in Europeans and North Americans
   d) Patients with ulcerative colitis have an increased risk of developing bowel cancer
   e) Don't know
21. The examination of the large bowel with a flexible camera is called a:
   a) Barium enema b) Biopsy c) Colonoscopy d) Don't know
22. Male patients who take sulphasalazine:
   a) Have reduced fertility levels that are reversible
   b) Have reduced fertility levels that are not reversible
   c) The drug does not have any effect on male fertility
   d) Don't know
23. The length of the small bowel is approximately:
   a) 2 feet
   b) 12 feet
   c) 20 feet
   d) Don't know
24. The function of the large bowel is to absorb:
   a) Vitamins b) Minerals c) Water d) Don't know
25. Another name for an ileorectal anastomosis operation with formation of a reservoir is:
   a) Purse b) Pouch c) Stoma d) Don't know
26. If a part of the bowel called the terminal ileum is removed during surgery the patient will have impaired absorption of:
   a) Vitamin C b) Vitamin A c) Vitamin B12 d) Don't know
27. Patients with IBD need to be screened for cancer of the colon. Which one of the following statements about screening is false? Screening should be offered to all patients with ulcerative colitis:
   a) Which affects only the rectum
   b) Which has lasted for 8–10 years
   c) Which started before the age of 50
   d) Don't know
28. There are millions of tiny "hairs" in the small bowel to increase the absorptive surface. They are called:
   a) Villi b) Enzymes c) Bile salts d) Crypts e) Don't know
29. Which one of the following is not a common symptom of inflammatory bowel disease?
   a) Abdominal pain b) Change in bowel habit
   c) Headache d) Fever e) Don't know
30. If a child has inflammatory bowel disease; he/she probably will not:
   a) live beyond the age of 45 b) be as tall as his or her friends
   c) be as intelligent as his or her friends d) Don't know

Table VII: Short Inflammatory Bowel Disease Questionnaire (short-IBDQ)

1. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 wk? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 wk by picking one option from (Systemic):
   a) All of the time
   b) Most of the time
   c) A good bit of the time
   d) Some of the time
   e)A little of the time
   f) Hardly any of the time
   g) None of the time
2. How often during the last 2 wk have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from (Social):
   a) All of the time
   b) Most of the time
   c) A good bit of the time
   d) Some of the time
   e)A little of the time
   f) Hardly any of the time
   g) None of the time
3. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done over the last 2 wk? Please choose an option from (Social):
   a) A great deal of difficulty, activities made impossible
   b) A lot of difficulty
   c) A fair bit of difficulty
   d) Some difficulty
   e) A little difficulty
   f) Hardly any difficulty
   g) No difficulty; the bowel problems did not limit sports or leisure activities
4. How often during the last 2 wk have you been troubled by pain in the abdomen? Please choose an option from (Bowel):
   a) All of the time
   b)Most of the time
   c) A good bit of the time
   d) Some of the time -A little of the time
   e) Hardly any of the time
   f) None of the time
5. How often during the last 2 wk have you felt depressed or discouraged? Please choose an option from (Emotional):
   a) All of the time
   b) Most of the time
   c) A good bit of the time
   d) Some of the time
   e)A little of the time
   f) Hardly any of the time
   g) None of the time
6. Overall, in the last 2 wk, how much of a problem have you had passing large amounts of gas? Please choose an option from (Bowel):
   a) A major problem
   b) big problem
   c) A significant problem
   d) Some trouble
   f) A little trouble
   g) Hardly any trouble
   h) No trouble
7. Overall, in the last 2 wk, how much of a problem have you had maintaining or getting to the weight you would like to be? Please choose an option from (Systemic):
   a) A major problem
   b) big problem
   c) A significant problem
   d) Some trouble
   f) A little trouble
   g) Hardly any trouble
   h) No trouble
8. How often during the last 2 wk have you felt relaxed and free of tension? Please choose an option from (Emotional):
   a) None of the time
   b) A little of the time
   c) Some of the time
   a) A good bit of the time
   b) Most of the time
   c) Almost all of the time
   d) All of the time
9. How much of the time during the last 2 wk have you been troubled by a feeling of having to go to the toilet even though your bowels were empty? Please choose an option from (Bowel):
   a) All of the time
   b) Most of the time
   c) A good bit of the time
   d) Some of the time
   e)A little of the time
   f) Hardly any of the time
   g) None of the time
10. How much of the time during the last 2 wk have you felt angry as a result of your bowel problem? Please choose an option from (Emotional):
   a) All of the time
   b) Most of the time
   c) A good bit of the time
   d) Some of the time
   e)A little of the time
   f) Hardly any of the time
   g) None of the time

Table VIII: Simple Clinical Colitis Activity Index (SCCAI)

Scoring system for the Powell-Tuck Index		***Scoring system for the complex integrated disease activity index (Seo et al7)***			***Clinical scoring system for the Simple Clinical Colitis Activity Index***	
Symptoms and Signs	Score	Variable	Score	Weighting	Symptoms	Score
Symptoms		Bloody stool		x60	Bowel frequency (day)	
Bowel frequency:		Little or none	0		1–3	0
3–6	1	Present	1		4–6	1
>6	2	Bowel movements/day		x13	7–9	2
Stool consistency		<4 1	1		>9	3
Formed	0	5–7 2	2		Bowel frequency (night)	
Semi-formed	1	>8 3	3		1–3	1
Liquid	2	Erythrocyte sedimentation rate (mm/h)		x0.5	4–6	2
Abdominal pain		Haemoglobin (g/dl) ´ −4		x-4	Urgency of defecation	
Before/after bowel motions	1	Albumin (g/dl) ´ −15		x-15	Hurry	1
Prolonged	2	Constant 200		200	Immediately	2
Anorexia	1				Incontinence	3
Nausea/vomiting	1				Blood in stool	
General health					Trace	1
Normal	0				Occasionally frank	2
Slightly impaired	1				Usually frank	3
Activities restricted	2				General well being	
Unable to work	3				Very well	0
Extracolonic manifestations					Slightly below par	1
One/mild	1				Poor	2
More than one/severe	2				Very poor	3
Signs					Terrible	4
Abdominal tenderness					Extracolonic features	1 per manifestation
Mild	1					
Marked	2					
Rebound	3					
Body temperature (°C)						
<37.1	0					
37.1–38	1					
>38	2					
Blood in stool						
Trace	1					
More than trace	2					
Sigmoidoscopy						
Non-haemorrhagic	0					
Friable	1					
Spontaneous bleed	2					

Walmsley *et al.* [79] attempted to develop a simplified clinical colitis activity index (SCCAI) to aid in the initial evaluation of exacerbations of colitis. The aim of this study was to devise an accurate, easily calculated index of disease activity using a small number of clinical criteria. The final index could then act as an initial guide to appropriate changes in treatment and be an aid in identifying those patients requiring more detailed assessment. The information for development of the simple index was initially evaluated in 63 assessments of disease activity in patients with ulcerative colitis. The clinical scoring is presented in Table VIII according the symptoms of the patient.

Chapter 4

The Belief about Medicine Questionnaire (BMQ); Pharmacotherapy

BMQ is the self-administered questionnaire, which directly assess the beliefs of the patients about the use of medicine and the efficacy of the prescribed medication. BMQ can be employed in a variety of diseases, especially in choric diseases, where long time medications are needed.

4.1 Beliefs about Medicine Questionnaire description

The aim of BMQ [78] is the assessment of the fairly broad range of beliefs, which people hold about their specific and general medication. Thus, the questionnaire is divided into two scale or sections, where each of them is also divided in two subscales. First scale concerns to the belief of patients about their prescribed medication, while in the second one patients are inquired for their opinion generally about the medicines and their use. More specifically the two sections of BMQ are:

i) The BMQ-Specific, where the patients assess their opinion about their specific medication. It consists of 11 items, which are further categorized as Specific-Necessity or Specific-Concerns. Specific-necessity items include questions such as “My health, at presents, depends on my medicine” or “My life would be impossible without my medicine”. There are 6 items in the Specific-Necessity subscale, which focuses on the beliefs of the patient about the efficacy of his medication. Specific-Concerns items assess thought and fears of patient to potential adverse outcomes or side effects of lifelong medication. For example, “my medicines are mystery to me” or “I sometimes worry about long term effects of my medicine” are phrases that patient have to declare about their agreement or not.

ii) The BMQ-General, where assess their general beliefs about efficacy, dangers and use of medicines. 8 items in this scale are further divided into General-Harm or Specific-Concerns. 4 of them are included in General-Harm subscale such as “Medicine do more harm than good” or

"Medicines are poisons", while the other 4 such as "Doctor prescribe too many medicine" or "if doctors spent more time with patient, they would prescribe less" comprises the General-Overuse subscale. The degree of agreement for each item is denoted by the patients, using a 5-point Linkert scale, from "1" that corresponds to strong disagreement to "5" which means strongly agreement.

4.2 BMQ in chronic Conditions

BMQ questionnaire is a self-administer questionnaire, which focus directly to the beliefs and concerns of the patients about the use and efficacy of medicines. It can be used to a wide range of diseases, where prescribed medication is required. Many studies have been already presented in the literature for the adherence measurement of chronic conditions. Most of these studies employ mixed datasets, in terms of the diseases. Even the firsts studies by Horne *et al.* [78, 80] uses data from a Chronic Illness sample, comprising asthmatic, diabetic and psychiatric patients from hospital clinics and cardiac, general medical and renal (haemodialysis recipients) in-patients. The six illness groups from which patients were sampled were chosen to reflect a variety of disease and treatment characteristics. The same sample or other mixed dataset with chronic diseases have been employed from several research groups [81-86]. The most unconditional sample presents by Marbdy et al. [87], where the participant are selected using only thee inclusion criteria: a) to understand Swedish language, b) to be over 18 years old, and c) to take a queue number to a specific prescription counter for Swedish pharmacies. As a result, this sample holds none limitation about the disease of the patient.

Apart from the studies, which analyzed mixed datasets, a number of studies performed statistical analysis for specific diseases using homogenous and specific samples. The adherence to the medication for maintenance asthma control has been investigated from different research groups [88-89]. Menckeberg et al. [89] investigate whether beliefs about inhale corticosteroid, as measured by the BMQ, relate to adherence objectively measured by prescription refill records. They finally concluded that patients' beliefs about ICS correlate not only with adherence by self-report but also with a more objective measure of medication adherence calculated by pharmacy dispensing records.

Both groups Horne et al. [90] and Gaucher et al. [91] analyze the BMQ records for the behavior of HIV patients in highly active antiretroviral therapy (HAART). It is common sense that adherence to medical regimens is extremely important for HIV patients. The results of the above studies revealed that adherence and patients beliefs about treatment, satisfaction with treatment, confidence in the

physician and duration of treatment and illness are significantly correlated. It is also revealed the necessity and the concerns factors of BMQ could be useful for understanding patient perspectives of HAART and predicting uptake and adherence.

Diabetes patient samples are analyzed by Aikens & Piette [92] to reveal patient beliefs about antihyperglycemic and antihypertensive treatment and medication underuse. The authors also examined diabetes in another point of view, such as the patients beliefs about their medication necessity and potential harmfulness in an economically distressed community. According to their findings diabetic patients with low health literacy are concerned about medication harmfulness, which is in turn associated with medication underuse and higher blood pressure. To enhance adherence and outcomes, interventions should address patients' underlying concerns about potential adverse treatment effects and focus on both cultural factors and health literacy. Another study for diabetes chronic condition presented by Fall et al. [93], where the French translation of BMQ is validated.

The role of patient adherence in therapies for autoimmune diseases is extremely significant, due to the fact that insufficient medication could lead to irreversible disorders. Kumar et al. [94] and Treharne et al. [95] employed the BMQ to measure the adherence in patients with rheumatoid arthritis and systemic lupus erythematosus, while Neame & Hammond [96] investigate what factors are related to medication beliefs about rheumatoid arthritis, and whether these beliefs influence adherence. All these studies concluded that most people with rheumatoid arthritis have positive beliefs about the necessity of their medication. However, levels of concern are high and associate with helplessness and non-adherence. The Beliefs about Medicines Questionnaire may identify people at risk of poor adherence and provide a focus for patients to discuss their beliefs, providing opportunities to improve adherence.

Finally, some other chronic conditions have been investigated in the literature such as mental disorder, heamophilia and hypertension. Especially, in Psychiatric patient patient adherence plays significant role for the patient himself, as well as for his environment. Thus, several studies have been present in the literature, where the beliefs of patient about their medication have been analyzed [97-99]. The adherence for patient with Haemophilia [100] and hypertension [101] has also quantified by Llewellyn et al. and Ross et al. respectively.

The achievements of the Beliefs about Medicine Questionnaire have been approved due to the attempts for translations in several languages. Since the beliefs of peoples are strongly related to their culture, as well as the diverse variety of demographic, psychosocial, and economic factors, it was meaningful to investigate the behavior of the patients in different countries. The first translation presented by Beléndez et al. [81] in Spanish, where diabetic patients have been participated. Cuevas et al. [98] and Torderas et al. [88] revalidated the Spanish translation for Psychiatric disorders and Asthma treatment respectively. BMQ have been translated also in Swedish [87], French [93], Japanese [84], German [85], and Italian [86]. Finally, Komninos *et al.* [83] presented a translation and adaptation in Greek language, in order to validate the BMQ it in primary patients in Greece. Table IX shows a variety of stydies which employed translations of BMQ.

Table IX: Several works with translated of BMQ

Work	Disease	Language Translation
Beléndez et al. 2007 [81]	Diabetes, Chronic Diseases	Spanish
Cuevas et al. 2011 [98]	Psychiatric Outpatients	Spanish
Marbdy et al. 2007 [87]	Pharmacy clients	Swedish
Fall et al. 2014 [93]	Diabetes type2, HIV	French
Komninos et al. 2012 [83]	Chronic Diseases	Greek
Lihara et al. 2010 [84]	Chronic (Liver, GI, Nervous system)	Japanese
Mahler et al. 2012 [85]	Chronic Diseases	German
Tibaldi et al. 2009 [86]	Chronic (cardiac, asthma, diabetes, depression)	Italian
Tordera et al. 2008 [88]	Asthma	Spanish

4.3 BMQ in GastroIntestinal Diseases

The use of BMQ is extremely widespread especially in chronic disease, it could be validated more extensively in GastroIntestinal (GI) diseases. Only five works have been presented in the literature, where BMQ is employed to measure the patient compliance. Gastrointestinal diseases involve the whole gastrointestinal tract, so that a number of chronic disorders/diseases could be investigated

regarding the persistent of the patients to their medication and the consequences of non-adherence. Such diseases where BMQ has been employed by research groups are presented below:

Gastro-oesophageal reflux disease (GORD) causes some of the most frequently seen symptoms in both primary and secondary care; between 20% and 30% of a 'Western' adult population experience heartburn and/or reflux intermittently [102]. Treatment of GORD includes a range of options, both medical and surgical. The simplest is self-administered antacids with advice to alter lifestyle factors such as dietary modification, smoking cessation and weight reduction. The role of surgery has traditionally been confined to the treatment of those with severe symptoms not responding to medication in appropriate dosage and medically fit for surgery. Grant et al. [90] focus on the effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease. Relative clinical effectiveness was assessed by a randomised trial (with parallel non-randomised preference groups) comparing a laparoscopic surgery based policy with a continued medical management policy. The economic evaluation compared the cost-effectiveness of the two management policies in order to identify the most efficient provision of future care and describe the resource impact that various policies for fund application would have on the NHS. For the above purpose a combination of BMQ and Beliefs about Surgery Questionnaire (BSQ) has been employed in 810 patients. Amongst patients requiring long-term medication to control symptoms of GORD, surgical management significantly increases general and reflux specific health-related quality of life measures, at least up to 12 months after surgery.

Adherence of patient after liver transplantation is measured by O'Carroll et al. [103]. Liver transplant recipients have diverse histories, ranging from an impulsive paracetamol overdose, to long-term alcoholic cirrhosis, to the autoimmune disorder primary biliary cirrhosis. However, regardless of cause, lifelong adherence to immunosuppressant medication is essential for the survival of each recipient. Non-adherence rates within the transplant population have been reported as ranging from 20 to 50%. Four different questionnaires have been employed in this study, including the BMQ. The results indicated that low self-reported patient adherence was related to greater concerns regarding the potential adverse effects of medication, and a stronger belief that medicines in general are harmful.

Crohn 's Disease (CD) and Ulcerative Colitis are chronic Inflammatory Bowel Diseases that affect primary young adults worldwide. IBD patients necessitate lifelong treatment or maintenance medication and quality of healthcare to improve their QoL [104]. About 6 per 100,000 inhabitants

are affected with CD, while 10 per 100,000 are diagnosed with UC, each year. Totally, more than 2 million Europeans suffer from IBDs. Most of them are young people less than 30 years of age [105-106]. Furthermore, several researchers have explored the correlation between progress of severity or long duration of UC, and known risk factors for Colorectal Cancer development [107-109].

It is a common sense that more investigation about the role of the adherence of IBD patient is needed. IBDs affect in a great degree the QoL of patients, as well as patients are extremely exposed when they deny to follow their prescribed medication. van Dongen et al. [110] developed an online questionnaire with 24 items in order to measure the compliance of IBD patients in treatment with enema. The questionnaire focuses in sociodemographic and clinical characteristics, enema use, adherence, perceived advantages/disadvantages of enema use, ideal enema design, and patient views on medication, and on drugs and medical care in general. For validation purposes the Medication Adherence Report Scale and Beliefs about Medicines Questionnaire are also used. According to the results of the study, responders were aware of the importance of adherence with their enema, but mainly did not regard it as convenient or easy to administer, and reported discomfort with enema use.

Another work that BMQ is employed to measure adherence of patients in IBDs has been presented by Moshkovska et al. [111]. This study attempts to extract correlation of non-adherence to 5-ASA therapy in UC patients, between BMQ findings and urine analysis. More specifically, medication adherence was assessed using self-report data and urinary drug excretion measurements. The study uses a total of 169 responders that complete the self report adherence data, however only 151 of them provide also urine samples. The authors of this study conclude to their serious suspicions about the efficiency of self-report methods and report difficulties of accurately assessing medication compliance.

A study presented by Fu et al. 2012 [112] attempt to quantify the compliance of adolescents in their prescribed. In a total of 112 adolescents, two separated groups is generated. The first group (59 patients) consists of adolescents who attended transition clinics, while the rest of the patient did not. According to the conclusions of the study, significantly different attitudes and beliefs in medicine are noted between the two groups. Adolescents attended transition clinics are more ambivalent and less skeptical towards medicine. Furthermore, transition patients have a stronger belief that medicine is necessary, and likely highly necessary compared to controls, but are ambivalent towards it. The authors claim that the above observations might be due to knowledge that patients gain, during the transition clinics, regarding the risk and benefits of medication.

In 2009, Horne et al. [103] presented an extensive study to assess patients' attitudes to maintenance for IBD, which includes the beliefs about personal need for treatment maintenance and potential adverse effects. The aim of the study was to identify whether such beliefs are associated with adherence to treatment maintenance. For this reason 1871 participates in a cross-sectional survey completing the MARS and the BMQ questionnaires. The authors use the answers from MARS to investigate the relation between socialdemographics data and the adherence in treatment maintenance, as well as the BMQ answers to extract the attitudinal analysis. Concluding the findings, revealed that the way in which patients judge their personal need for maintenance relative to their concerns about maintenance, can be a significant barrier to adherence. Interventions to facilitate optimal adherence to maintenance for IBD should address such perceptual barriers.

TABLE X: Employing BMQ in GI

Work (year)	***Aim***	***Disease***	***Dataset (number of patients)***	***Conclusions***
Grant *et al.* [82] (2014)	effectiveness and cost-effectiveness of minimal access surgery in GORD	GORD	810	surgical management significantly increases general and reflux specific health-related quality of life
O'Carroll et al. [103] (2006)	Measurement of patients compliance after liver transplantation	Several liver disorders	308	Low self-reported patient adherence was related to greater concerns regarding the potential adverse effects
van Dongen *et al.* [110] (2013)	Investigation of adherence in treatment with enema	IBDs	112	Patients not regard enema as convenient or easy to administer, and reported discomfort with enema use
Moshkovska *et al.* [111] (2009)	Validation of BMQ using also urine analysis	IBDs	169	Report the difficulty of accurately assessing medication adherence

Fu *et al.* [112] (2012)	Adherence measurement in adolescents groups	IBDs	112	stronger belief that medicine is necessary in adolescents who attended transition clinics
Horne et al [113] (2009)	If beliefs are associated with adherence to treatment maintenance	IBDs	1871	concerns about maintenance can be a significant barrier to adherence

Table X presents a summary of the studies for compliance in GI diseases. As a result, the conclusions of the studies, which employ the BMQ questionnaire for GI diseases and more specifically, for IBDs seem to be confusing. This fact shows the necessity for better investigation in this research field.

4.4 BMQ experience in Greek IBD patients

Guidelines for our study in UC patients provides our previous experience in the field [114]. By using the Greek version of BMQ in IBD patients we presented our previous experience, analyzing the results in a dataset of 163 patients. More specifically, the study cohort consisted of 163 patients (85 males, 78 females) diagnosed with IBD (150 UC, 13 CD). IBD was active in 23 patients while in the majority (140 patients) IBD was in remission phase. Diagnosis of IBD was established using standard diagnostic criteria including patient medical history, symptoms, laboratory indices, radiology and endoscopy with biopsy. All patients had at least a 6-month IBD diagnosis and are followed by our center. Our center, which is based in the University Hospital of Ioannina, is a referral center in the whole area of northwestern Greece and currently follows more than 1300 IBD patients.

Inclusion criteria for participants were: being patients with well-established IBD and follow up exceeding six months and receiving long-term medication for one or more chronic diseases including IBD. Patients were excluded if they were having problems with cognitive decline (Mini-Mental State Examination, MMSE≤24), patients without ability to clearly understand Greek language and patients receiving no medication. Furthermore, patients providing incomplete information during completion of the questionnaire or any missing or conflicting data were also excluded from the study and subsequent analysis.

Initially, descriptive statistics, such as frequency analysis and mean/standard deviation of the demographic-associated variables, were calculated in order to assess the demographic characteristics of the dataset; all related results are presented in Tables XII and XIII. Then, the data were analyzed to assess the BMQ factor subscales importance/validity in the dataset. The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was used for confirmatory factor analysis. KMO was applied using the Bartlett's test of Sphericity, with Principal Component Analysis (PCA) and the correlation matrix for factors extraction, considering only factors with eigen value > 1.0, while the varimax rotation method with Kaiser normalization was used to simplify the factors. Confirmatory factor analysis results are presented in Tables XIV and XV. Also, BMQ factor subscales were analyzed using descriptive statistics in terms of mean value and standard deviation (Table XVI). Cronbach's alpha was calculated to assess the internal validity of the BMQ factor subscales (Table XVII).

Pearson's correlation coefficient between the BMQ factor subscales was also calculated using analysis of variance (ANOVA), and the results are presented in Table XVIII. Finally, univariate associations between the BMQ scales and the demographic characteristics were assessed using analysis of variance (ANOVA) for categorical variables (Table XIX) and Pearson's r correlation coefficient for continuous variables (Table XX). Statistical analysis was carried out using the Statistical Package for Social Sciences v.21 (SPSS Inc. Chicago, IL, USA).

In this study 163 patients were participated, with a slightly higher number of males (52.1%) over females (47.9%). The majority of the respondents were private servants (33.7%) and retired (25.8%), with secondary (41.1%) or university/polytechnic (28.2%) educational level. The participants were almost equally distributed among rural/semi-urban (50.9%) and urban (49.1%) areas. The 92% were UC patients while 8% were CD patients (Table XII). The average age of the participants was 52.2 years and (σ: 16.15), with 15.7 average years after diagnosis (Table XIII).

Table XII. Frequency analysis of the demographic characteristics

	N	***%***
Sex		
Men	**85**	**52.1**
Woman	**78**	**47.9**
Occupational Status		
Farmer/Breeder	**15**	**9.2**
Household	**20**	**12.3**
Private servant	**55**	**33.7**
Public servant	**14**	**8.6**
Retired	**42**	**25.8**
Unemployed	**17**	**10.4**
Educational Level		

Analphabetic	**1**	**0.6**
Elementary school	**23**	**14.1**
Secondary	**67**	**41.1**
Further Commercial/Technical	**26**	**16.0**
University/polytechnic	**46**	**28.2**
Residence		
Rural area	**32**	**19.6**
Semi-urban area	**51**	**31.3**
Urban area	**80**	**49.1**
Disease		
CD	**13**	**8.0**
UC	**150**	**92.0**
Clinical Stage		
Active	**23**	**14.1**
Inactive	**140**	**85.9**

Table XIII. Descriptive statistics of the demographic characteristics

	μ	σ
Age	**52.2**	**16.15**
Years after diagnosis	**15.7**	**8.59**
Number of chronic conditions	**1.2**	**0.41**
Number of drugs	**2.5**	**0.56**

The data adequacy for factor analysis was determined using the KMO measure and the Bartlett's test of Sphericity (Table XIV). The obtained results for KMO were >0.5 for all cases. Also, the Bartlett's test of Sphericity proved significant inter-item correlations in all cases. Taken together, KMO measure and the Bartlett's test of Sphericity indicate that the dataset is adequate for factor analysis [115].

Table XIV. Data adequacy for factor analysis

	KMO measure	***Bartlett's test of Sphericity***		
		X^2	*df*	
Specific Questions	**0.775**	**592**	**55**	*
Necessity	**0.679**	**264**	**10**	*
Concerns	**0.634**	**149**	**15**	*
General Questions	**0.786**	**175**	**28**	*
Harm	**0.637**	**53**	**10**	*
Overuse	**0.592**	**35**	**3**	*
Overall	**0.761**	**929**	**171**	*

** p-value<0.05*

Table XV. Confirmatory factor analysis of the BMQ factor subscales

	Factor loadings			
	Specific Questions		**General Questions**	
	Necessity	Concerns	Harm	Overuse
Without my medicines I would be very ill	**0.786**			
My life would be impossible without my medicines	**0.769**			
My health, at present, depends on my medicines	**0.811**			

My health in the future will depend on my medicines.	**0.832**			
My medicines protect me from becoming worse	**0.549**			
I sometimes worry about becoming too dependent on my medicines		**0.516**		
My medicines disrupt my life		**0.757**		
My medicines are a mystery to me		**0.730**		
Having to take medicines worries me		**0.557**		
I sometimes worry about long-term effects of my medicines		**0.639**		
These medicines give me unpleasant side effects		**0.687**		
Medicines do more harm than good			**0.719**	
All medicines are poisons			**0.443**	
Most medicines are addictive			**0.478**	
People who take medicines should stop their treatment for a while every now and again			**0.524**	
Natural remedies are safer than medicines			**0.750**	
Doctors use too many medicines				**0.718**
If doctors had more time with patients they would prescribe fewer medicines				**0.606**
Doctors place too much trust on medicines				**0.507**

Table XVI. Descriptive statistics of the BMQ factor subscales

		μ	σ
Specific Questions			
	Necessity	**11.72**	**3.41**
	Concerns	**16.45**	**3.53**
General Questions			

	Harm	**15.04**	**2.74**
	Overuse	**9.34**	**1.79**

Table XVII. Internal validity of the BMQ factor subscales

		Cronbach's α
Specific Questions		**0.795**
	Necessity	**0.732**
	Concerns	**0.623**
General Questions		**0.691**
	Harm	**0.528**
	Overuse	**0.515**
Overall		**0.757**

Table XVIII. Pearson's correlation coefficient between the BMQ factor subscales

	Pearson's r		
	Necessity	Concerns	Harm
Concerns	**0.620***		
Harm	**-0.069**	**0.258***	
Overuse	**0.020**	**0.139**	**0.570***

** p-value<0.05*

Tables XIX and XX demonstrate the univariate associations of the BMQ subscales with the demographic characteristics. Statistically significant associations was found for the Occupational

Status variable with the Necessity subscale (F=4.26, df=157, p<0.001) and the Concerns subscale (F=2.81, df=157, p<0.05). Also, age was found to significantly correlate with Necessity and Concerns subscales, while Necessity subscale was also found to correlate positively with the years after diagnosis variable. Number of chronic conditions did not correlated with any of the BMQ subscales, while number of drugs was found to correlate positively with the Harm subscale.

Table XIX. Univariate associations between demographic characteristics and the BMQ factor subscales

	N	*μ σ*	*μ σ*	*μ σ*	*μ σ*
		Specific Questions		**General Questions**	
		Necessity	Concerns	Harm	Overuse
Sex					
Men	**85**	**11.3 3.10**	**16.5 3.40**	**15.3 2.86**	**9.4 1.88**
Woman	**78**	**12.24 3.66**	**16.45 3.68**	**14.7 2.58**	**9.3 1.71**
Occupational Status		*	*		
Farmer/Breeder	**15**	**12.7 4.03**	**16.7 3.50**	**14.3 2.77**	**9.1 1.88**
Household	**20**	**12.8 2.84**	**16.5 2.84**	**15.2 1.96**	**9.4 1.54**
Private servant	**55**	**12.4 3.48**	**17.3 3.10**	**14.1 2.98**	**9.3 2.17**
Public servant	**14**	**12.2 2.94**	**17.6 2.76**	**15.5 3.11**	**9.9 1.10**
Retired	**42**	**9.8 2.48**	**14.9 3.70**	**15.4 2.86**	**9.1 1.75**
Unemployed	**17**	**11.8 4.01**	**16.0 4.68**	**14.6 2.18**	**9.6 1.23**
Educational Level					
Analphabetic	**1**	**13 -**	**15 -**	**12 -**	**10 -**
Elementary school	**23**	**11.4 3.65**	**16.5 3.34**	**15.0 1.87**	**9.3 1.43**
Further Commercial/Technical	**26**	**11.7 3.40**	**17.7 3.62**	**15.7 3.47**	**9.5 2.04**
Secondary	**67**	**12.0 3.48**	**16.0 3.58**	**15.1 2.68**	**9.3 1.79**

University/polytechnic	**46**	**11.4 3.28**	**16.3 3.49**	**14.7 2.74**	**9.3 1.88**
Residence					
Rural area	**32**	**11.6 3.57**	**16.2 3.14**	**14.7 2.73**	**9.3 1.79**
Semi-urban area	**51**	**11.7 3.51**	**16.0 3.72**	**15.27 2.66**	**9.4 1.70**
Urban area	**80**	**11.8 3.32**	**16.8 3.56**	**15.0 2.81**	**9.3 1.87**
Disease					
CD	**13**	**11.8 3.14**	**17.5 4.01**	**16.1 2.19**	**9.8 1.57**
UC	**150**	**11.7 3.44**	**16.4 3.49**	**14.9 2.77**	**9.3 1.81**
Clinical Stage					
Active	**23**	**11.9 3.74**	**15.5 4.12**	**14.4 3.01**	**9.3 2.18**
Inactive	**140**	**11.7 3.36**	**16.6 3.42**	**15.1 2.69**	**9.4 1.73**

** p-value<0.05*

Table XX. Univariate correlations between demographic characteristics and the BMQ factor subscales

	Pearson's r			
	Specific Questions		**General Questions**	
	Necessity	Concerns	Harm	Overuse
Age	**-0.294 ***	**-0.246 ***	**0.057**	**-0.027**
Years after diagnosis	**-0.211 ***	**-0.119**	**0.060**	**-0.018**
Number of chronic conditions	**0.091**	**0.034**	**0.026**	**0.031**
Number of drugs	**-0.072**	**0.132**	**0.212 ***	**0.048**

** p-value<0.05*

Regarding this study, the dataset was proven to be adequate for factor analysis based on the results obtained from the KMO measure and the Bartlett's test of Sphericity. Factor analysis indicated several significant correlations among the factors and the variables: Necessity subscale revealed the

most correlations, being with the age, the years after diagnosis and the occupational status variables. Concerns subscale also correlates positively with the age and the occupational status variables, while harm subscale was found to correlate positively with the number of drugs variable. Overuse subscale did not present any significant correlations with any of the recorded variables. Also, several positive correlations emerged among subscales.

Based on a mid-point split in Necessity and Concerns subscales (using the median value), four beliefs groups are defined [86, 89] (Fig. 4.1): Accepting (high Necessity, low Concerns), Ambivalent (high Necessity, high Concerns), Indifferent (low Necessity, low Concerns) or Skeptical (low Necessity, high Concerns). The analysis revealed low vales for both Accepting (16%) and Skeptical (11.7%) groups.

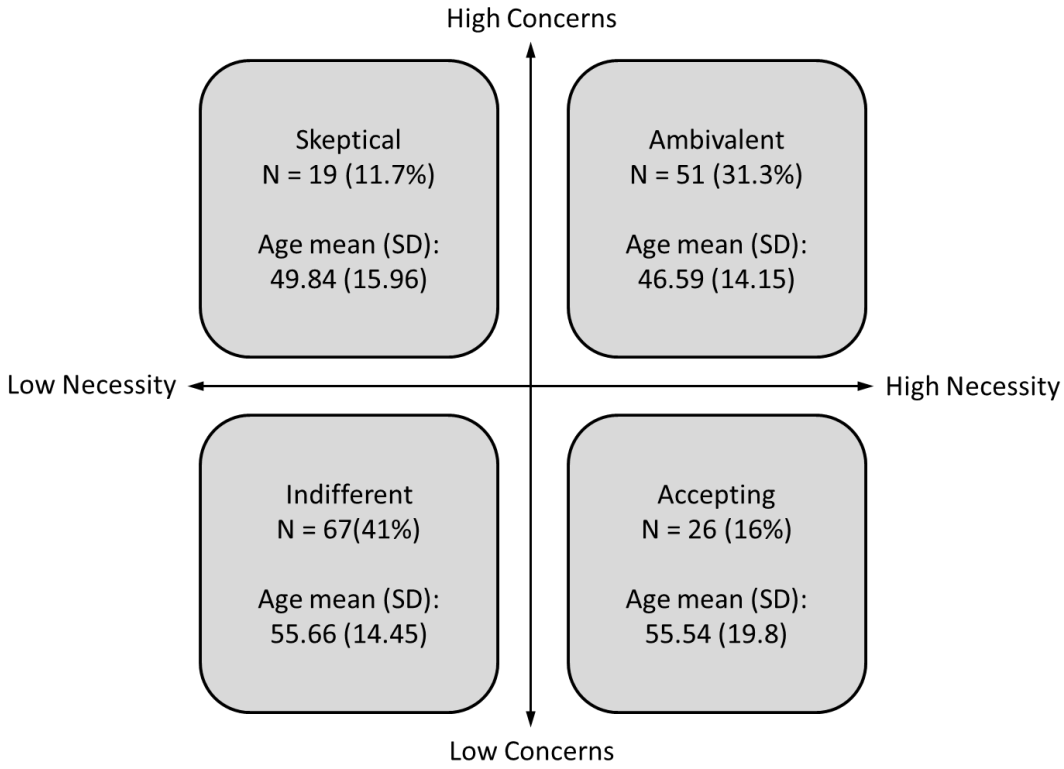

Figure 4.1. Patient distribution across beliefs groups.

4.5 Pharmacotherapy

An interesting investigation would be the relation between several sociodemographic and medical-related data of patients, with BMQ factors. Indeed, several studies presented in the literature have

examined how the age, the gender, the education level of the patient, or the number of prescribed medicine taken, affect the beliefs about their treatment and drug efficacy. Especially the age of patient and the number of prescribed medicines per day, could be two meaningful factors to transform the patient beliefs. For example, young people could control their prescribed treatment with lightness more than older ones. Furthermore, large number of medicine per day could be an extremely tiresome issue for all the patients. Table XI presents an extensive summary of the literature, including large number of studies, which employs BMQ.

Work	Disease	# of Patients
Aikens & Piette 2009 [92]	Diabetes	803
Beléndez et al. 2007 [71]	Diabetes, Chronic Diseases	412
Clatworthy et. al 2009 [97]	Bipolar Disorders	223
Cuevas et al. 2011 [98]	Psychiatric Outpatients	843
Fall et al. 2014 [93]	Diabetes Type II, HIV	376
Fu at al. [112]	IBD Adolescents	112
Gauchet et al. 2007 [91]	HIV HAART	127
Grant et al. 2008 [82]	Chronic (Asthma, Diabetes, Renal, Cardiac, GORD)	1274
Horne at al. 1999 [76]	Chronic (Asthma, Diabetes, Renal, Cardiac)	524
Horne et al. 1999 [80]	Chronic (Asthma, Diabetes, Renal, Cardiac)	324
Horne et al. 2007 [90]	HIV (HAART Treatment)	136
Horne et al. 2009 [113]	IBD	1871
Jonsdottir et al. 2008 [99]	Mental Disorders	280
Komninos et al. 2012 [83]	Chronic Diseases	150
Kumar et al. 2008 [94]	Rheumatoid Arthritis & Systemic Lupus Erythematosus	200
Lihara et al. 2010 [84]	Chronic (Liver, GI, Nervous system)	613
Llewellyn et al. 2002 [100]	Heamophilia	104
Mahler et al. 2012 [85]	Chronic Diseases	485
Marbdy et al. 2007 [87]	Pharmacy Clients	324
Menckeberg et al. 2008 [89]	Asthma	233
Moshkovska et al. 2012 [111]	IBD	169
Neame & Hammond 2005 [96]	Rheumatoid Arthritis	600

O'Carroll et al. 2006 [103]	After Liver Transplantation	435
Ross et al. 2004 [101]	Hypertension	514
Tibaldi et al. 2009 [86]	Chronic (Cardiac, Asthma, Diabetes, Depression)	427
Tordera et al. 2008 [88]	Asthma	126
Treharne et al. 2004 [95]	Rheumatoid Arthritis	85
Van Dongen et al. 2013 [110]	IBD - enema use	112

Chapter 5

BMQ in UC patients

In our study, we included UC patients. The patients were divided in two age categories, 20-45 years old and 46-65 years old. BMQ questionnaire is employed similarly to our previous work [114], where IBD patient have answered it.

5.1 Patient Cohort

The patient cohort used in this study consisted of 125 patients (64 males, 61 females) diagnosed with UC, while the age distribution was 56 patients in first category (20-45 years old) and 69 in the second category. IBD was in remission phase in the majority of patients (102 patients) and it was active in 23 patients. Again, diagnosis of IBD was established using standard diagnostic criteria including patient medical history, symptoms, laboratory indices, radiology and endoscopy with biopsy, while all patients had at least a 6-month IBD diagnosis and are followed by our center.

5.2 Study Protocol

This study was conducted using the Greek version of the BMQ that has been translated from English into Greek language by a professional bilingual translator and then translated back into English by a native English speaker in a previous study [83]. In that study, cognitive validation was conducted in a group of 7 individuals by 2 independent interviewers in order to test alternative wording and to check the understandability, interpretation and cultural relevance of the translation from English to Greek. According to authors all items of the BMQ, both in the special and the general part of the BMQ, performed extremely well, indicating that there was no need for any modifications of the Greek version of the questionnaire. Of note, both raters scored most questions of the BMQ with the codebook's highest possible score.

All UC patients completed the BMQ (Beliefs about Medicines Questionnaire) after signing the informed consent form. Afterwards, all confidential information that was related to UC and other medical history was extracted from each patient's medical record. In a special file and in addition to the BMQ data several demographic characteristics were included (age, gender, residence, occupational status, educational status) as well as additional medical information including number of concomitant chronic diseases and number of medicines that were taken on daily basis.

Every questionnaire was anonymous and before completing the questionnaire all patients provided written informed consent. Ethical approval for this study was provided by the Ethics Committee of the University Hospital of Ioannina, Greece.

5.3 Statistical analysis & Obtained Results

Data analysis followed similar statistical methodology. Descriptive statistics results are presented in Tables XXI, XXII and XXIII, while confirmatory factor analysis results (KMO and Bartlett's test of Sphericity) are presented in Tables XXIV and XXV. BMQ factor subscales descriptive statistics are presented in Table XXVI and the results of the internal validity assessment using Cronbach's alpha are presented in Table XXVII. Pearson's correlation coefficient between the BMQ factor subscales results are presented in Table XXVIII, while univariate associations between the BMQ scales and demographic characteristics are presented in Tables XXIX and XXX.

In this study cohort, 125 patients were participated, with a slightly higher number of males (51.2%) over females (48.8%). The distribution over the age categories was 44.8% for patients 20-45 years old, and 55.2% for patients 46-65 years old. The most of the participants were private servants (43.2%), while all other occupational status categories varied from 8% to 13.6% (10 to 13 patients). More than half (50.4%) had an urban residence, while rural and semi-rural residence were 20.8% and 28.8%, respectively.

Table XXI. Frequency analysis of the demographic characteristics		
	N *(# of Patients)*	***%***
Sex		
Men	**64**	**51.2**
Woman	**61**	**48.8**
Age		
Category 1: 20-45	**56**	**44.8**
Category 2: 46-65	**69**	**55.2**
Occupational Status*		
Farmer/Breeder	**13**	**10.4**
Household	**17**	**13.6**
Private servant	**54**	**43.2**
Public servant	**13**	**10.4**
Retired	**10**	**8.0**
Unemployed	**17**	**13.6**
Educational Level*		
Analphabetic	**0**	**0.0**
Elementary school	**15**	**12.0**
Secondary	**23**	**18.4**
Further Commercial/Technical	**52**	**41.6**
University/polytechnic	**34**	**27.2**
Residence		
Rural area	**26**	**20.8**

Semi-urban area	**36**	**28.8**
Urban area	**63**	**50.4**
Clinical Stage		
Active	**23**	**18.4**
Inactive	**102**	**81.6**

*0.8% missing values (1 patient).

Regarding drug intake, 53.6% (67 patients) are on a single-drug therapy, 40% (50 patients) take two drugs while 6.4% (8 patients) take three drugs. The drug's active substance distribution is presented in Table XXIII.

Table XXII. Drug intake

	N *(# of patients)*	***%***
Drug Active Substance		
adalimumab	**1**	**0.8**
azathioprine	**36**	**28.8**
infliximab	**31**	**24.8**
mesalazine	**81**	**64.8**
methotrexate	**5**	**4.0**
methylprednizolone	**42**	**33.6**

Table XXIII. Descriptive statistics of the demographic characteristics		
	μ *(mean value)*	***σ*** *(Standard Deviation)*
Years after diagnosis	**13.3**	**7.67**
Number of chronic conditions	**1.1**	**0.31**
Number of drugs (IBD)	**1.5**	**0.62**
Number of drugs (non IBD)	**1.0**	**0.00**
Number of drugs (Total)	**2.4**	**0.63**

Table XXIV. Confirmatory factor analysis of the BMQ factor subscales

	Factor loadings			
	Specific Questions		**General Questions**	
	Necessity	Concerns	Harm	Overuse
Without my medicines I would be very ill	**0.782**			
My life would be impossible without my medicines	**0.628**			
My health, at present, depends on my medicines	**0.790**			
My health in the future will depend on my medicines.	**0.802**			
My medicines protect me from becoming worse	**0.580**			
I sometimes worry about becoming too dependent on my medicines		**0.509**		
My medicines disrupt my life		**0.790**		
My medicines are a mystery to me		**0.741**		
Having to take medicines worries me		**0.618**		
I sometimes worry about long-term effects of my medicines		**0.685**		
These medicines give me unpleasant side effects		**0.670**		

Medicines do more harm than good	**0.742**	
All medicines are poisons	**0.383**	
Most medicines are addictive	**0.447**	
People who take medicines should stop their treatment for a while every now and again	**0.565**	
Natural remedies are safer than medicines	**0.622**	
Doctors use too many medicines		**0.728**
If doctors had more time with patients they would prescribe fewer medicines		**0.707**
Doctors place too much trust on medicines		**0.559**

The obtained results for KMO were >0.6 for all cases, while the Bartlett's test of Sphericity proved significant inter-item correlations in all cases. Taken together, KMO measure and the Bartlett's test of Sphericity indicate that the dataset is adequate for factor analysis.

Table XXV. Data adequacy for factor analysis

	KMO measure	***Bartlett's test of Sphericity***		
		X^2	*df*	
Specific Questions	**0.814**	**484**	**55**	*
Necessity	**0.697**	**206**	**10**	*
Concerns	**0.653**	**137**	**15**	*
General Questions	**0.817**	**179**	**28**	*
Harm	**0.699**	**63**	**10**	*
Overuse	**0.610**	**40**	**3**	*
Overall	**0.804**	**794**	**171**	*

** p-value<0.05*

Table XXVI. Descriptive statistics of the BMQ factor subscales

		μ *(mean value)*	***σ*** *(Standard deviation)*
Specific Questions			
	Necessity	**12.29**	**3.70**
	Concerns	**16.85**	**3.69**
General Questions			
	Harm	**14.74**	**2.94**
	Overuse	**9.18**	**1.91**

Table XXVII. Internal validity of the BMQ factor subscales

		Cronbach's α
Specific Questions		**0.813**
	Necessity	**0.761**
	Concerns	**0.650**
General Questions		**0.742**
	Harm	**0.606**
	Overuse	**0.591**
Overall		**0.784**

Table XXVIII. Pearson's correlation coefficient between the BMQ factor subscales

	Pearson's r Correlation		
	Necessity	Concerns	Harm
Concerns	**0.630***		
Harm	**-0.055**	**0.325***	
Overuse	**-0.057**	**0.169**	**0.598***

** p-value<0.05*

Tables XXIX and XXX demonstrate the univariate associations of the BMQ subscales with the demographic characteristics. Statistically significant associations was found for the Number of drugs for IBD variable with the Harm subscale (F=3.56, df=2, p<0.05). Also the total number of drugs variable correlated positively with Harm (F=3.01, df=3, p<0.05) and Overuse (F=2.62, df=3, p<0.05) subscales.

Table XXIX. Univariate associations between demographic characteristics and the BMQ factor subscales

	N	***μ σ****	***μ σ***	***μ σ***	***μ σ***
		Specific Questions		**General Questions**	
		Necessity	Concerns	Harm	Overuse
Sex					
Men	**64**	**11.9 3.71**	**17.2 3.68**	**15.0 3.08**	**9.3 1.99**
Woman	**61**	**12.7 3.69**	**16.5 3.69**	**14.5 2.79**	**9.1 1.82**
Age					
Category 1: 20-45	**56**	**12.9 3.77**	**17.4 3.95**	**14.7 3.13**	**9.2 1.91**
Category 2: 46-65	**69**	**11.8 3.61**	**16.4 3.44**	**14.8 2.80**	**9.2 1.91**
Occupational Status					
Farmer/Breeder	**13**	**12.8 4.25**	**16.7 3.17**	**14.8 2.17**	**9.4 1.26**

Household	**17**	**11.9**	**3.48**	**15.7**	**3.79**	**15.2**	**2.19**	**9.2**	**1.60**
Private servant	**54**	**12.6**	**3.91**	**17.4**	**3.57**	**14.7**	**3.14**	**9.2**	**2.19**
Public servant	**13**	**13.1**	**3.20**	**18.4**	**2.57**	**15.5**	**3.76**	**9.4**	**1.50**
Retired	**10**	**10.6**	**2.46**	**14.9**	**4.25**	**13.2**	**3.91**	**8.1**	**2.69**
Unemployed	**17**	**11.7**	**3.95**	**16.6**	**4.43**	**14.7**	**2.18**	**9.4**	**1.37**
Educational Level									
Analphabetic	**0**	-	-	-	-	-	-	-	-
Elementary school	**15**	**10.5**	**4.24**	**15.0**	**4.66**	**14.1**	**2.52**	**8.9**	**1.71**
Secondary	**23**	**12.9**	**3.98**	**16.9**	**3.72**	**14.9**	**3.03**	**9.3**	**1.89**
Further Commercial/Technical	**52**	**12.4**	**3.47**	**17.4**	**3.43**	**14.6**	**3.10**	**8.9**	**2.17**
University/polytechnic	**34**	**12.2**	**3.06**	**17.4**	**3.26**	**14.8**	**2.99**	**9.4**	**1.91**
Residence									
Rural area	**26**	**11.4**	**3.84**	**16.3**	**3.06**	**15.2**	**2.70**	**9.5**	**1.53**
Semi-urban area	**36**	**12.6**	**3.92**	**16.4**	**3.92**	**14.6**	**2.53**	**9.1**	**1.96**
Urban area	**63**	**12.5**	**3.52**	**17.3**	**3.79**	**14.7**	**3.26**	**9.1**	**2.03**
Clinical Stage									
Active	**23**	**12.5**	**3.50**	**16.0**	**4.45**	**13.8**	**3.21**	**8.7**	**2.32**
Inactive	**102**	**12.2**	**3.76**	**17.0**	**3.50**	**14.9**	**2.85**	**9.3**	**1.79**

μ: mean value, σ: standard deviation

Table XXX. Univariate correlations between demographic characteristics and the BMQ factor subscales

	Pearson's r			
	Specific Questions		**General Questions**	
	Necessity	Concerns	Harm	Overuse
Years after diagnosis	**-0.194**	**-0.128**	**-0.161**	**-0.028**
Number of chronic conditions	**0.009**	**-0.079**	**-0.032**	**0.022**
Number of drugs	**-0.148**	**0.067**	**0.233***	**0.102**
Number of drugs (Total)	**-0.164**	**0.053**	**0.250***	**0.177***

** p-value<0.05*

Chapter 6

Discussion & Conclusions

Summarizing the results of our study, discussion could be emphasized in patient distribution across beliefs groups, as well as the comparison between the obtained results of the study and results of several works presented in the literature. Specifically, in this chapter a summary of the literature is presented according to the Cronbach's α, the KMO, the correlations between subscales and variables and the Correlations among subscales the correlations among subscales. Furthermore, a comparative study which is focus on patient age, as well as the number of drug per day is also performed.

Regarding our study, adequacy of the dataset for factor analysis was proven based on the results obtained from the KMO measure and the Bartlett's test of Sphericity. Factor analysis indicated several significant correlations among the factors and the variables: Harm and subscale revealed the most correlations, being with the number of drugs for IBD and the total number of drugs, while Overuse subscale also correlated positively with the total number of drugs variable. Necessity and Concerns subscales did not present any significant correlations with any of the recorded variables. Also, several positive correlations emerged among subscales.

A mid-point split in Necessity and Concerns subscales using the median value, defined the four beliefs groups. The majority of the patients were categorized in the Indifferent (40%) and Ambivalent (31.2%) groups, while both Accepting (12.8%) and Skeptical (16%) were significantly smaller (Fig. 6.1).

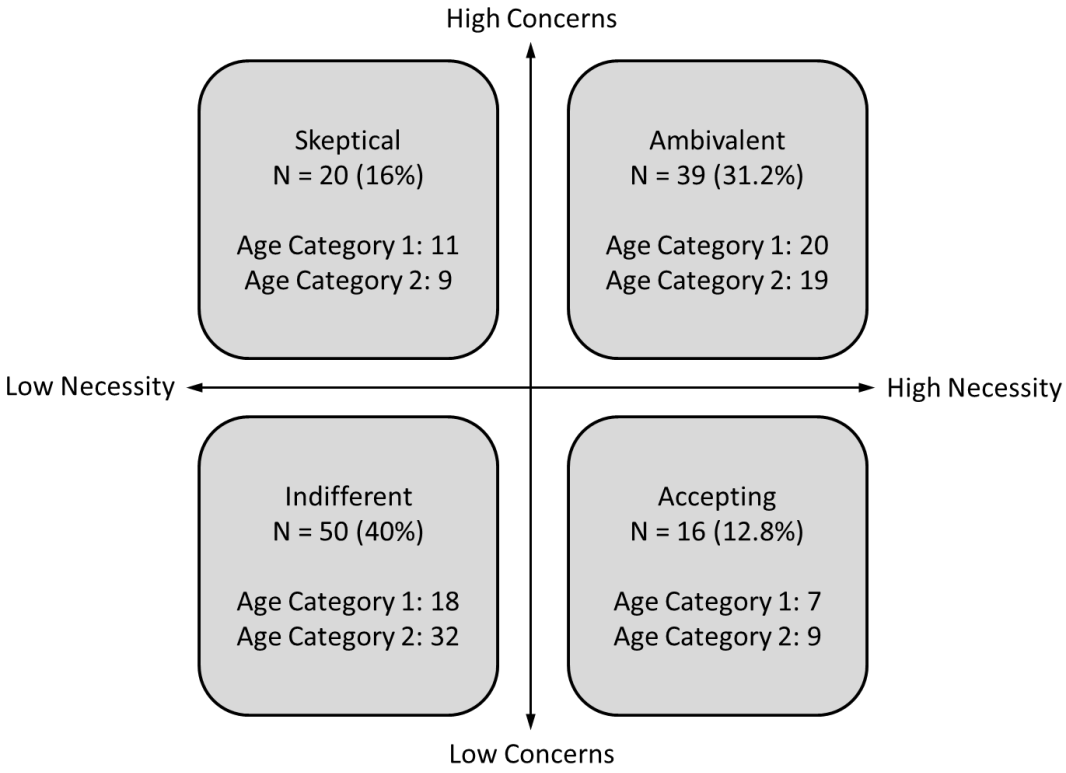

Figure 6.1. Patient distribution across beliefs groups.

In Table XXXI, a synopsis of results from similar studies is presented. The Cronbach's a values vary 0.63-0.83, with the value being 0.757 and 0.784 for the first and second studies, respectively. Also, most of the researches reported significant correlations among BMQ subscales. An interesting finding for both studies is that they resulted to the lowest accepting belief group ratio (16% and 12.8% for the previous IBD study and current study, respectively) along with the highest results for ambivalent and indifferent belief group ratios (31.3% and 41% for our previous IBD study, and 31.2% and 40% for the UC study, respectively).

Table XXXI. Results presented in similar studies

Work (Year)	*Cronbach's α*	*KMO*	*Correlations between subscales and variables*	*Correlations among subscales*	*Belief groups (%)*			
					Accepting	Skeptical	Ambivalent	Indifferent
Alhalaiqa *et al.* [116] (2014)	**0.71**			**Yes**				
Fall *et al.* [117] (2014)	**0.63/0.7**			**Yes**				
Komninos *et al.* [83] (2012)	**0.676-0.852**	**0.81/0.788**	**Yes**	**Yes**				
Menckeberg *et al.* [89] (2008)	**0.66-0.81**			**Yes**	**30**	**19**	**24**	**27***
Mahler *et al.* [85] (2010)	**0.79-0.83**			**Yes**				
Russell *et al.* [118] (2008)					**59**	**4**	**24**	**13**
Salgado *et al.* [119] (2013)	**0.7**	**0.75**		**Yes**				
Sjölander *et al.* [120] (2013)	**0.647-0.823**			**Yes**				
Tibaldi *et al.* [86] (2009)	**0.78/0.72**				**59**	**4**	**29**	**8**
Viktil *et al.* [121] (2013)	**0.82**			**Yes**				
Tsianou et al. 2016 [114]	**0.757**	**0.761**	**Yes**	**Yes**	**16**	**11.7**	**31.3**	**41**
Current work:	**0.784**	**0.804**	**Yes**	**Yes**	**12.8**	**16**	**31.2**	**40**

* calculated from Fig. 2 of [89]

Table XXXII presents results from the statistical relation between the age of patient and the number of medicines per day with BMQ factor from several works. The results of our studies are also provided in the last rows of the the table

Table XXXII: Summary of the already presented works in the literature. Correlations with age and number of prescribed medicines.

Work	Disease	# of Patients	Correlation with age	Correlation with number of medicine per day
Aikens & Piette 2009 [92]	Diabetes	803	Spearmans-based (Necessity: -0.11, Concerns: -0.18)	Spearmans-based (Necessity: 0.22, Concerns: 0.05)
Beléndez et al. 2007 [81]	Diabetes, Chronic Diseases	412	-	-
Clatworthy et. al 2009 [97]	Bipolar Disorders	223	Logistic regression from MARS (significance=0.29)	-
Cuevas et al. 2011 [98]	Psychiatric Outpatients	843	Pearson: Necessity (r=0.20) Harm (r=-0.11)	Pearson: Necessity (r= 0.34)
Fall et al. 2014 [93]	Diabetes Type II, HIV	376	Pearson: Necessity Diabetes (r=0.15), HIV (r=0.28)	-
Fu at al. [112]	IBD Adolescents	112	-	-
Gauchet et al. 2007 [91]	HIV HAART	127	none sociodemographic or medical-related variable related to adherence	none sociodemographic or medical-related variable related to adherence
Grant et al. 2008 [82]	Chronic (Asthma, Diabetes, Renal, Cardiac, GORD)	1274	-	-
Horne at al. 1999 [76]	Chronic (Asthma, Diabetes, Renal, Cardiac)	524	no significant relation	-
Horne et al. 1999 [80]	Chronic (Asthma, Diabetes, Renal, Cardiac)	324	-	no significant relation
Horne et al. 2007 [90]	HIV (HAART Treatment)	136	no significant relation	-
Horne et al. 2009 [113]	IBD	1871	Logistic regression from MARS (significance 0)	only type of medicine
Jonsdottir et al. 2008 [99]	Mental Disorders	280	-	-
Komninos et al. 2012 [83]	Chronic Diseases	150	Pearson: Necessity (r=0.45) concerns (r=0.23) Overuse (-0.04) Harm (r=0.23)	Pearson: Necessity (r=0.52) concerns (r=0.28) Overuse (-0.12) Harm (r=-0.01)
Kumar et al. 2008 [94]	Rheumatoid Arthritis & Systemic Lupus Erythematosus	200	Spearmans: Necessity (ρ=0.16)	-
Lihara et al. 2010 [84]	Chronic (Liver, GI, Nervous system)	613	-	-

Llewellyn et al. 2002 [100]	Heamophilia	104	-	-
Mahler et al. 2012 [85]	Chronic Diseases	485	-	-
Marbdy et al. 2007 [87]	Pharmacy Clients	324	-	-
Menckeberg et al. 2008 [89]	Asthma	233	-	-
Moshkovska et al. 2012 [111]	IBD	169	-	-
Neame & Hammond 2005 [96]	Rheumatoid Arthritis	600	Pearson: Necessity (r=-0.07), concerns (r=-0.12)	Pearson: Necessity (r=-0.26), concerns (r=0.20)
O'Carroll et al. 2006 [103]	After Liver Transplantation	435	-	-
Ross et al. 2004 [101]	Hypertension	514	specific-necessity Older: (OR=2.0) Younger: (OR=0.5)	no significant relation
Tibaldi et al. 2009 [86]	Chronic (Cardiac, Asthma, Diabetes, Depression)	427	-	-
Tordera et al. 2008 [88]	Asthma	126	-	-
Treharne et al. 2004 [95]	Rheumatoid Arthritis	85	-	-
Van Dongen et al. 2013 [110]	IBD - enema use	112	-	-
Tsianou et al. 2016 [114]	IBD (UC and CD)	163	Necessity (Pearson's r = -0.294) Concerns (Pearson's r = -0.246)	Harm (Pearson's r = 0.250)
Current work	**UC**	**125**	**-**	**Harm (Pearson's r = 0.212) Overuse (Pearson's r = 0.177)**

As it is shown in Table XXXI, several studies calculated the statistical correlation between the age of patient and BMQ factors. Pearson's and Spearman's correlation or Odds ratio, have been employed to quantify this relation. There is no study that separates in groups the patients according to their age. From the above results, it seems that there is strong correlation between the age of the patients and the necessity factor. This means that older peoples believe in necessity of prescribed treatment more than younger peoples do. Some of the studies indicated also a weak relation between the age and the concerns factor. The role of the number of medicine taken per day, have also been examined in some

studies, however obtained findings are confusing. According to our study, significant correlations have been discovered: in our previous IBD study the age of the patients correlates with all specific subscales (i.e. Necessity and Concerns) and also with one of the general subscales (i.e. Harm). In the UC study, although no significant correlations have been revealed for the age, the number of drugs correlated significantly with all general subscales (i.e. Harm and Overuse).

As a conclusion, the Greek version of the Beliefs about Medicines Questionnaire presented satisfactory psychometric/measurement properties indicating its reliability for use in patients with UC who receive care in an outpatient hospital clinic. The BMQ is a useful tool that will provide important information to gastroenterologists regarding patient's perceptions on medications in general, and about their prescribed medication. This knowledge may facilitate decisions about adequate therapeutical approaches, and guide appropriate interventions that will foster a successful patient – physician communication. Further research is needed in order to study the relationship between beliefs about medication and other factors that may be related to non-adherence to medications.

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ABSTRACT

PRELIMINARY ANALYSIS OF DRUG ADHERENCE OF PATIENTS WITH ULCERATIVE COLITIS

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Aim of diploma thesis: To investigate the role of the beliefs of patients suffering with Ulcerative Colitis about medicines according to age group (group 1: age between 20-45 years old versus group 2: age between 46-65 years old). The study employs the Belief about Medicine Questionnaire to measure the adherence of patients with Ulcerative Colitis in Greece.

Method: This study was conducted using the Greek version of the BMQ that has been translated from English into Greek language by a professional bilingual translator and then translated back into English by a native English speaker in a previous study.

Results: Our study is resulted to the lowest accepting belief group ratio (12.8%) along with the highest results for ambivalent and indifferent belief group ratios (31.2% and 40%, respectively).

Conclusion: The Greek version of the Beliefs about Medicines Questionnaire presented satisfactory psychometric/measurement properties indicating its reliability for use in patients with IBD who receive care in an outpatient hospital clinic. The BMQ is a useful tool that will provide important information to gastroenterologists regarding patient's perceptions on medications in general, and about their prescribed medications .

ABSTRAKT

Pilotní studie lékové adherence nemocných trpících ulcerózní kolitidou

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Cíl: analyzovat roli důvěry ve farmakoterapii u dvou věkových skupin pacientů (skupina 1 (20 – 45let) a skupina 2 (46 – 65let)) trpících ulcerózní kolitidou.

Metoda: Byla využita řecká verze dotazníku „Belief about Medicine Questionnaire (BMQ). Dotazník byl přeložen z anglické verze do řečtiny profesionální překladatelem a pak přeložen zpět do angličtiny v předchozí studii.

Výsledky: Účastníci studie vykazují nízkou důvěru ve farmakoterapii(pouze 12,8%) s největším podílem ambivalentního (31,2%) nebo indiferentního charakteru důvěry (40%).

Závěr: Řecká verze BMQ je dobrý nástroj pro psychometrické sledování vztahu pacienta k lékům a je možné jej užít u ambulantních pacientů. Přináší důležité informace gastroenterologům o percepci pacientů k farmakoterapii.

APPENDIX

Table 1: Answers of Patient in BMQ Questions

AA	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Necessity	Concerns	Harm	Overuse
1	2	2	2	2	2	2	2	2	2	2	2	4	3	3	3	3	4	3	3	10	12	16	10
2	3	5	1	1	2	4	3	3	2	1	5	4	4	4	3	5	5	4	4	12	18	20	13
3	4	2	4	4	2	4	4	2	2	2	2	2	4	2	2	4	4	2	2	16	16	14	8
4	5	2	4	4	2	4	4	4	4	2	4	2	2	2	2	2	4	2	2	17	22	10	8
5	1	2	1	4	2	4	2	4	4	1	4	4	3	3	5	5	5	3	4	10	19	20	12
6	1	1	1	1	1	1	1	2	2	2	2	4	2	2	2	2	4	2	2	5	10	12	8
7	2	2	2	3	2	2	2	2	2	2	4	4	4	2	4	3	4	2	2	11	14	17	8
8	2	4	2	2	4	4	2	4	4	2	4	4	2	3	4	2	4	4	2	14	20	15	10
9	2	4	4	3	4	3	3	4	4	2	4	4	2	4	3	4	4	4	3	17	20	17	11
10	2	2	2	2	2	3	2	4	2	2	4	4	3	4	3	4	4	4	4	10	17	18	12
11	1	1	2	2	2	2	2	1	1	1	2	2	4	2	4	4	4	2	2	8	9	16	8
12	4	2	4	4	2	2	4	2	2	4	2	4	2	2	2	2	2	4	2	16	16	12	8
13	1	2	2	2	2	2	2	4	4	2	4	3	3	4	3	3	4	2	3	9	18	16	9
14	1	1	1	1	1	1	1	2	2	2	1	2	2	4	4	2	4	3	4	5	9	14	11
15	1	2	2	2	2	2	2	2	2	1	2	4	3	2	3	2	3	2	4	9	11	14	9
16	3	1	4	2	2	2	2	2	4	2	2	2	2	3	4	4	4	2	3	12	14	15	9
17	2	5	4	4	4	5	2	5	4	1	5	3	4	5	3	5	5	2	3	19	22	20	10
18	2	2	2	2	2	4	2	4	3	1	4	3	4	3	3	3	5	5	3	10	18	16	13
19	2	3	4	2	2	4	2	4	4	2	4	4	2	4	4	3	4	2	2	13	20	17	8
20	1	4	2	2	2	4	2	4	4	2	2	2	4	2	4	4	4	2	2	11	18	16	8
21	3	2	4	4	2	2	3	2	4	2	4	2	2	3	2	2	4	4	2	15	17	11	10
22	2	2	2	2	2	4	2	1	2	2	2	4	2	2	2	2	2	2	2	10	13	12	6
23	2	2	2	3	2	3	3	4	4	2	4	4	3	3	4	4	4	3	2	11	20	18	9
24	1	2	2	1	2	3	1	4	1	1	4	2	3	2	3	2	4	3	3	8	14	12	10
25	1	4	3	2	2	4	1	1	4	1	1	3	3	3	3	4	4	3	2	12	12	16	9
26	3	2	4	4	2	2	4	3	4	3	4	4	3	3	3	4	4	4	4	15	20	17	12
27	2	2	4	4	4	4	2	4	4	2	4	3	3	4	3	3	3	3	2	16	20	16	8
28	2	2	2	2	2	4	2	2	2	2	3	2	2	4	2	4	3	4	2	10	15	14	9

29	2	2	4	4	2	2	4	4	4	2	4	2	2	2	2	2	2	2	1	14	20	10	5
30	2	3	2	3	2	4	2	4	4	2	4	3	3	3	3	4	4	3	3	12	20	16	10
31	1	1	3	4	2	4	3	4	2	2	4	3	3	4	3	3	4	2	3	11	19	16	9
32	3	2	4	3	2	4	3	3	2	2	3	3	3	4	3	4	4	4	3	14	17	17	11
33	2	4	2	2	2	4	3	2	4	2	4	4	4	3	3	2	4	4	3	12	19	16	11
34	2	2	2	2	2	2	2	4	2	2	4	4	4	4	2	4	4	4	2	10	16	18	10
35	2	2	2	2	2	2	2	2	2	2	2	1	2	2	3	2	4	2	1	10	12	10	7
36	2	2	2	2	4	2	2	3	4	1	4	2	5	4	3	2	4	4	3	12	16	16	11
37	1	2	3	3	2	3	2	4	2	2	4	2	2	2	3	4	4	2	2	11	17	13	8
38	1	2	2	3	2	4	2	2	1	3	1	4	4	3	3	2	4	4	3	10	13	16	11
39	4	2	4	4	3	4	4	4	2	2	4	4	3	2	4	4	4	4	4	17	20	17	12
40	3	1	2	4	2	4	4	1	3	4	2	5	1	3	1	2	3	2	2	12	18	12	7
41	2	2	2	2	2	1	3	2	4	2	4	2	2	2	2	2	3	3	4	10	16	10	10
42	2	1	2	2	2	2	2	4	2	2	1	2	4	4	2	2	3	2	4	9	13	14	9
43	2	4	4	2	2	4	4	4	2	2	4	2	3	4	3	4	4	2	2	14	20	16	8
44	4	2	4	4	4	4	2	2	4	2	4	2	4	4	2	4	4	4	4	18	18	16	12
45	3	2	3	4	1	2	3	2	2	3	1	1	3	4	2	1	3	2	2	13	13	11	7
46	4	4	4	4	2	4	4	4	4	2	4	3	2	3	2	4	4	2	3	18	22	14	9
47	3	4	4	4	2	4	3	2	2	4	2	2	2	3	2	3	4	3	2	17	17	12	9
48	2	2	2	2	2	2	2	2	1	2	2	2	4	2	4	2	4	4	1	10	11	14	9
49	2	1	4	4	2	4	4	4	2	2	2	5	2	2	3	3	3	3	3	13	18	15	9
50	2	4	2	2	3	4	2	2	3	2	2	2	3	3	2	2	4	3	3	13	15	12	10
51	2	2	4	2	2	2	2	4	4	2	4	3	2	4	2	3	4	2	4	12	18	14	10
52	3	3	2	2	2	3	3	2	2	2	2	2	2	4	3	2	4	4	3	12	14	13	11
53	2	2	2	2	2	4	3	4	4	2	4	4	4	4	4	4	4	4	4	10	21	20	12
54	3	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	4	4	3	7	12	10	11
55	2	4	2	2	4	4	3	4	4	2	2	4	4	4	2	2	3	2	2	14	19	16	7
56	1	2	1	1	1	4	2	2	1	1	1	2	1	3	3	2	4	2	2	6	11	11	8
57	2	2	3	2	1	2	2	4	2	2	4	3	3	3	3	3	4	3	2	10	16	15	9
58	2	4	3	3	2	4	3	4	4	1	5	3	3	3	3	4	4	3	4	14	21	16	11
59	2	4	2	2	2	4	2	2	4	2	3	4	3	4	3	2	4	4	2	12	17	16	10
60	2	2	1	1	1	2	2	1	1	1	4	2	3	2	2	2	3	3	2	7	11	11	8
61	1	2	2	1	1	1	1	1	2	1	1	3	2	2	2	3	4	4	3	7	7	12	11
62	1	1	1	1	2	2	1	2	4	1	4	4	4	2	4	2	3	4	3	6	14	16	10
63	4	2	4	4	2	4	4	2	2	1	2	4	2	3	4	2	4	3	2	16	15	15	9
64	2	2	2	2	2	2	2	2	2	2	4	2	2	2	2	2	4	2	2	10	14	10	8
65	2	2	2	2	2	4	2	2	2	2	4	4	4	4	2	4	4	2	2	10	16	18	8
66	2	1	2	2	1	4	2	4	1	2	3	4	2	4	3	2	3	2	2	8	16	15	7
67	2	2	3	2	2	2	3	3	3	2	4	4	3	2	3	3	3	2	2	11	17	15	7
68	1	1	1	1	2	2	1	2	3	1	2	2	3	2	4	2	3	4	2	6	11	13	9

69	2	2	4	4	4	4	3	4	4	2	4	4	2	3	3	2	4	2	4	16	21	14	10
70	4	4	4	2	4	4	3	4	4	2	4	4	3	4	4	4	4	3	4	18	21	19	11
71	4	2	5	4	2	4	5	1	3	4	1	2	1	2	3	3	3	3	1	17	18	11	7
72	4	2	4	4	4	2	4	2	2	2	2	4	2	2	2	3	4	4	2	18	14	13	10
73	4	4	2	2	4	4	4	2	4	2	4	2	3	4	3	2	4	2	3	16	20	14	9
74	3	4	3	3	2	3	2	4	2	2	4	4	4	4	3	3	4	4	3	15	17	18	11
75	2	2	2	2	2	4	3	2	2	2	4	4	3	4	4	3	4	4	3	10	17	18	11
76	1	1	1	1	2	2	2	2	2	2	2	2	3	3	4	3	3	2	2	6	12	15	7
77	4	4	4	4	4	4	4	4	2	2	4	2	2	2	2	4	2	2	2	20	20	12	6
78	2	4	4	4	2	4	4	4	2	2	4	2	4	4	2	4	4	2	4	16	20	16	10
79	1	2	2	2	1	3	4	4	5	2	4	5	4	4	4	4	4	3	3	8	22	21	10
80	2	2	2	2	2	2	2	2	4	2	4	4	3	2	3	2	3	2	3	10	16	14	8
81	2	2	2	2	2	2	2	2	2	2	2	2	2	4	2	2	2	2	2	10	12	12	6
82	1	4	1	1	3	5	1	5	5	1	5	1	2	4	3	5	5	2	3	10	22	15	10
83	1	1	2	2	2	4	2	4	2	2	4	4	2	2	2	2	4	4	4	8	18	12	12
84	2	1	1	2	2	3	2	2	2	2	2	4	4	4	4	4	4	4	4	8	13	20	12
85	2	1	1	1	1	2	3	2	4	2	4	3	2	3	3	2	3	4	2	6	17	13	9
86	4	1	4	4	4	2	4	2	4	4	4	3	1	1	1	1	2	2	1	17	20	7	5
87	2	2	4	3	2	2	1	4	4	2	4	4	3	4	4	3	4	3	4	13	17	18	11
88	2	3	2	4	4	3	2	4	4	2	4	3	4	3	3	3	4	2	3	15	19	16	9
89	1	2	2	2	2	4	2	4	2	2	4	3	4	3	3	3	4	3	4	9	18	16	11
90	2	2	4	4	4	4	4	4	4	2	4	4	4	4	3	4	4	3	3	16	22	19	10
91	1	1	2	2	3	2	2	2	4	2	2	3	2	3	4	4	2	4	2	9	14	16	8
92	1	1	1	1	2	4	1	1	4	1	1	4	4	4	3	2	4	2	3	6	12	17	9
93	1	1	1	1	1	1	1	4	1	1	4	4	4	3	4	3	4	4	3	5	12	18	11
94	2	2	4	3	2	4	2	2	2	2	2	2	2	4	2	2	3	2	2	13	14	12	7
95	2	4	2	2	4	4	2	4	4	2	4	4	3	4	2	4	4	4	3	14	20	17	11
96	2	4	4	2	2	2	4	2	4	2	2	4	2	4	2	2	4	2	4	14	16	14	10
97	2	2	2	2	2	2	2	2	4	2	2	4	3	4	2	2	4	2	2	10	14	15	8
98	2	2	1	2	1	4	1	1	4	1	1	2	4	4	2	2	2	2	2	8	12	14	6
99	2	2	2	2	2	2	2	2	2	2	4	4	2	4	3	2	3	4	3	10	14	15	10
100	2	2	2	2	2	2	2	2	2	2	2	3	2	4	5	2	3	2	4	10	12	16	9
101	1	2	2	2	1	2	2	2	2	2	2	4	2	2	4	2	4	2	4	8	12	14	10
102	1	2	2	2	1	4	2	2	5	2	5	4	4	4	4	4	4	2	3	8	20	20	9
103	2	2	2	2	2	3	2	2	4	2	2	4	3	4	3	4	5	3	2	10	15	18	10
104	3	4	1	1	3	4	1	2	3	2	4	4	2	4	3	2	2	4	4	12	16	15	10
105	2	4	2	2	2	4	2	4	2	1	4	2	4	2	2	2	3	3	3	12	17	12	9
106	2	2	2	2	2	1	2	2	2	1	4	2	2	2	1	1	2	1	1	10	12	8	4
107	2	2	2	2	4	4	4	4	2	2	4	4	4	4	4	2	4	3	2	12	20	18	9
108	4	4	2	2	2	2	4	2	4	2	2	2	2	2	2	2	2	4	4	2	14	16	10	10

109	2	3	2	2	2	2	2	3	2	2	3	3	2	3	3	2	4	3	2	11	14	13	9
110	2	2	2	2	2	4	4	4	4	2	4	2	4	4	4	4	4	4	2	10	22	18	10
111	2	2	2	2	2	4	2	4	4	2	4	4	2	4	4	4	4	4	3	10	20	18	11
112	1	4	2	2	2	2	2	2	2	2	2	3	2	2	3	2	2	2	2	11	12	12	6
113	2	2	2	2	2	2	2	2	3	2	2	4	2	2	2	2	4	2	2	10	13	12	8
114	3	2	3	4	2	4	3	2	2	3	2	2	2	4	2	2	4	3	3	14	16	12	10
115	2	4	2	2	4	4	2	4	4	2	4	2	4	2	4	4	4	2	2	14	20	16	8
116	1	3	1	1	2	2	1	1	2	1	1	3	4	2	4	4	5	2	4	8	8	17	11
117	2	4	4	4	2	4	2	4	1	2	4	2	2	2	4	5	4	4	2	16	17	15	10
118	4	2	4	4	2	4	2	2	4	2	4	2	2	4	4	4	4	4	4	16	18	16	12
119	1	1	2	1	1	4	1	2	2	1	2	4	4	4	2	4	4	2	2	6	12	18	8
120	2	4	2	2	2	2	4	4	4	2	4	3	4	4	4	4	4	4	4	12	20	19	12
121	2	2	2	4	4	4	4	4	4	2	4	4	2	2	3	2	4	2	3	14	22	13	9
122	5	2	4	4	2	4	4	4	2	4	2	2	2	2	2	4	4	2	2	17	20	12	8
123	2	2	2	2	2	3	2	2	2	2	4	4	3	3	2	2	2	2	2	10	15	14	6
124	2	4	2	2	4	4	2	4	2	4	4	4	3	3	2	3	4	4	3	14	20	15	11
125	2	4	2	3	4	3	2	4	4	2	4	4	3	4	3	4	4	3	4	15	19	18	11

Table 2: Demographic and Disease Data

AA	Sex	Age	Occupation	Education	Residence	Disease	Clinical Stage	Year of Diagnosis	Years after diagnosed
1	men	53	Unemployed	Secondary	Urban area	UC	Inactive	1994	20
2	women	58	Household	Secondary	Rural area	UC	Inactive	2007	7
3	women	82	Household	Elementary school	Semi-urban area	UC	Active	1985	29
4	women	26	Unemployed	Further Commercial/Technical	Urban area	UC	Inactive	2009	5
5	women	44	Public servant	University/polytechnic	Urban area	UC	Inactive	1991	23
6	women	60	Farmer/Breeder	Secondary	Rural area	UC	Inactive	1997	17
7	women	45	Farmer/Breeder	Elementary school	Rural area	UC	Inactive	1991	23
8	women	70	Household	Elementary school	Rural area	UC	Inactive	1982	32
9	men	41	Farmer/Breeder	Secondary	Rural area	UC	Inactive	1996	18
10	men	53	Private servant	Secondary	Semi-urban area	UC	Inactive	2008	6
11	women	39	Household	Further Commercial/Technical	Urban area	UC	Active	1997	17
12	women	48	Farmer/Breeder	Elementary school	Semi-urban area	UC	Inactive	1982	32
13	women	65	Household	Secondary	Urban area	UC	Inactive	2005	9
14	men	41	Unemployed	Elementary school	Semi-urban area	UC	Inactive	2007	7
15	men	65	Retired	Secondary	Semi-urban area	UC	Inactive	2005	9
16	men	26	Private servant	Further Commercial/Technical	Rural area	UC	Active	2009	5
17	men	40	Public servant	Secondary	Urban area	UC	Inactive	1995	19
18	men	63	Retired	University/polytechnic	Urban area	UC	Inactive	2002	12
19	men	46	Private servant	Secondary	Urban area	UC	Inactive	1990	24
20	men	23	Unemployed	University/polytechnic	Urban area	UC	Inactive	2007	7
21	women	28	Private servant	Further Commercial/Technical	Urban area	UC	Inactive	2006	8
22	women	64	Retired	Elementary school	Rural area	UC	Inactive	1989	25
23	women	65	Retired	University/polytechnic	Semi-urban area	UC	Inactive	2005	9
24	women	50	Private servant	University/polytechnic	Urban area	UC	Inactive	1991	23
25	men	76	Retired	Secondary	Semi-urban area	UC	Inactive	2010	4
26	men	32	Private servant	University/polytechnic	Semi-urban area	UC	Inactive	2008	6
27	men	42	Private servant	University/polytechnic	Urban area	UC	Inactive	2004	10
28	women	38	Household	Secondary	Urban area	UC	Inactive	2006	8
29	men	40	Private servant	Further Commercial/Technical	Urban area	UC	Active	2001	13
30	men	32	Private servant	Further Commercial/Technical	Urban area	UC	Inactive	2007	7
31	men	76	Retired	Elementary school	Semi-urban area	UC	Inactive	1990	24
32	men	85	Retired	Elementary school	Urban area	UC	Inactive	1991	23
33	men	64	Retired	Secondary	Semi-urban area	UC	Active	1995	19
34	men	65	Retired	Elementary school	Rural area	UC	Inactive	1994	20
35	men	63	Retired	University/polytechnic	Urban area	UC	Inactive	1984	30
36	men	82	Retired	Secondary	Semi-urban area	UC	Inactive	1986	28

37	men	32	Private servant	Secondary	Urban area	UC	Inactive	2008	6
38	women	63	Farmer/Breeder	Elementary school	Rural area	UC	Active	1997	17
39	women	44	Private servant	Further Commercial/Technical	Semi-urban area	UC	Active	1991	23
40	men	65	Retired	University/polytechnic	Urban area	UC	Inactive	1996	18
41	men	24	Unemployed	Further Commercial/Technical	Rural area	UC	Inactive	2009	5
42	women	55	Private servant	Secondary	Semi-urban area	UC	Inactive	2001	13
43	men	36	Public servant	University/polytechnic	Urban area	UC	Inactive	2010	4
44	women	32	Private servant	University/polytechnic	Urban area	UC	Inactive	2002	12
45	women	25	Private servant	University/polytechnic	Urban area	UC	Inactive	2009	5
46	women	56	Household	Elementary school	Rural area	UC	Inactive	2002	12
47	men	28	Unemployed	Further Commercial/Technical	Urban area	UC	Inactive	2003	11
48	men	65	Retired	Secondary	Semi-urban area	UC	Inactive	2008	6
49	women	52	Farmer/Breeder	Secondary	Semi-urban area	UC	Inactive	1990	24
50	women	74	Retired	Analphabetic	Rural area	UC	Inactive	2002	12
51	women	25	Household	Secondary	Urban area	UC	Inactive	2004	10
52	women	69	Retired	Secondary	Semi-urban area	UC	Inactive	1986	28
53	men	37	Private servant	University/polytechnic	Urban area	UC	Inactive	2002	12
54	men	58	Private servant	University/polytechnic	Urban area	UC	Active	1999	15
55	women	57	Household	Secondary	Rural area	UC	Inactive	1993	21
56	women	67	Retired	University/polytechnic	Urban area	UC	Active	2000	14
57	women	42	Private servant	Secondary	Semi-urban area	UC	Inactive	1998	16
58	men	36	Private servant	University/polytechnic	Urban area	UC	Inactive	2007	7
59	men	70	Retired	University/polytechnic	Urban area	UC	Inactive	2000	14
60	women	63	Retired	University/polytechnic	Urban area	UC	Inactive	1992	22
61	women	78	Retired	University/polytechnic	Urban area	UC	Inactive	1971	43
62	women	79	Retired	Elementary school	Rural area	UC	Inactive	1984	30
63	women	59	Household	Secondary	Semi-urban area	UC	Inactive	2005	9
64	men	38	Private servant	Secondary	Semi-urban area	UC	Inactive	1991	23
65	women	44	Household	Elementary school	Rural area	UC	Inactive	2006	8
66	men	51	Private servant	Further Commercial/Technical	Urban area	UC	Inactive	1985	29
67	men	24	Unemployed	University/polytechnic	Urban area	UC	Active	2004	10
68	men	44	Unemployed	Elementary school	Rural area	UC	Inactive	2008	6
69	women	56	Private servant	Secondary	Urban area	UC	Inactive	2003	11
70	women	37	Private servant	Secondary	Urban area	UC	Inactive	2005	9
71	men	44	Private servant	University/polytechnic	Urban area	UC	Inactive	2009	5
72	men	47	Farmer/Breeder	Secondary	Rural area	UC	Inactive	2010	4
73	women	45	Private servant	Secondary	Urban area	UC	Inactive	2010	4
74	women	45	Household	Secondary	Rural area	UC	Inactive	2003	11
75	men	60	Farmer/Breeder	Secondary	Rural area	UC	Inactive	1995	19
76	men	54	Private servant	Secondary	Semi-urban area	UC	Inactive	1996	18

77	women	45	Private servant	Secondary	Semi-urban area	UC	Inactive	2006	8
78	women	21	Unemployed	Secondary	Urban area	UC	Inactive	1997	17
79	men	65	Retired	Further Commercial/Technical	Semi-urban area	UC	Inactive	1998	16
80	men	62	Public servant	University/polytechnic	Urban area	UC	Inactive	1999	15
81	men	81	Retired	Secondary	Urban area	UC	Inactive	2005	9
82	men	25	Unemployed	University/polytechnic	Urban area	UC	Inactive	2001	13
83	men	43	Private servant	Elementary school	Rural area	UC	Inactive	2009	5
84	men	70	Retired	Further Commercial/Technical	Semi-urban area	UC	Inactive	2001	13
85	men	53	Farmer/Breeder	Elementary school	Rural area	UC	Inactive	2000	14
86	women	60	Private servant	Secondary	Semi-urban area	UC	Active	1991	23
87	men	61	Private servant	Secondary	Semi-urban area	UC	Inactive	1995	19
88	women	49	Household	Elementary school	Semi-urban area	UC	Inactive	1993	21
89	men	37	Unemployed	Further Commercial/Technical	Rural area	UC	Inactive	2003	11
90	men	48	Public servant	University/polytechnic	Urban area	UC	Inactive	2003	11
91	men	101	Retired	Elementary school	Rural area	UC	Inactive	1988	26
92	men	68	Retired	Secondary	Semi-urban area	UC	Inactive	1989	25
93	women	74	Retired	University/polytechnic	Urban area	UC	Inactive	1991	23
94	men	64	Retired	University/polytechnic	Urban area	UC	Inactive	1991	23
95	men	65	Farmer/Breeder	Secondary	Rural area	UC	Inactive	1993	21
96	men	44	Public servant	University/polytechnic	Urban area	UC	Active	1990	24
97	women	44	Household	Secondary	Urban area	UC	Inactive	2013	1
98	men	64	Retired	Further Commercial/Technical	Urban area	UC	Inactive	1989	25
99	men	65	Public servant	University/polytechnic	Urban area	UC	Active	1979	35
100	women	50	Private servant	Further Commercial/Technical	Semi-urban area	UC	Inactive	1999	15
101	women	34	Private servant	Further Commercial/Technical	Semi-urban area	UC	Inactive	1998	16
102	men	45	Private servant	Further Commercial/Technical	Urban area	UC	Inactive	1993	21
103	men	70	Retired	Secondary	Semi-urban area	UC	Inactive	2004	10
104	men	67	Private servant	Elementary school	Urban area	UC	Inactive	1989	25
105	women	54	Household	Secondary	Semi-urban area	UC	Inactive	2005	9
106	men	65	Farmer/Breeder	Secondary	Rural area	UC	Inactive	1985	29
107	women	53	Private servant	Secondary	Urban area	UC	Inactive	1992	22
108	women	58	Public servant	University/polytechnic	Urban area	UC	Inactive	2002	12
109	women	56	Household	Secondary	Rural area	UC	Inactive	2002	12
110	men	60	Retired	University/polytechnic	Urban area	UC	Inactive	1992	22
111	women	50	Public servant	Further Commercial/Technical	Urban area	UC	Inactive	1982	32
112	men	59	Retired	University/polytechnic	Semi-urban area	UC	Inactive	2007	7
113	women	64	Retired	Secondary	Semi-urban area	UC	Inactive	1992	22
114	men	63	Public servant	University/polytechnic	Urban area	UC	Inactive	2008	6
115	women	27	Unemployed	Further Commercial/Technical	Semi-urban area	UC	Inactive	2008	6
116	women	35	Unemployed	Secondary	Semi-urban area	UC	Active	2003	11

117	men	23	Unemployed	University/polytechnic	Urban area	UC	Inactive	2009	5
118	women	31	Household	University/polytechnic	Urban area	UC	Inactive	1997	17
119	men	65	Retired	University/polytechnic	Urban area	UC	Inactive	1986	28
120	women	58	Private servant	Further Commercial/Technical	Urban area	UC	Inactive	1989	25
121	women	67	Farmer/Breeder	Elementary school	Rural area	UC	Inactive	1985	29
122	women	42	Farmer/Breeder	Secondary	Rural area	UC	Active	2009	5
123	women	49	Private servant	University/polytechnic	Urban area	UC	Inactive	1997	17
124	men	57	Private servant	Elementary school	Semi-urban area	UC	Inactive	2006	8
125	women	32	Private servant	Further Commercial/Technical	Semi-urban area	UC	Active	2007	7

Table 3A: Pharmacotherapy Data

AA	IBD Drug 1 Trade Name	IBD Drug 2 Trade Name	IBD Drug 3 Trade Name	Total Number of IBD drugs	In hospital part of drug therapy	IBD Drug 1 Active Substance	Drug ATC Code	Drug Strength
1	Mezavant	Azathioprine		2	No	mesalazine	A07EC02	tab 500mg , 2x3
2	Remicade	Mezavant		2	Yes	infliximab	L04AB02	100mg vial 20ml for injection
3	Medrol	Azathioprine		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
4	Mezavant	Azathioprine		2	No	mesalazine	A07EC02	tab 500mg , 2x3
5	Mezavant	Medrol	Methotrexate	3	No	mesalazine	A07EC02	tab 500mg , 2x3
6	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
7	Medrol	Azathioprine		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
8	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
9	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
10	Medrol	Mezavant	Methotrexate	3	No	methylprednizolone	D07AA01	tab 16mg , 1x1
11	Remicade	Medrol		2	Yes	infliximab	L04AB02	100mg vial 20ml for injection
12	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
13	Remicade	Mezavant		2	Yes	infliximab	L04AB02	100mg vial 20ml for injection
14	Azathioprine			1	No	azathioprine	L04AX02	tab 50mg, 1x2
15	Remicade	Mezavant		2	Yes	infliximab	L04AB02	100mg vial 20ml for injection
16	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
17	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
18	Azathioprine	Mezavant		2	No	azathioprine	L04AX02	tab 50mg, 1x2
19	Azathioprine	Mezavant		2	No	azathioprine	L04AX02	tab 50mg, 1x2
20	Remicade	Medrol		2	Yes	infliximab	L04AB02	100mg vial 20ml for injection
21	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
22	Medrol	Azathioprine		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
23	Humira			1	No	adalimumab	L04AB04	40mg in 1ml prefiled grass syringe
24	Remicade	Mezavant		2	Yes	infliximab	L04AB02	100mg vial 20ml for injection
25	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
26	Humira	Medrol		2	No	adalimumab	L04AB04	40mg in 1ml prefiled grass syringe
27	Medrol	Azathioprine		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
28	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
29	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
30	Medrol	Mezavant	Methotrexate	2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
31	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
32	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
33	Medrol	Mezavant		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
34	Medrol	Mezavant		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1

35	Medrol			1	No	methylprednizolone	D07AA01	tab 16mg , 1x1
36	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
37	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
38	Azathioprine	Mezavant		2	No	azathioprine	L04AX02	tab 50mg, 1x2
39	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
40	Medrol			1	No	methylprednizolone	D07AA01	tab 16mg , 1x1
41	Mezavant	Azathioprine		2	No	mesalazine	A07EC02	tab 500mg , 2x3
42	Medrol			1	No	methylprednizolone	D07AA01	tab 16mg , 1x1
43	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
44	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
45	Remicade	Medrol		2	Yes	infliximab	L04AB02	100mg vial 20ml for injection
46	Azathioprine	Mezavant		2	No	azathioprine	L04AX02	tab 50mg, 1x2
47	Azathioprine	Mezavant		2	No	azathioprine	L04AX02	tab 50mg, 1x2
48	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
49	Medrol			1	No	methylprednizolone	D07AA01	tab 16mg , 1x1
50	Medrol			1	No	methylprednizolone	D07AA01	tab 16mg , 1x1
51	Medrol			1	No	methylprednizolone	D07AA01	tab 16mg , 1x1
52	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
53	Azathioprine	Mezavant		2	No	azathioprine	L04AX02	tab 50mg, 1x2
54	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
55	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
56	Azathioprine			1	No	azathioprine	L04AX02	tab 50mg, 1x2
57	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
58	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
59	Mezavant	Azathioprine		2	No	mesalazine	A07EC02	tab 500mg , 2x3
60	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
61	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
62	Azathioprine	Mezavant		2	No	azathioprine	L04AX02	tab 50mg, 1x2
63	Medrol			1	No	methylprednizolone	D07AA01	tab 16mg , 1x1
64	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
65	Medrol	Mezavant		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
66	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
67	Remicade	Medrol		2	Yes	infliximab	L04AB02	100mg vial 20ml for injection
68	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
69	Azathioprine			1	No	azathioprine	L04AX02	tab 50mg, 1x2
70	Mezavant	Azathioprine		2	No	mesalazine	A07EC02	tab 500mg , 2x3
71	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
72	Medrol	Mezavant		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
73	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
74	Azathioprine	Mezavant		2	No	azathioprine	L04AX02	tab 50mg, 1x2

75	Azathioprine	Mezavant		2	No	azathioprine	L04AX02	tab 50mg, 1x2
76	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
77	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
78	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
79	Azathioprine	Mezavant		2	No	azathioprine	L04AX02	tab 50mg, 1x2
80	Medrol	Mezavant		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
81	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
82	Azathioprine	Medrol		2	No	azathioprine	L04AX02	tab 50mg, 1x2
83	Medrol			1	No	methylprednizolone	D07AA01	tab 16mg , 1x1
84	Methotrexate			1	No	methotrexate	L01BA03	tab 2.5mg , 5x1 every 2days/week
85	Medrol	Azathioprine		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
86	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
87	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
88	Azathioprine	Mezavant		2	No	azathioprine	L04AX02	tab 50mg, 1x2
89	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
90	Azathioprine	Medrol		2	No	azathioprine	L04AX02	tab 50mg, 1x2
91	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
92	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
93	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
94	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
95	Medrol	Mezavant	Methotrexate	3	No	methylprednizolone	D07AA01	tab 16mg , 1x1
96	Azathioprine			1	No	azathioprine	L04AX02	tab 50mg, 1x2
97	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
98	Remicade	Medrol		2	Yes	infliximab	L04AB02	100mg vial 20ml for injection
99	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
100	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
101	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
102	Azathioprine	Mezavant		2	No	azathioprine	L04AX02	tab 50mg, 1x2
103	Medrol	Mezavant		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
104	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
105	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
106	Mezavant	Azathioprine		2	No	mesalazine	A07EC02	tab 500mg , 2x3
107	Medrol	Azathioprine		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
108	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
109	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
110	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
111	Remicade	Medrol		2	Yes	infliximab	L04AB02	100mg vial 20ml for injection
112	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
113	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3

114	Remicade	Azathioprine		2	No	infliximab	L04AB02	100mg vial 20ml for injection
115	Medrol	Mezavant		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
116	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
117	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
118	Remicade			1	Yes	infliximab	L04AB02	100mg vial 20ml for injection
119	Remicade	Medrol		2	Yes	infliximab	L04AB02	100mg vial 20ml for injection
120	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
121	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
122	Mezavant			1	No	mesalazine	A07EC02	tab 500mg , 2x3
123	Medrol	Mezavant		2	No	methylprednizolone	D07AA01	tab 16mg , 1x1
124	Medrol	Mezavant	Methotrexate	3	No	methylprednizolone	D07AA01	tab 16mg , 1x1
125								

Table 3B: Pharmacotherapy Data

AA	Drug Dosage Schema	Number of Chronic Conditions	Type 1 non-IBD chronic condition	Non-IBD Drugs 1	Number of Non-IBD Drugs	Number of ALL Drugs
1	tab 500mg , 2x3	2	asthma	inhaled steroids	1	3
2	5 mg/kg of body weight every 8 weeks	1			1	3
3	tab 16mg , 1x1	2	depression	serotonin receptor inhibitors	1	3
4	tab 500mg , 2x3	1			1	3
5	tab 500mg , 2x3	1			1	4
6	tab 500mg , 2x3	1			1	2
7	tab 16mg , 1x1	1			1	3
8	tab 500mg , 2x3	2	asthma	inhaled steroids	1	2
9	tab 500mg , 2x3	2	dermatitis	fluconazole cream	1	2
10	tab 16mg , 1x1	1			1	4
11	5 mg/kg of body weight every 8 weeks	2	panic disorder	benzodiazepines	1	3
12	tab 500mg , 2x3	2	hypothyroidism	thyroxin	1	2
13	5 mg/kg of body weight every 8 weeks	1			1	3
14	tab 50mg, 1x2	1			1	2
15	5 mg/kg of body weight every 8 weeks	2	hypothyroidism	thyroxin	1	3
16	tab 500mg , 2x3	1			1	2
17	tab 500mg , 2x3	1			1	2
18	tab 50mg, 1x2	2	depression	serotonin receptor inhibitors	1	3
19	tab 50mg, 1x2	1			1	3
20	5 mg/kg of body weight every 8 weeks	1			1	3
21	tab 500mg , 2x3	1			1	2
22	tab 16mg , 1x1	1			1	3
23	40 mg every week	2	asthma	inhaled steroids	1	2
24	5 mg/kg of body weight every 8 weeks	1			1	3
25	5 mg/kg of body weight every 8 weeks	1			1	2
26	40 mg every week	1			1	3
27	tab 16mg , 1x1	1			1	3
28	tab 500mg , 2x3	1			1	2
29	tab 500mg , 2x3	1			1	2
30	tab 16mg , 1x1	1			1	3
31	tab 500mg , 2x3	2	panic disorder	benzodiazepines	1	2
32	5 mg/kg of body weight every 8 weeks	2	depression	serotonin receptor inhibitors	1	2
33	tab 16mg , 1x1	2	hypothyroidism	thyroxin	1	3
34	tab 16mg , 1x1	2	panic disorder	benzodiazepines	1	3
35	tab 16mg , 1x1	1			1	2

36	tab 500mg , 2x3	2	hypothyroidism	thyroxin	1	2
37	tab 500mg , 2x3	1			1	2
38	tab 50mg, 1x2	1			1	3
39	tab 500mg , 2x3	1			1	2
40	tab 16mg , 1x1	1			1	2
41	tab 500mg , 2x3	1			1	3
42	tab 16mg , 1x1	1			1	2
43	tab 500mg , 2x3	1			1	2
44	tab 500mg , 2x3	1			1	2
45	5 mg/kg of body weight every 8 weeks	1			1	3
46	tab 50mg, 1x2	1			1	3
47	tab 50mg, 1x2	1			1	3
48	5 mg/kg of body weight every 8 weeks	1			1	2
49	tab 16mg , 1x1	1			1	2
50	tab 16mg , 1x1	2	depression	serotonin receptor inhibitors	1	2
51	tab 16mg , 1x1	1			1	2
52	tab 500mg , 2x3	1			1	2
53	tab 50mg, 1x2	1			1	3
54	5 mg/kg of body weight every 8 weeks	1			1	2
55	tab 500mg , 2x3	2	hypothyroidism	thyroxin	1	2
56	tab 50mg, 1x2	1			1	2
57	tab 500mg , 2x3	1			1	2
58	tab 500mg , 2x3	1			1	2
59	tab 500mg , 2x3	1			1	3
60	tab 500mg , 2x3	2	irritable bowel	trimebutin	1	2
61	tab 500mg , 2x3	1			1	2
62	tab 50mg, 1x2	1			1	3
63	tab 16mg , 1x1	1			1	2
64	5 mg/kg of body weight every 8 weeks	1			1	2
65	tab 16mg , 1x1	1			1	3
66	5 mg/kg of body weight every 8 weeks	1			1	2
67	5 mg/kg of body weight every 8 weeks	1			1	3
68	tab 500mg , 2x3	1			1	2
69	tab 50mg, 1x2	1			1	2
70	tab 500mg , 2x3	1			1	3
71	tab 500mg , 2x3	2	asthma	inhaled steroids	1	2
72	tab 16mg , 1x1	1			1	3
73	5 mg/kg of body weight every 8 weeks	1			1	2
74	tab 50mg, 1x2	1			1	3
75	tab 50mg, 1x2	1			1	3

76	tab 500mg , 2x3	1			1	2
77	tab 500mg , 2x3	1			1	2
78	tab 500mg , 2x3	1			1	2
79	tab 50mg, 1x2	1			1	3
80	tab 16mg , 1x1	1			1	3
81	5 mg/kg of body weight every 8 weeks	2	panic disorder	benzodiazepines	1	2
82	tab 50mg, 1x2	2	depression	serotonin receptor inhibitors	1	3
83	tab 16mg , 1x1	1			1	2
84	tab 2.5mg , 5x1 every 2days/week	1			1	2
85	tab 16mg , 1x1	1			1	3
86	tab 500mg , 2x3	1			1	2
87	tab 500mg , 2x3	1			1	2
88	tab 50mg, 1x2	1			1	3
89	tab 500mg , 2x3	1			1	2
90	tab 50mg, 1x2	1			1	3
91	tab 500mg , 2x3	2	irritable bowel	trimebutin	1	2
92	tab 500mg , 2x3	2	asthma	inhaled steroids	1	2
93	5 mg/kg of body weight every 8 weeks	1			1	2
94	tab 500mg , 2x3	1			1	2
95	tab 16mg , 1x1	2	irritable bowel	trimebutin	1	4
96	tab 50mg, 1x2	1			1	2
97	5 mg/kg of body weight every 8 weeks	1			1	2
98	5 mg/kg of body weight every 8 weeks	1			1	3
99	tab 500mg , 2x3	1			1	2
100	tab 500mg , 2x3	1			1	2
101	tab 500mg , 2x3	1			1	2
102	tab 50mg, 1x2	1			1	3
103	tab 16mg , 1x1	1			1	3
104	tab 500mg , 2x3	1			1	2
105	tab 500mg , 2x3	1			1	2
106	tab 500mg , 2x3	2	asthma	inhaled steroids	1	3
107	tab 16mg , 1x1	1			1	3
108	tab 500mg , 2x3	1			1	2
109	tab 500mg , 2x3	1			1	2
110	5 mg/kg of body weight every 8 weeks	1			1	2
111	5 mg/kg of body weight every 8 weeks	1			1	3
112	5 mg/kg of body weight every 8 weeks	1			1	2
113	tab 500mg , 2x3	1			1	2
114	5 mg/kg of body weight every 8 weeks	1			1	3
115	tab 16mg , 1x1	1			1	3

116	5 mg/kg of body weight every 8 weeks	1			1	2
117	tab 500mg , 2x3	1			1	2
118	5 mg/kg of body weight every 8 weeks	1			1	2
119	5 mg/kg of body weight every 8 weeks	1			1	3
120	tab 500mg , 2x3	1			1	2
121	tab 500mg , 2x3	2	depression	serotonin receptor inhibitors	1	2
122	tab 500mg , 2x3	1			1	2
123	tab 16mg , 1x1	1			1	3
124	tab 16mg , 1x1	1			1	4
125	tab 500mg , 2x3	1			1	2