PSYCHOLOGICAL STRESS AND ITS THERAPEUTIC IMPLICATIONS IN INFLAMMATORY BOWEL DISEASE

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ABSTRACT

There is increasing evidence that psychological stress and associated mood disorders are linked with, and can adversely affect the course of inflammatory bowel disease (IBD). Stress is perceived to be relieved by smokers, and this, like a lack of knowledge about its adverse effects, and nicotine dependence, could contribute to continued smoking by patients with Crohn's disease (CD). Stress has previously been shown to influence disease course in patients with inactive ulcerative colitis (UC) but its influence in acute severe UC is not known. Emerging trial evidence supports the suggestion that psychologically-orientated therapy may ameliorate IBD-associated mood disorders, but there is no strong data yet to indicate that stress management has a beneficial effect on the activity or course of IBD. In addition gut-focussed hypnotherapy has been successfully used in the setting of functional bowel disorders.

The 4 main hypotheses tested in thesis are:

1. In patients with IBD: (1) poor knowledge of the effects of smoking on their disease and/or (2) high nicotine dependence explain the higher prevalence of smoking in CD than UC
2. Anxiety, depression and stress are more common and worsen outcome in patients with acute severe UC.
3. Stress management in the form of psychotherapy given by a counsellor has a beneficial effect on the activity and course of IBD.
4. Gut-focussed hypnotherapy reduces the relapse rate in patients with UC.

The major findings are as follows:

1. Despite more patients with CD being smokers, they were better informed about the effects of smoking on their own disease than UC patients. Nicotine dependence was no higher in patients with CD than UC. In IBD patients as a whole, nicotine dependence was lower than in smokers' clinic clients and comparable to that of the general population, suggesting that most IBD patients could be weaned off smoking successfully in the IBD clinic.

2. Perceived stress levels are greater in patients with ASUC than in those in remission and anxiety scores are highest in patients newly presenting with UC, but neither stress nor anxiety influenced disease outcome.

3. In IBD patients with psychosocial stress, IBD-focussed counselling may improve not only patients' psychological well-being and stress resolution but also the activity and course of their IBD

4. Gut-focussed hypnotherapy does not have a major clinically useful effect in preventing relapse or altering psychological status in patients with ulcerative colitis who are withdrawing from treatment with thiopurines.

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STATEMENT OF ORIGINALITY

The projects described in the thesis were designed and performed by myself except as stated below:

A draft protocol for the clinical study of hypnotherapy for the prevention of relapse in ulcerative colitis had been prepared prior to my commencement as a Clinical Research Fellow. I completed the protocol, prepared the applications to the Ethics committee, designed the Case Report Form, recruited and monitored the patients, and finally analysed the data.

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CHAPTER 1: INTRODUCTION

This thesis focuses on the role of psychological factors and their management in IBD. The Introduction will firstly provide a brief overview of IBD including its pathogenesis and in particular the role of smoking in IBD; it will then discuss psychological stress and mood disorders, and finally the role of psychological treatments in IBD.

1.1 INFLAMMATORY BOWEL DISEASE

Crohn's disease (CD) and ulcerative colitis (UC) are chronic, relapsing and remitting inflammatory diseases of the gastrointestinal tract. The clinical manifestations of CD and UC are highly variable, with significant diversity in the phenotypes of the diseases. This diversity is manifested by differences in the location and distribution of the diseases, their natural history and disease outcomes

1.1.1 Crohn's disease

CD is characterised by chronic transmural intestinal inflammation affecting any part of the GI tract and often in discontinuation to form skip lesions (1, 2). The Montreal classification defines the age of onset, site and behaviour of disease (3). Behaviour has been divided into 3 categories; inflammatory disease (without the presence of strictures or fistulae), stricturing and penetrating disease (3)

1.1.2 Ulcerative colitis

The inflammation in UC, in contrast to CD, only involves the mucosa with disease confined to the colon, although rarely there may be a backwash ileitis. UC usually starts in the rectum and may extend proximally, with approximately 40-50% of patients exhibiting disease confined to the rectum or sigmoid colon, whereas 25-35% of patients will have a phenotype characterised by extensive disease (total colitis) (4)

1.2 AETIOLOGY

The pathogenesis of inflammatory bowel disease (IBD) is only partially understood, with the involvement of a number of genetic and environmental factors. The role for environmental factors is supported by recent trends in IBD epidemiology.

1.2.1 Genetic factors

Approximately 30% of IBD-related genetic loci are shared between CD and UC. Analyses of the function of the genes and genetic loci implicated in IBD show several pathways that are crucial for intestinal homeostasis, including barrier function, epithelial restitution, microbial defence, innate immune regulation, reactive oxygen species (ROS) generation, autophagy, regulation of adaptive immunity, endoplasmic reticulum (ER) stress and metabolic pathways associated with cellular homeostasis (5) (see Fig 1).

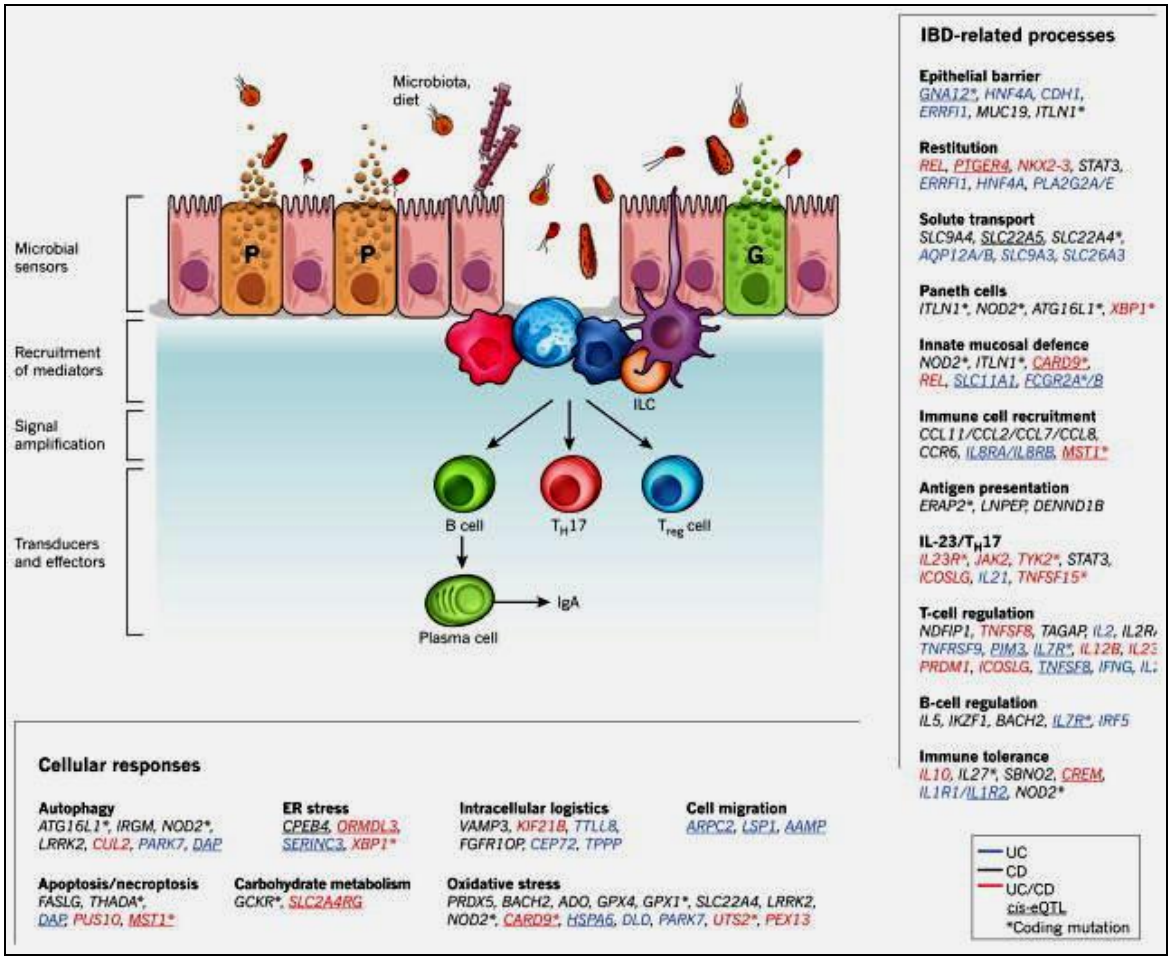
The first IBD-related gene mutations to be identified were three relatively common causal coding variants in NOD 2 (nucleotide-binding oligomerization domain-containing protein 2), otherwise known as CARD 1 (caspase recruitment domain-containing protein 15) (6). In addition, the autophagy genes ATG16L1 (autophagy-related 16-like 1) (7) and IRGM (immunity-related GTpase M) (8) have been shown to be risk factors for Crohn's disease. Within the innate immune response, these polymorphisms in NOD2 and the two autophagy-related genes implicate defects in the recognition and handling of intracellular bacteria contributing to the immunopathogenesis of IBD (further discussed in section 1.2.2.1).

Current genome-wide association scans (GWAS) are typically powered to characterize variants of >1% frequency and do not include the contributions from rare variants (<1% frequency). GWAS have revealed many genetic risk factors for both Crohn's disease and ulcerative colitis (Figure 1). IL-10RA (Interleukin 10 receptor alpha subunit) polymorphisms have been associated with the development of early-onset IBD (9). Re-sequencing studies in IBD have shown both known and new variants of CARD9, NOD2 and IL-23R, with independent effects on disease risk. The IL-23R variants were protective, supporting previous findings of a common protective IL-23R allele. In addition, T helper 17 (T_H17) cells generated ex vivo from subjects with a variant IL-23R allele (R381Q) show decreased production of the pro-inflammatory cytokine IL-17A in response to IL-23 stimulation, emphasizing the importance of IL-23-related pathways in human IBD (10).

Despite the discovery of these new genetic susceptibility loci with GWAS, the identified IBD markers account for only about 20% of the heritable risk (11).

Figure 1 A model for IBD pathways based on GWAS

Intestinal homeostasis involves the coordinated actions of epithelial, innate and adaptive immune cells. Barrier permeability permits microbial incursion, which is detected by the innate immune system, which then orchestrates appropriate tolerogenic, inflammatory and restitutive responses in part by releasing extracellular mediators that recruit other cellular components, including adaptive immune cells. Genetic variants, the microbiota and immune factors affect the balance of these signals. Text colour indicates whether the genes are linked to risk loci associated with Crohn's disease (CD; black), ulcerative colitis (UC; blue) or both (red). Asterisk denotes corresponding coding mutations; *cis*-eQTL effects are underlined. G, goblet cell; P, Paneth cell.



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1.2.2 Environmental factors

1.2.2.1 Gut microflora

The intestinal immune system defends against pathogens and entry into the mucosa of excessive intestinal microbes and at the same time maintains a state of immune tolerance to resident intestinal microbes. Disruption of this homeostasis has been shown in animal models to cause intestinal inflammation and is thought to predispose humans to IBD (12, 13). In transgenic murine models of CD, animals kept under germ-free conditions do not develop inflammation until bacteria are introduced (14).

The diversion of the faecal stream induces clinical improvement in CD which recurs after restoration of bowel continuity or infusion of luminal contents into the bypassed ileum (15, 16); these observations suggest that luminal contents provide a stimulus for intestinal inflammation.

Polymorphisms in patients with IBD (in the genes that regulate microbial recognition and innate immune pathways (e.g. NOD2), genes that control autophagy (e.g., ATG16L1, IRGM), and genes in the interleukin-23 pathway) indicate the important roles of host-microbe interactions in regulating intestinal immune homeostasis (12, 13). These NOD 2/CARD 15 polymorphisms have been shown to cause defective nuclear factor kappa-B activation resulting in inefficient epithelial clearance of invasive bacteria and defective defensin production (17).

In addition, IBD patients exhibit loss of immunologic tolerance to commensal bacteria (18) and alterations in the composition of commensal enteric bacteria including increased Escherichia coli, enterococci, and bacteroides and reduction in bifidobacterium and lactobacillus species (19).

Furthermore, the selective therapeutic manipulation of the enteric bacterial population by antibiotics and probiotics has shown benefit in IBD. In CD, antibiotics including metronidazole (20), ciprofloxacin (21), or in combination (22) have been used in the treatment of active disease and also in the prevention of post operative relapse (23). In pouchitis, metronidazole (24) and ciprofloxacin (25) have been shown to be effective. The probiotic E. coli Nissle has been shown to be as effective as low-dose 5-ASA in preventing relapse of ulcerative colitis (26). In combination, the probiotic VSL 3

(lactobacillus, bifidobacterium and S.salivarium species) prevented relapse of chronic pouchitis after induction of remission by antibiotics (27).

1.2.2.2 Diet

Nutrition has an important role in both the supportive and therapeutic management of IBD. In active CD enteral feeding is an effective primary therapy for patients who can tolerate it (28). In contrast, low fibre, high sugar, high animal fat diets have been proposed as a risk factor for the development of IBD (29, 30). Whilst there are many reports of the possible associations between diet and IBD, there is, as yet, no definitive evidence that diet contributes to the pathogenesis of IBD.

1.2.2.3 Appendectomy

A protective effect of appendectomy in UC has been shown in a meta-analysis of 17 case-control studies with an odds ratio of 0.31 (95% CI 0.26 – 0.37) (31). There is a suggestion that it is the appendicitis, and not the appendectomy which is associated with the reduction in the risk of UC (32). These studies suggest that alterations in mucosal immune responses leading to appendicitis or resulting from appendectomy may negatively affect the pathogenesis of UC. In addition, in some studies appendectomy decreased the risk of colectomy and immunosuppressant use in UC, whilst in CD it was associated with more ileal disease and increased risk of stricture but a lower risk of perianal fistula (33, 34).

1.2.2.4 The oral contraceptive pill

In a meta-analysis, which included the results of nine studies, the pooled relative risk (adjusted for smoking) associated with oral contraceptive use was 1.44 (1.12, 1.86) for CD and 1.29 (0.94, 1.77) for UC (35). These results suggest a modest association between the use of oral contraceptives and the development of CD and UC, also confirmed in a more recent meta-analysis (36).

1.3 SMOKING IN IBD

Smoking has been implicated as a risk factor for developing Crohn's disease (CD) and worsens its outcome (37, 38). Conversely, the onset of ulcerative colitis (UC) may be triggered by smoking cessation and nicotine patches are themselves effective in patients with active disease (39).

1.3.1 Effect of smoking on the risk of developing IBD

The risk of developing CD in active and passive smokers is shown below in Table 1.1. Of note, children who commence smoking aged less than 10 years have the greatest risk for developing CD. Smoking is protective against the development of UC (40-43).

Table 1.1 The effect of active and passive smoking on the risk of developing IBD (40-43).

	ODDS RATIO	**95% CI**
CROHN'S DISEASE		
LIFETIME RISK	2	1.65-2.47
PASSIVE CHILDHOOD	2.04	1.28-3.31
SMOKE CHILDHOOD AGE < 10YRS	3.65	1.44-11.2
SMOKE CHILDHOOD AGE < 15YRS	3.06	1.79-5.38
ULCERATIVE COLITIS		
SMOKERS VS NON-SMOKERS	0.41	0.34-0.48

1.3.2 Prevalence of smoking in IBD

The prevalence of smoking at the time of diagnosis in patients with CD has been reported to be 33-55% (37, 38, 44-47) and in UC 9-28% (44, 46, 47) (Table 1.2).

1.3.3 Effect of smoking and cessation on IBD phenotype and course

In CD, active smoking is associated with disease location; most studies report a higher prevalence of ileal disease and lower prevalence of colonic disease in smokers (37, 45, 48). Furthermore, smokers are more likely to develop stricturing and penetrating disease, higher relapse rates, increased steroid and immunosuppression use (49-52). In addition CD smokers are likely to need more surgery with higher rates of post operative relapse (51). Successful cessation of smoking has been shown to be beneficial in CD with lower relapse rates, steroid and immunosuppression use (53)

In contrast, in patients with UC, smoking has been reported to delay the onset and reduce the need for hospitalisation, oral steroids, colectomy, and is associated with less proximal extension of distal colitis (54-58).

Table 1.2 Prevalence of smoking in IBD patients: at diagnosis and current

STUDY	SMOKING STATUS	CROHN'S DISEASE		ULCERATIVE COLITIS	
		At diagnosis	Current	At diagnosis	Current
Linberg 1992 (45)	Smoker	51%	-	-	-
	Ex-smoker	17%	-	-	-
	Never Smoked	42%	-	-	-
Cosnes 1996 (38)	Smoker	55%	-	-	-
	Ex-smoker + never smoked	45%	-	-	-
Cosnes 1999 (50)	Smoker	-	49%	-	-
	Ex-smoker	-	17%	-	-
	Never Smoked	-	42%	-	-
Cosnes 2004 (41)]	Ever smokers (smokers & ex)	-	61% (Crohn's colitis)	-	42%
	Non smokers	-	39%	--	58%
Lakatos 2004 (44)	Smoker	51%	-	14%	-
	Ex-smoker	6 %	-	18%	-
	Never smoker	43%	-	67%	-
Requeiro 2005 (46)	Smoker	33%	-	9%	-
	Ex-smoker	-	-	-	-
	Never smoked	-	-	-	-
Aldous 2007 (37)	Smoker	44%	-	-	-
	Ex-smoker	13%	-		-
	Never Smoked	43%	-		-
Van der Heide 2009 (47)	Smoker	52%	26%	28%	10%
	Ex-smoker	12.6%	41%	30%	48%
	Never Smoked	35.3%	33%	43%	42%

1.3.4 Mechanisms of the effects of smoking

The mechanisms responsible for the effect of smoking in CD or UC are still unclear. Smoking affects both systemic and mucosal immunity and alters a wide range of both adaptive immune functions. Tobacco smoke contains hundreds of substances, including nicotine and carbon monoxide, which act on different targets: mucus layer, cytokine production, macrophage function, and the microvasculature. These effects may be modulated by gender, genes, disease location and activity, cigarette dose, and nicotine concentration (59). Nicotine may be beneficial by increasing mucin synthesis, decreasing IL-8 expression, and reducing tumour necrosis factor alpha (TNFα) production through its action on the nicotinic acetylcholine receptor. Carbon monoxide has been shown to reduce lipopolysaccaride-mediated secretion of TNFα, increase interleukin -10 (IL-10) and induce heme oxygenase 1, which provides protection against oxidative stress (60, 61).

In CD, increased carbon monoxide may amplify the impairment in vasodilatation capacity in the chronically inflamed microvessel, resulting in ischaemia, and perpetuating ulceration and fibrosis. A defect in bacterial clearance or macrophage deficiency may also have a detrimental role. As mentioned above, genetic predisposition may influence the effects of smoking on CD. In a recent study, use of micro-array analysis of the colonic mucosa in CD smokers compared to CD never smokers, revealed a number of genes (RNF138, MT2A, and STEAP3) to be expressed differently in the inflamed colons of CD smokers (62). Cigarette smoke extract has also been shown to delay TNFα-induced NOD2 mRNA expression and was associated with abnormal NOD2/receptor interacting serine-threonine kinase 2 (RIPK2) interaction (63).

1.3.5 Nicotine dependence

Nicotine dependence is a maladaptive pattern of tobacco use that leads to significant impairment or distress, as defined by the DSM-IV (Diagnostic and Statistical Manual-IV) classification. Nicotine dependence resembles other drug dependence disorders, featuring a pattern of repeated self-administration, tolerance, withdrawal, and compulsive drug-taking behaviours. In the setting of clinical research, several scales have been developed to facilitate measurement of the presence and severity of nicotine dependence, the most commonly used being the six item Fagerström Test for Nicotine

Dependence (FTND) (discussed further in chapter 3) (64). Successful smoking cessation is inversely related to nicotine dependence (65).

Cigarettes are thought to be addictive because they provide a flexible, easy and attractive way of ingesting nicotine. The mechanisms of nicotine addiction involve 3 processes: firstly, nicotine reward via nicotinic acetylcholine receptors in the ventral tegmental area of the midbrain stimulates nucleus accumbens to release dopamine; secondly, nicotine hunger in which the mechanisms of nicotine addiction motivational pathways are altered creating the 'need to smoke'; and finally, nicotine withdrawal leading to adverse mood and depression (64).

In the United Kingdom (UK), about two thirds of smokers declare that they want to stop smoking and just over a half of smokers had made a serious attempt in the last 5 years (66). However, only a small proportion of smokers attempting to stop currently use smoking cessation medications (23%) or attend a specialist cessation service (7%) (66).

1.3.6 Smoking and stress

Although smoking has been implicated to affect the course of CD adversely, patients often use smoking as means to relieve psychological stress (67). As stress has been shown to worsen the course of IBD (see below), this is a conflicting situation for patients. In a recent study, an impulsive sensation seeking personality was suggested to be associated CD current smokers (68). Conceivably, therefore, psychological interventions may have a role in achieving smoking cessation in patients with IBD.

1.3.7 Awareness of the effects of smoking in IBD patients

In a study assessing the knowledge of both doctors (general practitioners) and patients of the adverse effects of smoking in CD, only 2 out of 51 general practitioners and 13 out of 102 patients were aware of the association (69), although this study was carried out early (1996) in our understanding of the effects of smoking in CD. In a subsequent study published in 2003, in which 312 CD patients completed a self-administered questionnaire about the effects of smoking on health and their disease, only 9.5% recognized that smoking increases risk the of development of CD and 12% of re-operation in CD (70).

1.4 THE ROLE OF PSYCHOLOGICAL STRESS IN IBD

Since this thesis focuses on the role of psychological factors and their management in IBD, the remainder of this introduction will discuss these in the context of IBD.

Chronic psychological stress is associated with adverse effects on health (71-73). CD and UC historically were classified as psychosomatic disorders with early studies reporting a close association between IBD and psychiatric diagnoses. Recent well-designed studies have confirmed the anecdotal suggestion that psychological stress can trigger relapse in IBD. Here these topics are outlined before reviewing the evidence assessing psychotherapy and related modalities as therapeutic options in patients with IBD.

1.4.1 Stress

Stress can be defined as a threat or perceived threat to an organism's homeostasis. The initial stimulus (stressor) evokes a reaction in the brain (stress perception) that activates physiological fight-or-flight systems in the body (the stress response) (74). The duration and intensity of the stressor are the key determinants of the immune response to stress. Acute stress, such as narrowly avoiding a road traffic accident, lasts for minutes to a few hours, and causes physiological changes that enable survival, including immune enhancement. Chronic stress such as bereavement lasts for several hours per day, for weeks or months and leads to immunosuppression. Allostasis (the process of returning to stable homeostasis) requires a rapid physiological response to stress that is terminated once the stressor has abated (73).

Stressors. In animal studies, Selye showed that if an organism is severely damaged the resulting physiological and hormonal responses were the same regardless of the mechanism of the insult (75, 76). Selye proposed that the response to stress was dependent on the significance and chronicity of the stressor, suggesting that while stress may enhance function, a concept he termed eustress, persistent stress that cannot be resolved through adaptation leads to anxiety or withdrawal behaviour (distress) (77).

Stress perception. Psychologists challenged Selye's direct application of his results in experimental animals to man, arguing that in order for a psychosocial situation to be stressful, it must be appraised as such (78) and that this primary appraisal is influenced by personality and prior experience in

managing similar stressors (79). The term coping describes the thoughts and behaviours used to manage the internal and external demands of situations that are perceived as taxing (80). Coping theory states that an individual's resilience to stress depends both on their coping resources and the strategies they employ when stressed. Commonly quoted categories of coping behaviour, which are not mutually exclusive, include problem-solving, emotion-oriented, avoidance-oriented and supportant (81).

Physiological Stress Response. Multiple neural circuits are activated in order to meet the physiological demands of stress. In brief, stressful stimuli are relayed from the sensory cortices and ascending brainstem pathways carrying visceral and sensory stimuli to the amygdala, hypothalamus, and peri-aquaductal grey (limbic system) (82).

Once a situation has been appraised as stressful, neurons of the paraventricular nucleus (PVN) of the hypothalamus release corticotrophin-releasing hormone (CRH). CRH, by binding to the CRH1 receptor (CRHr1) activates nuclei of the autonomic nervous system (ANS) in the medulla, leading to the classic 'fight or flight' response mediated through the release of noradrenaline from end efferents and adrenaline from the adrenal medulla. CRHr1 stimulation also leads to activation of the hypothalamo-pituitary-adrenal (HPA) axis. CRH and vasopressin (AVP) are secreted into the portal vessel and in turn stimulate the anterior pituitary to produce pro-opiomelanocortin (POMC) which is processed to melanocortin, opioids and corticotrophin (ACTH) (83). ACTH, through its systemic action on the adrenal cortex leads to the release of cortisol. In the early, rapid phase of the stress response, cortisol binds to its high affinity, mineralocorticoid receptor (MR) in the limbic region of the brain, up-regulating the expression of genes encoding proteins that maintain the stress response, and behavioural vigilance. As serum cortisol levels peak, the low affinity glucocorticoid receptor (GR) is activated, which leads to adaptation. In order to return to normal homeostasis, the hypothalamus, at the same time as releasing CRH, releases two recently described proteins Urocortin II and III, which act on CRH receptor 2 (CRH-r2) (84). In animal models, intracerebroventricular administration of urocortin, in contrast to CRH which mimics the initial behavioural, autonomic and endocrine response to stress, has anxiolytic properties.

The key neurohumoral mediators of the stress response, including cortisol, adrenaline and noradrenaline, are biphasic in their actions, prolonged stress leading to immunosuppression (74).

Allostatic load refers to the physiological costs of chronic exposure to these mediators and is detrimental to health. It is increased by multiple exposures to different forms of stress, an inability to habituate to a repeated single stressor, and or an ineffectively terminated stress response. Inter-individual differences in psychological resilience have significant effects on the kinetics and peak levels of circulating stress mediators; importantly, they account for why some individuals generate stress responses long after the stressor has abated (73, 74).

How stress impacts on the gut is slowly being unravelled, and forms part of the new research field, psychoneuroimmunology, the study of the influence of cognition and emotion on neuroimmune functions (85).

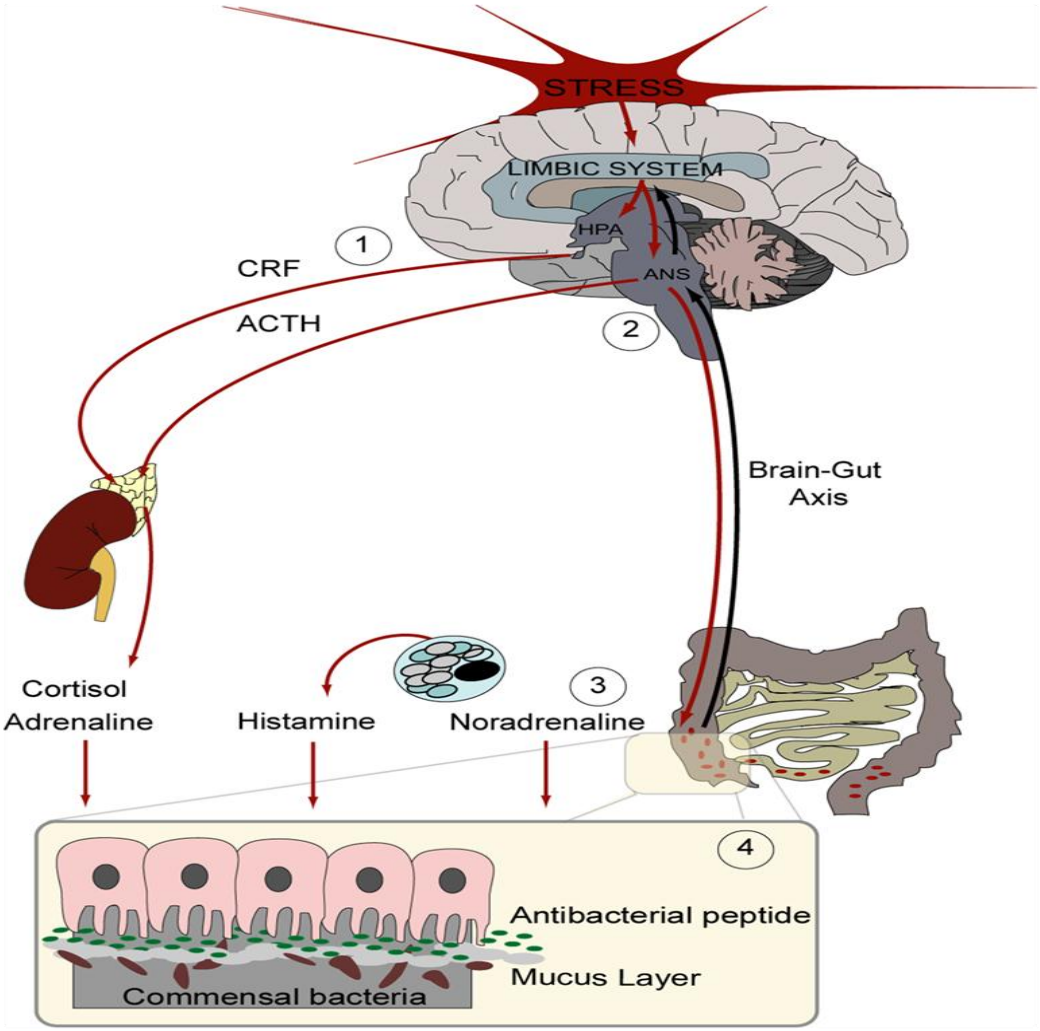
1.4.2 Psychoneuroimmunology of IBD

The enteric nervous system (ENS) contains 100 million neurones and regulates the motility, exocrine and endocrine functions, and the microcirculation of the GI tract. It communicates via efferent and afferent neurones of the sympathetic and parasympathetic nervous system ANS (the 'brain-gut' axis); unlike the other nervous systems in the body it can work without central input from the brain (the 'brain-in-the-gut'). It is now increasingly recognised that the HPA, ANS and ENS can interact directly with the immune system systemically and in the gut wall. Nerve fibres of the ANS form close associations with immunoregulatory cells in gut mucosa, mucosa-associated lymphoid tissue, lymph glands, bone marrow, thymus and spleen, and these cells are known to carry receptors for several neurotransmitters of the ANS, and HPA systems (72) (Figure 1.2).

Experimental stress studies involving the gut in animal models.

Much of what is known about the physiological effects of stress on the gut is extrapolated from rodent models. Standard models of acute stress induce physiological stress in a variety of ways: restraint, in which an animal is wrapped up and its movements restricted (restraint stress); extremes in temperature (cold stress); swimming to avoid drowning (forced swim stress); and pain (inescapable foot shock stress).

Figure 1.2 Psychoneuroimmunological pathways in IBD. Stress, via the limbic system, stimulates the HPA (1) and the autonomic nervous system (2) leading to the production of CRF, ACTH and then cortisol and the catecholamines. Noradrenaline is also released directly into the gut mucosa from sympathetic nerve endings of the ENS (3). In addition, mast cells lying close to enteric nerve endings degranulate releasing tryptase, histamine and other mediators (4). These neuromediators through poorly characterized mechanism, including activation of lymphocytes, stimulate epithelial chloride secretion and mucus production, increase epithelial permeability (both paracellullar, and transcellular across specialized M cells). Subsequent ingress of luminal bacteria into the mucosa triggers further immune and inflammatory events involving dendritic cells, macrophages and other cell types.



Acute stress promotes diarrhoea through increased intestinal chloride ion and water secretion (86), mucin production (87, 88), and by stimulating intestinal motility (87, 89). Acute stress also leads to alterations in nociception, increasing visceral sensitivity to distension stimuli (90), and is detrimental to the integrity of the intestinal barrier. It modulates tight junction protein expression increasing paracellular permeability to luminal bacteria (91-93). Regulation of gut permeability in response to acute stress is complex: cholinergic innervation (94), mast cell degranulation (91), and CRF (95) have all been shown to increase permeability. As well as having effects on intestinal epithelial cells, stress can directly modulate the faecal flora, which, as indicated earlier, is now recognised as playing a central role in the pathogenesis of IBD (12). In rodent models catecholamines have been implicated not only in increasing the numbers of *E.coli* but also their invasive potential (96, 97).

Perhaps more applicable to the effects of chronic psychological stress in man are the water avoidance test, in which an animal is made anxious by placing it on a platform surrounded by water; novelty stress, where animals are housed in new cages alone; and maternal deprivation, an accepted model of depression (98).

In experiments using water avoidance, chronic stress in rats increased colonic motility, mast cell dependent paracellular permeability (99, 100), and transcellular uptake of bacteria across M cells (101). Barrier integrity seems to be further impaired by incorporation of less mature cells as stress increases epithelial cell turnover and apoptosis (102). In related experiments in the skin, stress altered the expression of anti-microbial peptides (103), now recognized as playing a role in the pathogenesis of Crohn's disease (104). Antidepressants (105), PPARγ agonists (93) and probiotics (106) have all been shown to improve the integrity of the intestinal barrier in chronic maternal deprivation stress.

Acute and chronic stress in mouse models has profound effects on mucosal barrier function, leading to mucosal ingress of luminal commensals and subsequent activation of the mucosal gut immune system, which could theoretically worsen inflammation in IBD.

1.4.3 Stress in IBD

1.4.3.1 Experimental stress in animal models of colitis

Experimental psychological stress initiates and can reactivate inflammation in mouse models of colitis. Rats exposed to 4 days of restraint stress developed a more marked inflammatory response to the induction of colitis with trinitrobenzenesulfonic acid (TNBS) than control animals (107). Furthermore, restraint stress in animals that had recovered from TNBS colitis significantly lowered the dose of TNBS required to provoke colitis on rechallenge (108) and alone was enough to re-initiate an early inflammatory response (109). This susceptibility was transferable between mice by a population of CD4 lymphocytes, suggesting that stress primes immune cells, such that lower doses of antigen are required to initiate inflammation (108). The same group has shown that neonatal maternal separation, whilst leading to depression and increasing intestinal permeability, does not spontaneously cause inflammation. However, the severity of the colitis induced by dextran sulphate sodium was greater in adult animals that had experienced maternal separation compared to that occurring in un-separated litter mate controls (105). Furthermore, in subsequent experiments this group has shown that depression in mice reactivates experimental colitis, an effect prevented by desmethylimipramine (110) and mediated by inhibition of the vagal anti-inflammatory pathway acting through nicotinic acetylcholine receptors (111).

1.4.3.2 Experimental stress in human IBD

Experimental studies of the effects of psychological stress in human IBD, unlike in animals, are limited. Inter-individual differences in the appraisal of what constitutes stress makes them difficult to design and inherently they are difficult to blind. Furthermore exposing humans to severe or chronic stress is unethical.

The effects of the cold pressor test, where stress is induced repeatedly for short periods over several days by plunging a hand into iced water have been compared in healthy volunteers and in patients with IBD (112). This sub-acute stress led to activation of the HPA, and of mucosal mast cells, with an increase in mucosal reactive oxygen metabolite (ROM) production which was more marked in IBD patients than controls (112), suggesting that patients with IBD maybe primed for the effects of stress. Using a more acute stress protocol, patients with quiescent UC asked to complete a 50 minute IQ test whilst being distracted by dichotomous music showed increases in rectal mucosal release of ROMs

and tumour necrosis factor alpha (TNFα), and in LPS-stimulated whole blood TNFα, IL-6 and natural killer cell count (113). In addition, patients with UC may have abnormal autonomic function reflecting disturbed stress regulation and influencing relapse rate (114).

Few studies have examined experimental stress in man. Previous work has shown that a 50 minute session of acute mental stress (completing an IQ test while music of different types is played into each ear) causes inflammatory changes in the mucosa of patients with quiescent UC (113). Patients with quiescent UC, in the upper tertile on the basis of their perceived stress questionnaire (PSQ) score, had a greater rate of subsequent relapse (115). Furthermore a negative serum p-ANCA increases the risk of anxiety or depression-related flares of UC (116).

1.4.3.3 Stress as a cause of IBD

Little evidence supports the notion that stress is a primary cause of IBD in humans. In a retrospective study of more than 20,000 Danish parents who had suffered the death of a child, incidence rates of IBD over 16 years of follow up were comparable with those of more than 200, 000 controls (117).The increased incidence of ulcerative colitis observed in south Israeli Bedouin Arabs when re-housed in city flats during the 1960's (118) was as likely related to concurrent improvements in hygiene and/or dietary changes, as to stress, despite the parallels to the spontaneous colitis observed in cotton-top tamarinds (Saguinus oedipus) held in captivity (119).

1.4.3.4 Clinical studies of stress and mood disorders in IBD

Psychological stress has long been reported anecdotally to increase disease activity in IBD (120, 121) and patients with IBD frequently cite stress as a major determinant of relapse (122). Studies testing the hypothesis that psychological disorders are associated with IBD are difficult to design and perform (82, 120, 123-126). They require a long study period to allow a sufficient number of relapses to occur to test for correlation, and a high degree of patient compliance for the collection of detailed diary records of life events and symptoms. There are often confounding changes in medication during the study period. The definition of what constitutes a stressful life-event is variable; furthermore, particular life events, for example bereavement, will cause differing degrees of stress in different individuals. Few studies in IBD, have utilised questionnaires to assess personality type or coping strategies to explore the influence of these factors (125, 126).

1.4.3.5 Psychological stress as a determinant of relapse in IBD

Despite these limitations, a number of well-designed prospective studies conducted over several months, taken together demonstrate a significant association between psychological disorders and relapse of IBD (82, 124, 125). Of 13 longitudinal studies of the course of IBD, 9 reported that stress, adverse life events and/or depression worsened disease activity while 4 reported no effect (see Table 1.3) (115, 121, 127-137). All but one (136) of the negative studies included a mixed IBD patient sample. Studies containing mixed IBD populations are hard to interpret for two reasons. First, stress, through its physiological effects on gut function (see above) may affect standard symptom scores, such as the Crohn's disease activity index (CDAI), in UC and Crohn's to differing extents, particularly in relation to weighting for diarrhoea and well being. Second, it is possible, although unproven, that stress may affect the inflammatory process in different ways in the two forms of IBD.

1.4.3.6 Anxiety and depression in IBD

Psychological stress and stressful life events are well recognized risk factors for depression, and depression like chronic stress is characterized by activation of the HPA and hypercortisolaemia. Whilst all of us experience stress and stressful life events, the lifetime risk of depression in the general population is only 1:6 (138). Data from recent well-designed studies estimates the prevalence of depression in IBD at 25%-35%, double that of the healthy population (139, 140) and significantly greater than in other chronic inflammatory conditions, such as rheumatoid arthritis (141).

In a systematic review of 17 mixed methodology studies, 10 studies compared the prevalence of depression in UC with Crohn's disease: 6 reported that depression was more common in Crohn's disease, 4 were equivocal, and none reported that depression was more common in UC (141).

The prevalence of anxiety in IBD has been reported at 36-43%; factors associated were severe disease and socioeconomic deprivation (142-144). Compared to the general population, young patients with CD have a greater risk of developing anxiety disorders and depression and are more likely to receive psychotropic treatment (145). Mood disorders seem to be more prevalent during symptomatic relapse of IBD in some (146, 147) if not all studies (148).

Table 1.3 Longitudinal studies assessing the association between adverse life events, stress and depression with disease activity in IBD

† Denotes studies showing a positive association with disease activity at inclusion and relapse. (CD denotes CD; UC, Ulcerative colitis; IBD, Inflammatory bowel disease; CDAI, Crohns disease activity index; CAI, Colitis activity index; TWI, Truelove and Witts index; HBI, Harvey Bradshaw Index, SCCAI, Simple Clinical Colitis Activity Index; SRRS denotes Social Readjustment Rating Scale; BDI, Beck Depression Inventory; PLSE, Paykel Life Events Scale; PSQ R & G, Perceived Stress Questionnaire (recent and general); PERILES, Psychiatric Epidemiology Research Interview Life Events Scale; PSS, Perceived Stress Scale; SCL90R, Symptom checklist – 90R; BAI, Beck Anxiety Inventory; BHS, Beck Hopelessness Scale; RLC, multiple Holmes Recent Life Changes; STAI, Spielberger State-Trait Anxiety Inventory; IBDQ, Inflammatory Bowel Disease Questionnaire; PHQ-9, Patient Health Questionnaire 9 items; TAS-20, Toronto Alexithymia Scale – 20 items; SSL-I, Social Support List – Interactions; HS, Hassles Scale; CISS, Coping Inventory for Stressful Situations; HRQL, Health Related Quality of Life; CQ, Coping Behaviour; SF-12, Short Form – 12, MIBDI; Manitoba Inflammatory Bowel disease Index).

Psychological factor	Psychometric tool	Diagnosis of relapse	Patient Sample	Findings	Reference
Life events	SRRS BDI	Symptom scores	32 IBD (24 UC:8 CD)	No association over 2 years	North *et al* 1991 (121)
Life events	PLES HADS	Endoscopy †	92 UC	No association over 3 months	Riley *et al* 1990 (136)
Life events	SRE	Modified DAI	124 IBD (53 UC:77 CD)	Positive association over 6 months	Duffy *et al* 1991 (130)
Life events	PERILES PSS, SC90R	Endoscopy	60 UC	Positive association over 1 month	Bitton *et al* 2003 (128)

Life events	SRRS	CDAI/HBI (CD) † TWI/SCCAI (UC)	163 IBD (76 UC:79 CD)	No association over 11 months	Vidal *et al* 2006 (135)
Perceived stress & coping	HS, PSS, CISS, SCL-90R	CDAI	87 CD	Positive association over 1 year	Bitton *et al* 2008 (127)
Perceived stress	PSQ – R PSQ – G	Endoscopy †	62 UC	Positive association over 2 years	Levenstein *et al* 2000 (115)
Perceived stress	PSS	MIBDI Steroid requirement	451 IBD (176 UC :275 CD)	Positive association over 1 year	Bernstein *et al* 2009 (137)
Depression	BDI, BAI BHS, RLC	CDAI †	18 CD	Positive association 8-12 weeks later	Mardini *et al* 2004 (131)
Depression	BDI, STAI, IBDQ, PSQ, IBDQ	CDAI (CD) CAI (UC)	60 IBD (13 UC:47 CD)	Positive association over 18 months	Mittermaier *et al* 2004 (133)
Depression	PHQ-9, TAS-20, SSL-I	CDAI †	100 CD	Less likely to respond to infliximab	Persoons *et al* 2005 (134)
Depression	BDI, STAI, HRQL, CQ	Endoscopy † CDAI	87 CD	Positive over 4 years	Deter *et al* 2008 (129)
Depression	HADS, SCL-90R, SF-12	CDAI (CD) † SCCAI (UC)	59 IBD (27 UC:32 CD)	No association over 1 year	Mickoka-Walus *et al* 2008 (132)

1.5 ROLE OF PSYCHOLOGICAL TREATMENTS IN IBD

Whatever the mechanisms involved prove to be, if psychological stress does have an adverse effect on the natural history of IBD, then measures which reduce stress should help symptoms and activity of IBD. However, in assessing the efficacy of psychological interventions in IBD, potential improvements in mood and quality of life should not be disregarded, as a holistic approach to patient care should aim to improve not only IBD activity but also patients' general well-being. Unfortunately, appropriately controlled studies using non-pharmacological psychological interventions are difficult to blind and published results of heterogeneous studies are hard to interpret.

Several studies are confounded by the inclusion of mixed IBD populations, varying baseline disease activity, and a reliance on symptom scores as disease activity measures. Disease activity indices using stool frequency are subject to inaccuracy as well as to the effects of stress itself: endoscopic and laboratory indices give more reliable markers of disease activity.

There is also considerable variation in the psychological approaches used, and how they are offered. Psychological approaches are inevitably difficult to standardize and to deliver in a uniform way in clinical trials. Indeed, psychological therapy may be more effective if tailored to the stage of adjustment of individual patients to their IBD (Table 1.4) (149). Differences between and sometimes within studies include the use of different combinations of psychological treatments, individual versus group therapy sessions, the number of sessions given, the frequency and duration of treatments, and the therapist involved.

Despite the difficulties in interpreting published reports as a result of these limitations, a study of 302 patients with IBD using the ADAPT (Assessment of the Demand for Additional Psychological Treatment) questionnaire, showed that a third of patients wanted psychological support (150).

Table 1.4 An approach to selecting the appropriate psychological treatment (adapted from Maunder et al (149)). Interventions are selected according to the stage of adjustment and degree of psychological distress associated with IBD

STAGE OF ADJUSTMENT	**INTERVENTION**
Uncertainty about illness	Education Peer-counselling
Residual uncertainty	Supportive counselling
Distress	Reassess disease activity Relaxation and exercise Hypnosis Cognitive behavioural psychotherapy Antidepressants
Suffering	Psychiatric review

1.5.1 Psychotherapy

Psychotherapy is an interpersonal relational intervention between patient and therapist that employs a range of techniques designed to improve coping mechanisms and thereby mental health (81).

1.5.1.1 Psychoanalytic and psychodynamic psychotherapy

The term psychoanalysis applies to therapeutic procedures pioneered by Freud, entailing free association, dream analysis and transference (151). Psychodynamic therapies, of which there are several sub-types, have their roots in psychoanalytic theory. The central components comprise interpersonal and object relations theory and focus upon the correction of deeply ingrained and insecure patterns of attachment, or problematic ways of relating to others (152). Psychotherapy of these types has not unequivocally been shown to improve the course of IBD or patients' psychological status. Disappointingly few studies have been adequately designed to assess the impact of such psychotherapy on the course of disease: the single study that included endoscopic assessment was confounded by the controls having been poorly matched with respect to psychological status (153), and the remainder compromised by the inclusion of mixed IBD populations, and a reliance on symptom scores as IBD outcome measures (Table 1.5).

One of the earliest studies by O'Connor et al assessing the role of psychotherapy in patients with UC, was published in 1964 (153). 57 patients received individual psychoanalytic psychotherapy. The non-randomized controls were matched by disease severity, sex, age of onset and use of steroids. 56 out of 57 patients in the therapy group had psychiatric diagnoses: schizophrenia (19 patients); psychoneurotic (3); personality disorders (34); in contrast, the control group had fewer psychiatric diagnoses, namely schizophrenia (3 patients), psychoneurosis (3) and personality disorders (14). Patients receiving psychotherapy had up to 104 sessions over a 2 year period. Non-validated symptom scores and proctoscopy were used to evaluate disease activity periodically; these appeared to show improvement in the therapy group over a period of 8 years although no statistical analysis was provided. Likewise, there seemed to be improvement in the psychological status of treated patients, particularly those without schizophrenia.

A series of publications by Jantschek et al and Deter et al, reported the somatic and psychosocial course of 108 patients with Crohn's disease randomized on a 2:1 basis to an individualized psychodynamic psychotherapy and relaxation program carried out over a year, or to standard medical therapy; evaluation of outcome was undertaken at 2 years (154, 155). Neither the number of relapses, defined by CDAI, nor the need for surgery differed between the intervention group and controls. In addition, there were no differences in psychological status (measured using Beck's depression inventory and the State-trait Anxiety Inventory) or quality of life in the two groups. In a later sub-analysis of these patients, psychodynamic psychotherapy was associated with a greater decrease in the number of in-hospital days in the year after it was started in comparison with controls (156), a finding confirmed by a subsequent report focusing on high healthcare utilisers (129).

Lastly, Maunder et al explored the use of weekly supportive-expressive group psychotherapy for 20 weeks in 21 CD and 9 UC patients. There was no change in quality of life, anxiety, depression or IBD symptoms over the course of treatment, although there was a reduction in maladaptive coping (157).

1.5.1.2 Cognitive behavioural therapy

Cognitive behavioural therapy (CBT) is aimed at correcting psychological problems (emotional, cognitive and behavioural) and at improving coping skills to alleviate patient's distress. The main characteristics are that it is time-limited, structured and oriented towards problem-solving (152) with a focus on modifying maladaptive thoughts, in the interest of improving maladaptive behaviour and negative emotions. Unlike psychoanalytic and psychodynamic psychotherapy, CBT focuses on the here and now, rather than on past events and relationships. CBTs in IBD which focus on stress reduction include progressive muscle relaxation and training in coping strategies as well as supportive counselling and disease education. As this treatment has multiple components, it is not possible to dissect out which modality is beneficial in any particular context (Table 1.6).

In a randomized controlled trial of 80 IBD patients, Milne et al assessed whether practising stress management techniques would decrease activity and promote psychosocial functioning in IBD patients (158). The intervention group received six classes on stress management which included autogenics (self-directed relaxation training), personal planning skills and communication techniques. At 1 year, both the CDAI and IBD stress index dropped significantly from baseline in the treatment

group but not in the controls. However, CDAI at baseline was higher in the intervention than in the control group.

In a smaller randomized controlled study, Schwarz et al compared the effectiveness of a multi-component behavioural treatment package in 11 IBD patients, which included IBD education, progressive muscle relaxation, thermal biofeedback, and training in use of cognitive coping strategies, to symptom-monitoring in 10 controls (159). The controls actually improved more than the treated group with regard to symptoms and there were no differences in the psychological outcomes between the groups.

In a prospective study by Mussell et al to determine whether cognitive-behavioural group therapy in addition to standard care is effective in reducing psychological distress, 28 IBD patients completed 12 weekly treatment sessions, followed by a further 3 sessions at intervals of 3 months (160). The sessions consisted of 4 components: education about IBD given by a gastroenterologist; education about the role of cognition and emotions on the generation of distress; training in adaptive cognitive strategies for disease-related and everyday distress; and progressive muscle relaxation. At baseline patients were in clinical remission or had mildly active disease. Disease-related concerns fell during the 9 month follow-up period. Depressive coping also decreased significantly in women but not in men. However, these psychological improvements were not accompanied by any change in IBD activity.

Garcia-Vega and Fernandez-Rodriguez randomly assigned 45 patients with inactive Crohn's disease to stress management (progressive muscle relaxation to lessen the physiological effects of stress and improve coping skills), self-directed stress management (personal planning skills and autogenic training), or as a control group, conventional medical treatment (161). The patients underwent eight individual sessions. The patients who received training in stress management experienced significant post-treatment reductions in tiredness, constipation, abdominal pain and/or distension; whilst those who received training in self-directed stress management experienced a significant reduction in tiredness and abdominal pain; no changes were observed in the control group. Unfortunately, no validated symptom score, or laboratory measure, was used to assess Crohn’s disease activity.

Elsenbruch et al compared the effects of mind-body therapy on cellular immune and neuroendocrine measures, health-related quality of life and disease activity in 15 patients with inactive UC, with those in 15 randomly assigned standard care waiting controls. The mind-body therapy was described as a multi-component lifestyle modification aimed at improving psychosocial and physical well-being by teaching individuals to improve stress hardiness to integrate health-promoting behaviour. Intervention consisted of a structured 60-hour training program over 10 weeks which included stress management training, moderate exercise, Mediterranean diet, behavioural techniques and self-care strategies (162). Quality of life, perceived stress and disease activity were assessed with standard questionnaires. In response to therapy, patients in the intervention group showed significantly greater improvement in the SF-36 scale, Mental Health and the Psychological Health Sum score and IBDQ bowel symptoms compared to the control group. However, no significant differences in circulating lymphocyte subsets or endocrine parameters were observed in response to the active intervention. In a follow-up study, the same group found no discernible effect of this approach on the activity of their UC when patients were re-evaluated after 1 year (163).

In another controlled study by Diaz Sibaja et al, 57 patients with IBD from the Spanish Crohn's Disease and Ulcerative Colitis Association were randomly assigned to a psychological treatment program, or a control group. The intervention modules included illness information, an analysis of factors which may influence illness and an explanation of coping strategies, problem-solving techniques, relaxation, social skill training, distraction, and cognitive restructuring techniques. The treated group showed improvements in anxiety and depression variables when compared to the controls, but unfortunately IBD activity was not assessed (164).

Keefer et al determined the effect of a behavioural self-management program on incidence of flare within 12 months in IBD patients following behavioural intervention when compared to the natural history of flare incidence prior to program participation. Using a regression model the results indicated that those participants in the treatment group were 57% less likely to flare in the following 12 months (compared to 18% in the control group) (165).

In a recent controlled study, by Boye et al, 58 UC and 56 CD patients who had active disease or had relapsed over the previous 18 months with high levels of stress but without any serious psychiatric

disorders, were randomised to receive either usual treatment or usual treatment plus stress management psychotherapy. High stress levels were defined by a perceived stress questionnaire (PSQ) score ≥ 60. The psychotherapy consisted of three group sessions (psycho-education, problem-solving, relaxation) and 6-9 individual sessions based on cognitive behaviour therapy with 1-3 booster sessions at 6 and 12 months follow-up. Patients completed the IBDQ at baseline, 6, 12, and 18 months. The intervention did not improve disease or reduce relapse; however, it increased the IBDQ score. On analysis of UC and CD separately, improvement of IBDQ was only found in the UC group (166).

The studies described above have all focused on adults with IBD. In a report comprising of adolescents, by Szigethy et al, 41 with IBD of heterogeneous type, treatment and severity, together with mild to moderate sub-syndromal depression were randomized to either Primary and Secondary Control Enhancement Therapy-Physical Illness (PASCET-PI), a technique based on cognitive behavioural therapy, or to standard treatment. Depression improved in the intervention group but there were no discernible differences in the change IBD severity between the two groups (167, 168).

Table 1.5 Summary of longitudinal studies examining the effect of psychoanalytic and psychodynamic psychotherapy on IBD activity and associated mood disorders. † Denotes randomized controlled trials. (CD denotes Crohn's disease; UC, Ulcerative colitis; IBD, Inflammatory bowel disease; CDAI, Crohn's disease activity index; WB, Weschsler Bellevue; RT, Rorschach test; TAT, Thematic apperception test; BDI, Beck's depression inventory; STAI, State trait anxiety inventory; PSKB, Psychic and socio-communicative status (Psychischer und sozial-kummunikativer befund); HADS Hospital anxiety and depression scale; QOL, quality of life; QL, Quality of life questionnaire).

Type of Intervention	**Patient Sample (follow up period)**	**Baseline**		**Effect of Intervention (assessment method)**			**Reference**
		IBD activity	**Mood status**	**IBD**	**Mood**	**QOL**	
Individual *(Up to 104 sessions)* *1. Psychoanalysis*	UC 57 Intervention 57 Controls (8 years)	Mixed active / inactive	*Intervention* 56 psychiatric disorder *Controls* 20 psychiatric disorder	Possibly improved (Symptoms, proctoscopy)	Improved (WB,RT TAT)	Not assessed	O'Connor et al 1964 (153)
Individual *(26 sessions over 1 year)* *1. Short term psychodynamic* *2. Autogenic training*	CD† 72 Intervention 36 Controls (2 years)	Mixed active / inactive	–	No effect overall (CDAI); reduced in-hospital days in subgroups	No effect (BDI, STAI, PSKB)	No effect (QL)	Jantschek et al 1998, Deter et al 2007, Deter et al 2008 (129, 154, 156)
Group *(20 sessions over 20 weeks)* *1. Supportive expressive therapy*	IBD 21 CD 9 UC (20 weeks)	Mixed active / inactive	33% depressed 70% anxious	No effect (Symptoms)	No effect (HADS)	No effect (IBDQ)	Maunder et al 2001 (157)

Table 1.6 Longitudinal studies evaluating the effect of cognitive behavioural psychotherapeutic techniques in IBD. † Denotes randomized controlled studies. (CD denotes Crohn's disease; UC, Ulcerative colitis; IBD, Inflammatory bowel disease; CDAI, Crohns disease activity index; CAI, Colitis activity index; HBI, Harvey Bradshaw Index; PCDAI, Pediatric Crohns disease activity index; CSK, Clinical score of Kozarek; QOL, Quality of life; BDI, Beck's depression inventory; STAI, State trait anxiety inventory, CES-D, Center of Epidemiological Studies – Depression scale; SCL-90 R, Symptom check list 90 revised; SCL-90, Symptom check list 90; PSS, Perceived stress scale; HADS, Hospital anxiety and depression scale; CDI and CDI-P, Children's depression inventory, child and parent; K-SADS, Schedule for affective disorders and schizophrenia for school age children – present and lifetime; CGAS, Children's global assessment scale; PCSC, Perceived control scale for children; IBDQ, Inflammatory bowel disease questionnaire; IBD Stress, Inflammatory bowel disease stress index); PSQ, Perceived stress questionnaire.

Type of Intervention	**Patient Sample (follow up period)**	**Baseline**		**Effect of Intervention (assessment method)**			**Reference**
		IBD activity	**Mood status**	**IBD**	**Mood**	**QOL**	
Group (6 Sessions) *1. Personal planning skills* *2. Communication skills* *3. Autogenic training*	IBD† 40 Intervention 40 Controls (1 year)	Mixed active / inactive	_	Improved (CDAI)	_	Improved (IBD Stress)	Milne at al 1986 (158)
Individual *(12 Sessions)* *1. Progressive muscle relaxation* *2. Thermal biofeedback* *3. Cognitive coping strategies* *4. Education*	IBD† 11 Intervention 10 Controls (3 months)	Not clear	_ (excluded major depression, bipolar disorder, schizophrenia)	No effect (symptom score)	No effect (BDI, STAI)	Improvement (IBD Stress)	Schwarz et al 1991 (159)

Group *(15 Sessions)* *1. Psycho-education IBD* *2. Psycho-education cognition and emotion* *3. Adaptive coping strategies* *4. Progressive muscle relaxation*	IBD 14 CD 14 UC (9 months)	Mixed active / inactive	– (excluded psychiatric disorders)	No effect (CDAI, CAI)	Improved in women (CES-D, SCL-90 R)	–	Mussell et al 2003 (160)
Individual *(8 Sessions)* *1. Stress management group* *- progressive muscle relaxation* *- stress management* *2. Self-directed stress management group* *- personnel planning skills* *- autogenic training*	CD† 30 Intervention 15 Controls (12 months)	All inactive	Not assessed	Equivocal (HBI measured at baseline but not at follow up)	Not assessed	Not assessed	Garcia-Vega et al 2004 (161)
Group *(60 hours training)* *1. Stress management training* *2. Moderate exercise* *3. Mediterranean diet* *4. Behavioural techniques* *5. Self care strategies*	UC† 15 Intervention 15 Controls (10 weeks)	Mixed active / inactive	– (excluded psychiatric disorders)	Improved IBDQ bowel symptoms at 10 weeks but not at 1 year (no change in CAI)	No effect (PSS)	Improved (SF-36, IBDQ)	Elsenbruch et al 2005 (162) Longhurst et al 2007 (163)

Group *(10 sessions)* *1. Illness information* *2. Coping model* *3. Problem solving strategies* *4. Social skill training* *5. Distraction* *6. Cognitive restructuring techniques*	IBD 34 CD 23 UC (12 months)	All Inactive	18% depressed 35% anxious	Not assessed	Improved (HADS, BDI, SCL-90)	_	Diaz Sibaja et al 2007 (164)
Individual *(9-11 sessions)* *1. Education CBT, IBD, depression, problem solving* *2. Relaxation skills* *3. Cognitive therapy* *4. Coping skill* *5. Personnel planning*	IBD† (adolescents) 15 CD: 7 UC Intervention 14 CD:5UC Control (12-14 weeks)	Mixed active / inactive	All mild/ moderate subsyndromal depression	No effect PCDAI CSK	Improved (CDI and CDI-P, K-SADS, CGAS, PCSC)	_	Szigethy et al 2007, 2009 (167, 168)
Individual + Group *(9 -15 sessions)* *1.Psycho-education* *2. Problem solving* *3. Relaxation*	56 CD : 58 UC Intervention Control (18 months)	Active	Highly stressed (PSQ≥60)	No effect	-	Improved (IBDQ)	Boye et al, 2011 (166)

1.5.2 Social support/patient groups

Social support and close networks with friends and family are associated with happiness (169) and conversely social isolation is linked with depression and poor health. Attempting to strengthen patients' exogenous coping resources by manipulating their social environment is extremely difficult. Despite being unproven as a way of improving coping strategies and disease course, a supportive relationship between patients, whether in groups or as individuals, and their IBD team is likely to be important, as may be links with patient bodies such as the Crohn's and Colitis Foundation of America (CCFA) and Crohn's and Colitis (UK) (until recently, National Association of Colitis and Crohn's disease).

In the latter context, the effect of a one week IBD summer camp sponsored by CCFA was assessed in children and adolescents with IBD. The IMPACT-II questionnaire (35 questions measuring 6 quality of life domains) and State-Trait Anxiety Inventory were completed at the start and end of the week. Out of 125 individuals who consented to participate, 61 patients (47 CD, 14 UC) completed the questionnaires: improvements were seen in health-related quality of life, bowel symptom scores, social functioning and treatment intervention scores but not in anxiety scores; no formal assessments of IBD activity were undertaken (170).

1.5.3 Disease-specific education

Intrinsic to the forms of psychotherapy detailed above is disease-specific education. Prospective studies designed to evaluate the clinical effect of education in IBD, in the absence of coping training, are disappointing: they suggest that it has little effect on psychological status or disease course, although it may reduce healthcare utilization and increase patient satisfaction (Table 1.7).

There are a number of special difficulties relating to trials involving education programs. Many patients with IBD have complex disease; these require highly qualified staff to provide appropriate explanation and education. Education programs are expensive and time-consuming. What information patients require depends in part on the duration of their IBD, a factor often overlooked in randomly applied studies of the possible benefits of such programs.

In a prospective study, Larsson et al (171) evaluated changes in anxiety in a group-based educational intervention for IBD patients screened for high anxiety using the HADS questionnaire. Of 135 anxious

patients, 49 were recruited for 8 weekly group sessions consisting of medical information about IBD treatment, nutrition and diet, stress and stress management, as well as coping strategies. There was no significant change in the HADS-A score at 6 months in those who participated in the education program although participants reported they had gained better knowledge of their disease. Furthermore, the educational program did not improve IBD activity domains of the IBDQ.

Kennedy et al devised and assessed a broad-based patient-centered approach to IBD self-management (172). 635 patients, according to which of the 19 hospitals they attended, were allocated to intervention or control groups. The active intervention comprised 4 components: a patient guidebook with both lay and evidence-based knowledge about investigation, treatment, and self-management of IBD; a written self-management plan; a patient-centered approach to care provided by a trained clinician; and direct access to services. One year after initiation of the intervention, self-managing patients had made fewer hospital appointments without an increase in the number of primary care visits. Self-reported relapses were fewer in the intervention group, but were unfortunately not confirmed by physician assessment or investigation. There were no differences between the intervention and control groups in IBDQ or HADS scores at the end of the study period.

In a further study by Waters et al, 89 patients with IBD were randomized to either formal group IBD education in addition to standard care or to standard care alone (173). The education program was provided by a nurse practitioner over 4 weeks in 3-hour sessions, consisting of general information about gut and immune system anatomy and physiology, the pathophysiology of IBD, current and future treatments. At week 8, the education group had higher knowledge scores, perceived knowledge ratings and patient satisfaction. They showed a non-significant trend towards better medication adherence and lower healthcare use, but no difference in quality of life questionnaires; unfortunately, no details relating to IBD disease activity were shown.

Bregenzer et al prospectively analysed the effects of an education program in 145 IBD patients: 73 were allocated, on the basis of their distance from home to hospital, to receive 4 group education sessions (each session lasting 2 hours) and the other 72 patients to the control group (174). Each education session was carried out by specialists (gastroenterologists, surgeons, psychologists, social worker and nutrition advisor). The contents of the program included pathogenesis, diagnostic procedures and course of IBD; medical and surgical treatment; nutrition, social problems and support;

and finally stress management and coping with disease. IBD activity, measured using the CDAI or CAI (Colitis Activity Index) after 6 or 10 months, showed no differences between the 2 groups. The educational program also had no effect on depression, quality of life and, surprisingly, disease-related knowledge. However, subjectively most patients were very satisfied with the education program reporting that it improved their ability to self-manage their IBD.

Jaghult et al prospectively investigated whether an education programme could improve health related quality of life in 93 IBD patients. The intervention group attended a multi-professional education programme while the control group received regular information. Four questionnaires were used for measuring health-related quality of life. No significant differences were found when comparing the two groups at 6 months although the multi-professional education programme was highly appreciated by the patients (175).

In a further study by Oxelmark et al, 44 patients with IBD were randomized to either formal group IBD education sessions or to standard care alone (173). The education program consisted of 9 sessions over a 3 month period, provided by a physician, nurses, dieticians, surgeons; of which 4 sessions incorporated group therapy provided by a medical social worker and psychotherapist. The control group received conventional “on demand” medical and psychosocial/psychological treatment during the study period. Although the group-based intervention program was highly appreciated, there were no significant differences in average quality of life (IBDQ) or coping (measured using the Sense of Coherence scale) at month 12 (176).

Taken together, these studies suggest that a proportion of patients with IBD benefit in relation to health-related quality of life and mood disorders from a cognitive behavioural approach; psychodynamic psychotherapy and disease-specific education alone have little if any effect. Although the effects of all these interventions in ameliorating IBD appear disappointing, this could reflect the ‘one-size fits all approach’ necessary for these interventions in randomized controlled trial design, as well as to the difficulties with trial methodology referred to above.

Table 1.7 Longitudinal studies evaluating the effect of education techniques in IBD. † Denotes randomized controlled studies (CD denotes Crohn's disease; UC, Ulcerative colitis; CDAI, Crohns disease activity index; CAI, Colitis activity index; Seo AI, Seo Activity index; HADS, Hospital anxiety and depression scale; QOL, Quality of life; ADS, General depression scale; IBDQ, Inflammatory bowel disease questionnaire; SF-36, social functioning 36 questionnaire; GLQI, Gastrointestinal life quality index; SOC, Sense of Coherence scale.

Type of Intervention (follow up period)	**Patient Sample**	**Baseline**		**Effect of Intervention**			**Reference**
		IBD activity	**Mood status**	**IBD**	**Mood**	**QOL**	
Group *8 sessions x 2-3 hours* (6 months)	26 CD 23 UC	Mixed active / inactive	_	No change (symptom score)	No effect (HADS)	No effect (IBDQ, SF-36)	Larsson et al 2003 (171)
Individual *1 session* (1 year)	92 CD:177 UC† Intervention 139 CD:226 UC Control	Mixed active / inactive	_	Improved self-reported relapse, reduced hospital outpatient attendances	No effect (HADS)	No effect (IBDQ)	Kennedy et al 2004 (172)
Group *4 sessions x 3 hours* (8 weeks)	31 CD:14 UC† Intervention 26 CD:18 UC Control	Mixed active / inactive	Not measured	No details (CDAI, Seo AI)	_	No effect (IBDQ)	Waters et al 2005 (173)
Group *4 sessions x 2 hours* (10 months)	40 CD:33 UC† Intervention 49 CD:23 UC Control	Mixed active / inactive	Depression scale: normal range	No effect (CDAI, CAI)	No effect (ADS)	No effect (GLQI)	Bregenzer et al 2005 (174)
Group (6months)	93 IBD Intervention/ Controls	Remission	-	-	-	No effect	Jaghult et al 2007 (175)
Group 9 sessions (12 months)	24 IBD Intervention 20 IBD Control	Mixed active / inactive	Coping (SOC)	-	No effect (SOC)	No effects (IBDQ)	Oxelmark et al 2007 (176)

1.5.4 Anti-depressants

The effects of psychoactive drugs on disease activity in IBD have not yet been properly evaluated. Anti-depressants are probably the most widely used treatment for depression but they are successful in relieving psychological symptoms in only about 30% patients (138, 177).

Data from a single open label study of paroxetine (20-40mg) in 8 IBD patients with major depression treated for 8 weeks reported improvements in depression and social disability scores but not in IBD activity (178). Uncontrolled case studies which report the use of bupropion in patients with CD have suggested improvement in symptom scores, measured using CDAI (179, 180). In both instances, controlled trials are desirable; in the latter, design and results will need to take into account the effects of bupropion on discontinuation of smoking.

A preliminarily reported randomized placebo-controlled double blind trial of imipramine 10mg/day (titrated to a maximum dose 50mg/day if tolerated) for 8 weeks in 50 patients with mild to moderately active left-sided or distal UC claimed to show that the antidepressant improved both disease activity measured using the Powell-Tuck score and mood status measured using the Hamilton depression score (181). However, the study was compromised by four aspects of trial design. First, patients were randomized regardless of their mood status; at baseline the depression score was higher in the treated patients than in the controls. Second, the tricyclic antidepressant used may have improved the Powell-Tuck score through a direct anticholinergic constipating effect. Third, details of the sigmoidoscopic or laboratory measures of disease activity were not reported. Lastly, the dose of imipramine used was low, in the range frequently used for chronic pain and irritable bowel syndrome (182, 183) .

1.5.5 Exercise

Encouraging physical exercise is moderately effective in reducing stress and depression (184). Recent evidence suggests that a low intensity but not severe exhaustive exercise program may conceivably have a beneficial effect in patients with CD.

In an uncontrolled pilot study to evaluate the effects of regular light-intensity exercise, 12 sedentary patients with inactive or mildly active CD were enrolled into a thrice-weekly, half-hour walking program for 12 weeks. Improvements were seen in the IBD stress index, IBDQ, and Harvey Bradshaw Simple

Index (185). Another Canadian group prospectively compared the effects of a similar low-intensity walking program and of no exercise on the quality of life of 32 patients with mildly active or quiescent CD. Patients in the exercise but not in the sedentary group experienced improvements in IBDQ, IBD Stress Index and Harvey-Bradshaw index after 3 months (186).

1.6 HYPNOTHERAPY

1.6.1 Historical perspective

Franz Anton Mesmer, a Viennese physician, described “animal magnetism” in 1775. Mesmer believed that there is an invisible animal magnetic force or fluid in the atmosphere which he could harness, store in his body, and transmit to physically ill patients with curative effects, leading to the derivation of the word “mesmerism”.

Subsequently the term “hypnosis” (from the Greek “hypnos” meaning sleep) was coined by the Scottish surgeon, James Braid in 1843. It was in the late nineteenth century, when two French physicians, Ambroise Liebeault and Hippolyte Bernheim, built the structure of modern hypnotherapy (based on Braid’s principle of hypnotic induction by suggestion). Their collaborative effort became known as the Nancy School of Hypnotism. At the same time, the French neurologist, Jean-Martin Charcot whilst working at the Salpêtriere in Paris sought to demonstrate hypnosis as similar to hysteria. Charcot's pupils looked for physical signs in the hypnotised person to explain the hypnotic phenomenon.

1.6.2 Induction of trance

Hypnotherapy is a technique by which a practitioner induces a temporary trance-like state in patients: while they are in this state, the practitioner then uses suggestion (Figure 1.3). During hypnotic induction, participants are given a series of instructions, which, if followed, assist in achieving a trance state. Hypnotic procedures are intended to encourage focussed attention, inattention to surroundings, and absorption in the inner mental world. With practice, some people are able to enter the desired state very quickly, either spontaneously or by thinking through a hypnotic procedure. Hypnotic procedures are generally facilitated by encouraging the participant to be non-analytical in their

thinking, increasing the participant's motivation and willingness to actively involve themselves with the procedures, and raising participant's expectancies of a positive outcome.

Hypnotic suggestion is used to influence what a participant is thinking or feeling, and it is widely acknowledged that many of the interesting effects associated with hypnosis are actually brought about by suggestion. Suggestions differ from everyday kinds of instructions in that a 'successful' response is experienced by the subject as having a quality of involuntariness or effortlessness. One widely held belief is that being in a 'hypnotic state' facilitates responsiveness to suggestion. Suggestions are often enhanced by appropriate imagery but can also be produced by direct suggestion without imagery (for example, relaxation: "You are becoming more and more relaxed as time goes by").

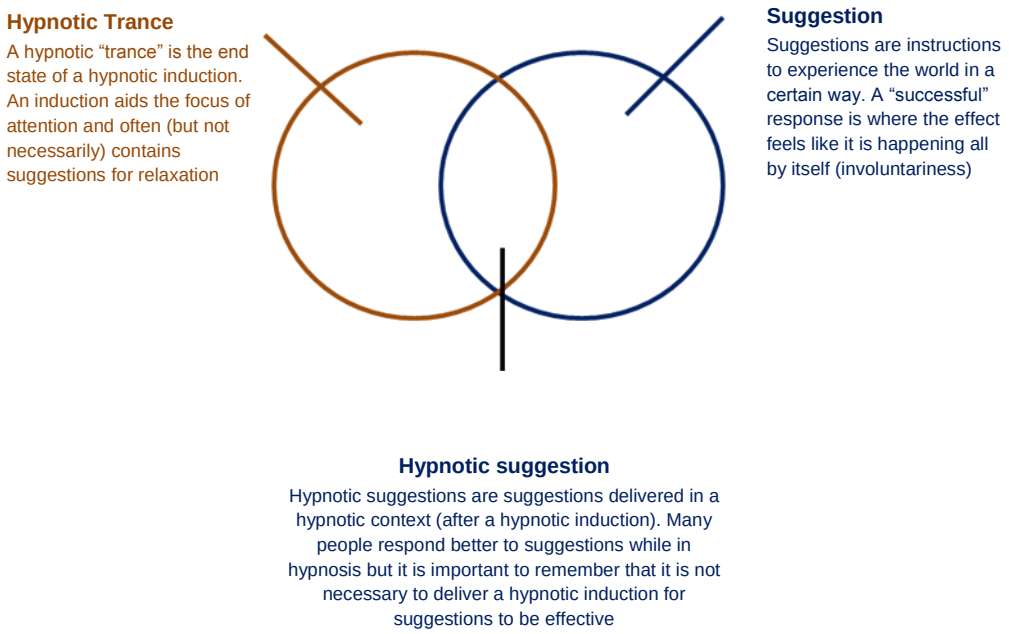
1.6.3 Hypnotherapy in medicine

Hypnotherapy has been used successfully for many years as a treatment for psychological disorders. It has also been used in a variety of medical diseases which are believed to have a psychosomatic component and to be worsened by stress; these include hypertension, asthma, and eczema and psoriasis (187-191).

1.6.4 Hypnotherapy in functional bowel disorders

In relation to its use to date in irritable bowel syndrome and IBD (see below), the practitioner then uses suggestion to induce relaxation as well as beneficial modification of the way in which the patient experiences the gut working (i.e. gut-focussed hypnotherapy). In gastrointestinal disease, hypnosis was first shown to be effective in patients with refractory IBS (192) and later in functional dyspepsia (193), prevention of duodenal ulceration (194) and also non-cardiac chest pain (195).

Figure 1.3 The trance and suggestion elements of hypnosis (adapted from Hypnosis UK 2009)



1.6.5 Mechanism of action of hypnotherapy in GI disorders

The mode of action of hypnotherapy has not been fully elucidated. In addition to psychological influences (196), there is evidence that hypnotherapy can influence gastrointestinal physiology, including motility, visceral sensation, immune function and central pain modulation. In patients with IBS, distal colonic motility has been shown to be reduced by hypnotherapy (197). Furthermore, the orocaecal transit time increased during hypnotic relaxation in healthy volunteers (198). Gut-focussed hypnotherapy has also been shown to normalise rectal sensitivity in patients with IBS (199) and modulate gastric acid secretion (200). Several reports have addressed the effects of hypnotherapy on the immune system. Two studies found that self-hypnotherapy of students antagonised decreases in NK cell T-cell counts induced by the stress of examinations (201, 202); changes in CD3+, CD4+, CD8+ lymphocyte counts before exams were also reduced by self-hypnotherapy (201-203). In our unit, the effects of one session of gut-focussed hypnosis on systemic and rectal mucosal inflammatory responses was assessed in 17 ulcerative colitis patients with active disease; it reduced serum IL-6 concentration by 53%, circulating NK cell numbers by 18%, and at the rectal mucosal level, release of

substance P by 81%, histamine by 35% and IL-13 by 53% (204). In addition, brain imaging techniques have shown that the anterior cingulated cortex plays a role in hypnotic pain modulation (205).

1.6.6 Hypnotherapy in inflammatory bowel disease

There are anecdotal reports, but limited formal data, of the benefit of hypnotherapy in patients with IBD (Table 1.8). In one unblinded study of 12 patients with active UC and Crohn's disease, after 6 weeks of gut-focussed hypnotherapy, there was a non-significant trend to improvement in IBDQ scores (206). More recently, similar findings were reported in 8 women with inactive IBD, in whom there was significant improvement in IBDQ scores (207).

Furthermore, a study of 15 IBD patients with either severe disease or disease refractory to corticosteroids received 12 sessions of gut-focussed hypnotherapy and were followed up for a mean of 5 years (208). 2 of the 15 failed to respond to hypnotherapy and required surgery. Of the remaining 13, 4 were in remission, 8 had mildly severe and 1 moderately severe disease at the end of the study; improvements in quality of life were seen in 12 and most patients managed to stop corticosteroids. These small uncontrolled reports emphasize the need for controlled studies of the efficacy of hypnotherapy in IBD.

More recently, in a paediatric study of 5 CD patients and 1 UC patient with active disease, older children received gut-focussed hypnotherapy whilst the younger children received therapy consisting of relevant stories, breathing techniques and imagery. Most of these patients had severe emotional stress. The children received between 4 and 12 sessions for a period of up to 3 months with no changes in other treatment modalities: they showed resolution of clinical symptoms and a decrease in inflammatory markers (209).

Table 1.8 Case histories and longitudinal studies evaluating the effect of hypnotherapy techniques in IBD. † Denotes randomized controlled study. (CD denotes Crohn's disease; UC, Ulcerative colitis; IBD, Inflammatory bowel disease; CDAI, Crohns disease activity index; IBDQ, Inflammatory bowel disease questionnaire).

Type of Intervention	**Patient Sample (& follow up)**	**Baseline**		**Outcome**		**Reference**
		IBD activity	**Mood status**	**IBD**	**QOL**	
Individual (No of sessions-unclear) *1. Hypnotherapy*	IBD (Adult) 2CD 1 UC (1 year, unclear)	Active	Pt 1 Anger Pt 2.Anger Pt 3.Rage	Pt 1. "cured" in few wks Pt 2. Needed surgery Pt 3. Remission at 1 yr	-	(210)
Individual *(Sessions-unclear, 6 months)* *1. Hypnotherapy* *2. Exercise* *3. IBD Support* *4. Immunosuppression (6-MP)*	1 UC (Adult) (4 yrs)	Active	Moderate depression	No significant flares for 4yrs	-	(211)
Individual (Sessions-unclear, 6 weeks) 1.Gut focused hypnotherapy	12 IBD	Active	-	-	Improvement (IBDQ) (non-significant)	(206)
Individual *(7 sessions over 3 months)* *1. Gut directed hypnotherapy* *+ Audiotape (self)*	IBD (Adult) 4 CD 4UC (12 months)	Inactive	-	-	Improvement (IBDQ)	(207)

Individual *(12 sessions)* *1. Gut focused hypnotherapy*	IBD (Adult) 3 CD 12 UC (5.4 yrs)	Active (on corticosteroids)	-	60% stopped steroids 4 pts remission 8 pts mild active 1 pt moderately active 2 pts no response	Improved	(208)
Individual *(4-12 sessions over 3 months)* *1. Gut focused hypnotherapy* *2. Breathing techniques, imagery*	IBD (Paediatric) 5 CD 1 UC (unclear)	Active	Severe emotional distress	Improvement clinical symptoms Decrease in inflammatory markers	_	(209)
Individual *(12 sessions over 3 months)* *1. Gut focused hypnotherapy*	2 CD (Adults) (6 months)	Inactive (pt1) Active (pt2)	Depression Significant depression	No change No change	No change No change	(212)

1.7 SUMMARY

Patients suffering with IBD vary dramatically in their psychological response to the illness: despite significant morbidity from their IBD, many appear heroically resilient. For those who develop or already have associated psychological stress or other mood disturbances, management should be holistic and, as far as possible, individualized; a cognitive behavioral approach is currently the best-documented option. The reasons for the apparent under-provision of psychological support to patients with IBD are likely to include a failure by gastroenterologists to recognize the benefits in quality of life which can be achieved by addressing concurrent mood disorders, a lack of proof, as yet, of the benefits to IBD itself of most psychological treatments and, in the UK at least, a shortage of health care funding.

Nevertheless, it is clear that at the same time as optimizing conventional treatment of their IBD, physicians should look out, and even formally screen for psychological stress and mood disorders in their patients. They should be ready and able to offer patients therapies directed at improving their psychological state, even if such approaches have not yet been shown to reduce IBD activity. At the very least, physicians should ensure that they have in place routes for prompt referral of their patients to colleagues with expertise in the management of psychological disorders. What remains unclear is which of the wide range of available interventions is most appropriate for individual patients with IBD who have associated psychological illness.

In this thesis we will address the following: firstly, smoking in IBD, in particular a comparison in Crohn's disease and UC of patients' knowledge of the effects of smoking and their level of nicotine dependence; secondly, the prevalence of mood disorders and stress in patients with patients with acute severe ulcerative colitis (ASUC); thirdly, the effects of psychotherapy given by a counsellor specially trained in IBD on the course of IBD in outpatients; and finally, a clinical trial of hypnotherapy for the prevention of relapse in patients with UC.

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CHAPTER 2: HYPOTHESES

The following hypotheses are tested in this thesis.

1) In patients with IBD: (1) poor knowledge of the effects of smoking on their disease and/or (2) high nicotine dependence explain the higher prevalence of smoking in CD than UC.

2) In acute severe UC (ASUC): (1) anxiety, depression and stress are more common in acute severe ulcerative colitis (ASUC) than in patients with inactive UC; (2) anxiety, depression and stress are more common in patients presenting for the first time with UC; (3) anxiety, depression and stress worsen outcome in ASUC.

3) The natural history of IBD can be altered by psychotherapy given by a counsellor specially trained in the management of IBD-related psychological problems.

4) Gut-focussed hypnotherapy reduces the relapse rate in patients with inactive UC after withdrawal from a thiopurine.

CHAPTER 3: TOBACCO DEPENDENCE AND AWARENESS OF HEALTH RISKS OF SMOKING IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

SUMMARY

- It is widely believed, and reported by many smokers, that cigarette usage helps relieve psychological stress.
- We hypothesised that (1) poor knowledge of the effects of smoking on their disease and/or (2) high nicotine dependence would explain the higher prevalence of smoking in CD than UC.
- We therefore assessed: firstly, the prevalence of smoking; secondly, patients' awareness of the effects of smoking; and finally nicotine dependence in IBD patients compared to healthy and disease-matched controls.
- 246 consecutive IBD outpatients completed a questionnaire on smoking habits and its effect on IBD. Smokers were assessed for dependence using the Fagerstrom Test for Nicotine Dependence (FTND) score and their results compared to those of age, sex and ethnicity-matched healthy and asthma controls attending a smoking cessation clinic.
- Patients with CD were better informed about the effects of smoking on their own disease than UC patients but there was no association between patients' knowledge and their smoking behaviour. Nicotine dependence was similar in CD and UC patients; in IBD patients as a whole it was lower than in smokers' clinic clients and comparable to that of the general population. Their low nicotine dependence suggests that most IBD patients could be weaned off smoking successfully in the IBD clinic and referral to a smoking cessation clinic offered to the minority who are highly dependent and others expressing interest in attending.

3.1 INTRODUCTION & AIMS

As outlined in chapter 1, the association between smoking and IBD was first made more than 25 years ago (213, 214). Smoking has been implicated as a risk factor for developing CD and worsens its outcome (39, 215). Conversely, the onset of UC may be triggered by smoking cessation and nicotine patches are themselves effective in patients with active disease (39).

In view of the adverse effects of smoking in CD, and on health in general, it is generally agreed that all patients with IBD should be advised to stop. As discussed in chapter 1, the factors influencing successful smoking cessation include awareness of the harmful effects of tobacco, and the severity of nicotine dependence (216, 217). Although smoking has been shown to affect the course of CD adversely, patients report the use of smoking as a way of relieving stress (67).

3.2 HYPOTHESES & AIMS

We hypothesise that:

(1) poor knowledge of the effects of smoking on their disease and/or

(2) high nicotine dependence would explain the higher prevalence of smoking in CD than UC.

To test these hypotheses, we first assessed the prevalence of smoking in our IBD patients, expecting that it might be lower than in some earlier reports (38, 44, 45). We also assessed patients' awareness of the effects of smoking on their type of IBD. Lastly, we compared the nicotine dependence of our smoking IBD patients with that of the general population (66) and of people attending a smoking cessation clinic, speculating that high nicotine dependence in patients with CD might adversely affect their ability to give up smoking.

3.3 METHODS

3.3.1 Patients and methods

331 consecutive patients with an established diagnosis of IBD (218) confirmed by conventional endoscopic, histological and radiological features attending our outpatient IBD clinic over 6 weeks in November 2008 - January 2009, were issued a questionnaire on smoking habits and its effect on IBD

(Appendix 1.1). 246 patients (173 CD, 73 UC) returned the completed questionnaire (response rate 74.3%). In the questionnaire, patients were asked their current smoking status; ex-smokers were asked when they stopped smoking in relation to their diagnosis and whether this was due to advice from their physician. All IBD patients were asked whether smoking made their type of IBD better, worse or had no effect.

Smokers were assessed for nicotine dependence using the Fagerstrom Test for Nicotine Dependence (FTND) (219) (Table 3.1). FTND is a validated and widely used measure of nicotine dependence in patients; it is a revision of the original Fagerström Tolerance Questionnaire devised in 1978 (220). The FTND score ranges from 0-10 (0-2 very low, 3-4 low, 5 medium, 6-7 high, 8-10 very high dependence).

To check whether smoking habits were markedly different in the 85 patients who did not complete the questionnaire, we assessed the prevalence of smoking in patients who did not respond using their case records, and when necessary by a telephone conversation with the patient.

From our Smoking Cessation Clinic database, we firstly obtained 210 healthy controls (5 subjects for each smoker with IBD) and secondly 44 asthma controls (1 subject for each smoker with IBD) each matched for age, sex and ethnicity to one of the group of smoking IBD patients who responded to the questionnaire. The smoking behaviour of IBD patients was also compared with the 2008/09 United Kingdom (UK) population data from the Office of National Statistics (66).

In addition, the phenotype of the patient was documented using the Montreal classification (3) (Appendix 1.2) based on the most recent conventional endoscopy (gastroscopy and ileocolonoscopy), histology and radiological investigations (barium follow through, MR and/or CT abdomen) prior to their clinic attendance**.** This, together with the use of immunosuppression (thiopurine, methotrexate or anti-TNF therapy) and surgical intervention was related to smoking status. Surgery for CD was defined as any intra-abdominal or perianal procedure, the latter including fistula surgery or the drainage of peri-anal sepsis. For UC, surgery was defined as colectomy.

Table 3.1 The Fagerstrom Test for Nicotine Dependence (FTND) (219).

How soon after you wake up do you smoke your first cigarette?	Within 5 mins	3
	6-30 mins	2
	31-60 mins	1
	> 60mins	0
Do you find it difficult to stop smoking in no smoking areas?	Yes	1
	No	0
Which cigarette would you hate most to give up?	The first of the morning	1
	Any other	0
How many cigarettes per day do you usually smoke?	10 or less	0
	11-20	1
	21-30	2
	30 or more	3
Do you smoke more frequently in the first hours after waking than during the rest of the day?	No	0
	Yes	1
Do you smoke if you are so ill that you are in bed most of the day?	No	0
	Yes	1

3.3.2 Statistical analysis

Differences between the IBD patients and their controls were sought in categorical data using Chi squared test or Fisher exact test and in continuous data using Wilcoxon signed rank (for comparing patients and their matched controls) or Mann Whitney U and Kruskal-Wallis tests (for comparing unpaired data). Outcome measures are shown as median values (ranges). Analysis was performed using GraphPad Prism (version 4.0) and SPSS (version 17.0) statistical software.

3.3.3 Ethical Considerations

This study was designed to assess a clinical service and did not require formal ethical approval, according to UK National Research Ethics Service (NRES) guidelines (221).

3.4 RESULTS

3.4.1 Smoking prevalence

Of the 246 IBD patients completing the questionnaire, 35 of 173 (20%) with CD and 9 out of 73 (12%) with UC were current smokers (p=0.15). Of the remaining 138 CD patients, 86 (50%) had never smoked and 52 (30%) were ex-smokers (Table 3.2). At diagnosis, the prevalence of smoking in CD was 67 of 173 (39%). Of the 52 ex-smokers with CD, 20 had stopped smoking prior to being diagnosed. The remaining ex-smoking 32 CD patients, with disease duration of 8.5 (1-41) years, stopped smoking 4 (1-35) years after their original diagnosis, 19 (59%) as a result of advice from their physician.

Likewise, in UC 36 (49%) patients had never smoked, with the remaining 28 (38%) being ex-smokers (Table 3.2). Of 18 of these UC ex-smokers, 10 stopped smoking 3 (1-15) years prior to their diagnosis.

The prevalence of smoking in the 85 patients who did not respond to the questionnaire was lower than in the study population; 3 of 38 (7.9%) CD and 4 of 47 (8.5%) UC patients who did not complete the questionnaire were current smokers. Of the remaining non-responders, 10 (28%) CD and 7 (15%) UC patients were ex-smokers.

IBD phenotype and previous course in non smokers, ex-smokers and smokers

As shown in Table 3.2, the phenotype of CD differed with regards to age at diagnosis with ex-smokers being significantly older at diagnosis than never-smokers and smokers; this difference persisted when comparing the 20 ex-smokers who stopped prior to diagnosis to the 67 patients who smoked at diagnosis (i.e. 35 current and 32 ex-smokers who gave up after diagnosis) and the 86 never smokers. There were no significant differences in location and behaviour of disease including peri-anal involvement, in the use of immunosuppression or surgery between those patients who had never smoked, ex-smokers and current smokers. In the patients with UC patients, ex-smokers were significantly older at diagnosis; however, smoking status was not related to the extent of disease, the use of immunosuppression or the need for colectomy (Table 3.2).

Table 3.2 Demographics and smoking habits of IBD patients. 35 of 173 (20%) with CD and 9 out of 73 (12%) with UC were current smokers. The phenotype of CD differed with regards to age at diagnosis with ex-smokers being older at diagnosis than never-smokers and smokers; however there were no significant differences in location and behaviour of disease including peri-anal involvement, in the use of immunosuppression or surgery between those patients who had never smoked, ex-smokers and current smokers. In the patients with UC, ex-smokers were significantly older at diagnosis; however, smoking status was not related to the extent of disease, the use of immunosuppression or the need for colectomy

P value for the differences between those patients who have never smoked, ex-smokers and current smokers calculated using the Chi squared test and Kruskal-Wallis. 5 ASA, 5-aminosalicylate, Anti-TNF, anti-tumour necrosis factor (infliximab, adalumimab). * Previous surgery for UC = colectomy.

	Crohn's disease (n=173)				**Ulcerative colitis (n=73)**			
	Never Smoked (n=86)	**Ex-smokers (n=52)**	**Current Smokers (n=35)**	*P value*	**Never Smoked (n=36)**	**Ex-smokers (n=28)**	**Current Smokers (n=9)**	*P value*
Age at testing (median (range) yrs)	34 (18-90)	46 (21-78)	36 (20-71)	*0.007*	36 (18-64)	50 (25-71)	35 (21-54))	*0.14*
Disease duration (yrs)	12 (1-53)	10 (1-41)	10 (1-46)	*0.29*	6 (1-54)	6 (1-39)	7 (3-27)	*0.97*
Age at diagnosis (yrs)	-	-	-	-	25 (7-61)	34 (14-66)	25 (13-49)	*0.03*
Male (no of patients)	44 (51%)	22 (42%)	16 (46%)	*0.59*	22 (61%)	16 (57%)	6 (67%)	*0.81*
Ethnicity Caucasian Asian Afro-Caribbean Oriental	 66 (77%) 12 (14%) 8 (9%)	 47 (90%) 2 (4%) 3 (6%)	 30 (86%) 5 (14%) 0	*0.11*	 21 (58%) 12 (33%) 2 (6%) 1 (3)	 26 (93%) 2 (7%) 0 0	 5 (56%) 3 (33%) 1 (11%) 0	*0.07*
Age at diagnosis A1. <17	 24 (28%)	 6 (11%)	 5 (14%)	*0.0008*	 -	 -	 -	 -

A2. 17-40	55 (64%)	29 (56%)	26 (74%)					
A3. >40	7 (8%)	17 (33%)	4 (11%)					
Location								
L1. Ileal	21 (24%)	17 (33%)	13 (37%)	*0.39*	-	-	-	-
L2. Colonic	18 (21%)	6 (12%)	4 (11%)					
L3. Ileo-colonic	47 (55%)	29 (56%)	18 (51%)					
L4. Upper GI	7 (8%)	2 (4%)	2 (6%)	*0.65*				
Behaviour								
B1. Inflammatory	40 (47%)	21 (40%)	14 (40%)	*0.73*	-	-	-	-
B2. Stricturing	25 (29%	16 (31%)	14 (40%)					
B3. Penetrating	21 (24%)	15 (29%)	7 (20%)					
P. peri-anal	31 (36%)	12 (23%)	8 (23%)	*0.29*				
Extent								
Proctitis	-	-	-	-	5 (13%)	1 (3%)	0	*0.45*
Left					9 (25%)	8 (28%)	2 (22%)	
Total					20 (55%)	19 (67%)	7 (78%)	
Medication								
5 ASA	46 (54%)	23 (44%)	14 (40%)	*0.33*	27 (75%)	24 (85%)	5 (55%)	*0.27*
Steroids	6 (7%)	2 (4%)	2 (6%)	*0.78*	2 (6%)	4 (14%)	0 (0%)	*0.59*
Thiopurine / Methotrexate	49 (57%)	23 (44%)	16 (46%)	*0.28*	15 (42%)	14 (50%)	6 (66%)	*0.46*
Anti-TNF	18 (21%)	5 (10%)	6 (17%)	*0.23*	0	0	1 (11%)	*0.03*
Previous Surgery*	43 (50%)	34 (65%)	20 (57%)	*0.73*	2 (6%)	4 (14%)	3 (33%)	*0.08*
No of operations (median (range))	0 (0-5)	1 (0-3)	1 (1-4)	*0.38*	-	-	-	-

3.4.2 Knowledge of the effects of smoking

Patients with CD were better informed about the effects of smoking on their own disease than were UC patients. 90 of the 173 (52%) CD patients knew that smoking worsens CD, whereas only 15 of the 73 (21%) UC patients knew of the beneficial effects of smoking on their disease (p=0.03). Knowledge was unrelated to smoking status in either CD or UC (p=0.82, p=0.54 respectively). Furthermore, in CD there no difference in knowledge between the current smokers (19 out 35 (54%)) and the ex-smokers (19 out of 32 (59%)), who stopped smoking after diagnosis (p=0.81). 88% CD smokers stated that they were interested in stopping smoking and 33% would consider attending a smoking cessation clinic.

3.4.3 Smoking dependency

In both CD and UC, the FTND scores were significantly lower than in healthy and asthma controls ($p<0.0001$) attending the smoking cessation clinic (Table 3.3). Only 7 of the 35 (20%) CD patients were highly dependent (FTND score ≥ 6). There was no difference in FTND dependence scores between CD and UC patients (p=0.16). In CD, patients' awareness of the adverse effects of smoking was no different in those highly (FTND score ≥ 6) than those less dependent (FTND score ≤ 5) (p=1.0). The number of cigarettes smoked per day in CD (8 (1-20)) was lower than in healthy (20 (2-50)), ($p<0.0001$) and in asthma controls (20 (2-40)) attending the smoking cessation clinic ($p<0.0001$). Similarly, the number of cigarettes smoked per day was again less in UC (5 (2-15)), than in healthy (20 (5-40)) and asthma controls (20 (5-35)) ($p<0.004$, p=0.002, respectively).

Table 3.3. Smoking dependence in IBD patients**.**

In both CD and UC, the FTND scores were significantly lower than in healthy and asthma controls attending the smoking cessation clinic. The Fagerstrom test for nicotine dependence is shown (both median (range) and mean (standard deviation) for ease of comparison to other studies). P values for the differences between CD or UC patients and their corresponding healthy or asthma smoking clinic controls, respectively, calculated using the Wilcoxon signed rank test (2-tailed).

Fagerstrom Test for Nicotine Dependence (FTND) score		
IBD patients	**Healthy controls**	**Asthma Controls**
Crohn's Disease (n=35)		
Median 3 (0-8)	7 (2-10) (p<0.0001)	6 (2-9) (p<0.0001)
Mean 2.69 (2.36)	6.81 (1.77)	6.17 (1.87)
Ulcerative Colitis (n=9)		
Median 1 (0-4)	6 (2-10) (p<0.004)	7 (4-10) (p<0.004)
Mean 1.33 (1.66)	6.26 (1.94)	7.11 (2.15)

3.5 DISCUSSION

3.5.1 Smoking Prevalence

The prevalence of current smoking (20%) in our CD patients was lower than previously reported (26-49%) (47, 50, 68, 222), but comparable to that of the general UK population (22% in 2008/9) (66). Similarly, the prevalence of smoking at diagnosis (39%) was towards the lower end of results from previous studies (33-55%) (37, 38, 44-47). Recently, Van der Heide et al reported smoking habit in a cohort of 380 CD patients over a 10 year period; at diagnosis, the prevalence of smoking was 52% in 1995 but 10 years later, only 26% of patients still smoked (47); a trend similar to the findings in our study.

In our UC patients, the prevalence of current smoking was also low at 12%, comparable to figures reported in an early UK study (8%) (213) and the recent Dutch study (10%) (47), but much lower than in a very recent Greek one (25%) (68) and than in the general population (22%) (66).

There may be several reasons for the low prevalence of current smoking seen in our patients with CD. Firstly, over the last decade there has been increasing education of patients in clinics provided by physicians and IBD nurse specialists, in parallel with the growing evidence of the adverse effects of smoking in CD. Secondly, the overall prevalence of smoking in the general population in the UK has fallen from about 35% in 1982, to 22% in 2008/9 (66), the latter coinciding with the smoking ban in public places in 2007; it is likely that societal factors influenced patients with CD as they have the rest of the population.

3.5.2 Disease phenotype and course

The effects of smoking on phenotype and disease progression in CD have been widely investigated previously (37, 41, 45, 51, 52). Although this study was not designed to assess the influence of smoking status on IBD phenotype or course, we have shown that at diagnosis ex-smokers were older than never or current smokers, an observation which has previously been reported (37) and may reflect a promoting effect of smoking on the development of CD in predisposed individuals. In our study, unlike in others (37, 41, 45, 51, 52), smokers with CD showed no differences from never

smokers with respect to disease location, behaviour or need for immunosuppression or surgery. Our negative findings findings may reflect not only our study design and a type II statistical error related to the low prevalence of smoking in our study, but also the low cigarette consumption and nicotine dependence of our patients.

In UC, smoking has been reported by some (54, 55, 57, 58), but not all authors (223) to delay the onset, to reduce the need for hospitalisation, oral steroids and colectomy, and to be associated with less proximal extension of distal colitis than occurs in non-smokers. Apart from a delayed onset seen in ex-smokers, we again failed to confirm the earlier observations, possibly for the same reasons as for our CD patients. In addition, the delayed onset in ex-smokers may reflect the protective effect of smoking in those with a genetic predisposition to the development of UC.

3.5.3 Knowledge of the effects of smoking

We had hypothesised originally that low levels of knowledge about its effects on their disease would be one factor contributing to a high prevalence of smoking in patients with CD. Indeed, in a study published in 1996, only 2/51 general practitioners and 13/102 patients were aware of the adverse effects of smoking in CD (69), and while in a more recent report, less than 10% of 312 patients with CD recognised that smoking increases the risk of development of CD and 12% of re-operation (70).

In contrast to our expectations, in our study we have shown that most patients with CD (52%), independent of their smoking status, are aware of the adverse effects of smoking on their disease. This may be a result of disease education in the clinic provided by physicians (who have become increasingly aware themselves of the expanding literature), wider access to the internet and education provided by support organisations, such as Crohn's and Colitis UK (formerly the National Association of Crohn's and Colitis). Knowledge of its risks to health is stated by smokers to be a major motivating factor in discontinuing the habit (66), and may explain in part the relative low prevalence of smoking in our CD population. Indeed, in our study more smokers (88%) with CD were interested in stopping smoking than in the general population (67%) (66).

3.5.4 Nicotine dependence

This is the first study to compare nicotine dependence in IBD patients with that in controls attending a smoking cessation clinic. We had expected that high levels of nicotine dependence would be found in smokers with IBD, especially those with CD who were aware of its adverse effects on their disease. In fact, low nicotine dependence was seen in both our CD and UC patients compared to healthy and disease controls attending a smoking cessation clinic. FTND scores in our IBD patients were in keeping with those of smokers in the general population, who in a large recent English study had a mean FTND of 3.1 (67), and in a recent study across 13 countries, had FTND scores of 2.8-4.6 (224). Similarly, a Canadian study reported low nicotine dependence (FTND<3) in 24%, moderate (FTND 3-5) in 43% and high in 33% of patients with CD, a profile of dependence resembling that of the USA population (222). Very recently, mean FTND scores in Greek patients with CD were 4.46 (±0.47, SE) and with UC 2.93 (±0.42), but no control data were quoted (68).

3.5.5 Limitations

We do not have data on our patients' education level and cannot therefore draw any conclusions about the relation between this factor and their knowledge about smoking and Crohns, or nicotine dependence. Furthermore, our interrogation of patients about their knowledge of its effects on IBD was limited.

The socioeconomic status of patients was not assessed in this study, which may be useful tool to further assess nicotine dependence and smoking cessation in IBD patients. The probability of abstinence of smoking after receiving cognitive behavioural therapy and nicotine patches in smokers has been shown to be greater in those with a higher socioeconomic status (225). In addition, smokers with higher income have been reported more likely to intend to quit smoking (226).

3.6 CONCLUSIONS

This study of IBD patients' smoking habits demonstrates that a smaller proportion of CD patients continue to smoke than has been reported previously. However, contrary to our hypothesis, patients with CD who smoke, do so despite recognising the detrimental effects of smoking on their disease. This is not explained by nicotine dependence which in our IBD patients is lower than in smokers' clinic clients and comparable to that of the general population.

Why patients who know the risks incurred by smoking, and who are not highly nicotine dependent continue to smoke is unclear. One speculative explanation might be that psychological stress contributes to their smoking habit (67), but unfortunately we did not assess this, or other mood characteristics, in this study. The level of interest in smoking cessation in our patients with IBD is high. Their knowledge about the risks to health of smoking and their low nicotine dependence suggests that most IBD patients could be helped to stop smoking successfully in the IBD clinic without specialist treatment. It would seem sensible to recommend smoking cessation to all patients, and consider a referral to a smoking cessation clinic to those highly dependent or expressing interest in this approach.

CHAPTER 4: ANXIETY AND PSYCHOLOGICAL STRESS IN ACUTE SEVERE ULCERATIVE COLITIS: PREVALENCE AND EFFECT ON OUTCOME

SUMMARY

- There is increasing evidence that psychological stress and associated mood disorders are linked with, and adversely affect the course of IBD. In this study we assessed whether stress anxiety and depression are more common in, and worsen outcome in acute severe ulcerative colitis (ASUC).

- 39 patients with ASUC requiring hospital admission and intravenous (iv) hydrocortisone with a Baron's sigmoidoscopic score ≥2, completed questionnaires to assess anxiety (Hospital Anxiety & Depression Score (HADS-A and HADS-D)) and stress levels (Perceived Stress Questionnaire). Outcomes were assessed using the Travis criteria (day 3) and colectomy rates at day 70, in relation to upper and lower tertiles of the anxiety, depression and stress scores.

- Although stress and depression scores were similar, anxiety levels were higher in the 11 newly presenting ASUC patients.

- Patients with ASUC had higher stress and depression levels than 27 patients with inactive UC but there was no difference in anxiety scores. There was no difference in those responding to iv hydrocortisone (by Travis criteria) or in day 70 colectomy rates between patients who were highly anxious or highly stressed compared to those less anxious or stressed.

- Perceived stress levels are greater in patients with ASUC than in those in remission and anxiety scores are highest in patients newly presenting with UC, but neither stress, anxiety nor depression influence disease outcome.

4.1 INTRODUCTION

UC is characterised by periods of relapse and remission, about 50% of patients having a relapse in any year (227). Severe exacerbations of UC are classically manifest as six or more bloody stools per day, with one or more of: temperature greater >37.8^{o}C, heart rate>90 bpm, haemoglobin <10.5g/dl or an erythrocyte sedimentation rate (ESR) >30mm/h (228).

Patients with severe attacks need admission to hospital, where the mainstay of treatment is intravenous steroids. Seventy percent of patients treated with intravenous steroids have a clinical response (229), while the remainder need second line treatment; options include ciclosporine, infliximab and surgery. The Travis score (24 hour stool frequency and serum C-reactive protein concentration) measured on the third day of intravenous steroid treatment has a central prognostic role: there is an 85% chance of the patient needing colectomy (or second-line drug treatment) if the number of stools passed daily exceeds 8, or the number of stools passed daily is between 3 -8 together with a serum CRP is >45 mg/L (230).

As indicated in chapter 1, there is increasing evidence that psychological stress and associated mood disorders are linked with, and adversely affect the course of IBD.

4.2 HYPOTHESES

In this study we hypothesised that:

1) anxiety, depression and stress are more common in acute severe ulcerative colitis (ASUC) than in patients with inactive UC

2) anxiety, depression and stress are more common in patients presenting for the first time with UC

3) anxiety, depression and stress worsen outcome in ASUC in that they will make patients less likely to respond to steroids and hence more likely to need second line medical therapy or colectomy.

4.3 METHODS

Study design:

This was a 4-centre (Barts and the Royal London NHS Trust, University College Hospitals NHS Foundation, Guy's and St Thomas' NHS Foundation Trust and West Middlesex University Hospital NHS Trust) prospective study, during the period Jan 2008 – April 2010.

There were 3 studies, one to assess the association between patients' psychological state and disease activity, one to assess its association with a new diagnosis of UC, and one to assess its impact on disease outcome in ASUC:

Study 1: ASUC vs Inactive UC (cross sectional).

Study 2: New diagnosis ASUC vs ASUC in those previously diagnosed with UC (cross sectional).

Study 3: Outcome of patients with ASUC (longitudinal).

4.3.1 ASUC patients

Inclusion criteria:

Inpatients (aged 16-75) with existing UC or first presentation of UC, diagnosed by standard clinical, radiological and pathological criteria (218), suffering an acute severe flare of their colitis. ASUC was defined by patients with a stool frequency > 8 on the day of presentation requiring hospital admission and iv hydrocortisone with a Baron's sigmoidoscopic score ≥ 2 (231). The Baron's sigmoidoscopic score, as shown in Table 4.1, incorporates a range between 0-3: a score of < 2 represents inactive colitis whilst scores of ≥ 2 indicate active disease.

Exclusion criteria:

Patients were excluded if their stool culture or clostridium difficile toxin was positive.

Clinical intervention

Patients were treated with intravenous steroids in the conventional manner (hydrocortisone 100mg qds iv) with their gastroenterologist overseeing their care in the standard way: the attending physicians were unaware of the stress and mood score results. All patients were given prophylactic sc low molecular weight heparin. Written informed consent was obtained.

Table 4.1 Baron's sigmoidoscopic score for assessment of UC (231).

Score	**Mucosal Appearance**
0	Normal
1	Loss of vascular pattern (oedema) but no bleeding
2	Friable, bleeding to light touch
3	Ulcerated and or spontaneously haemorrhagic

Clinical assessment of disease and activity:

Data on disease duration and extent, duration of current relapse, maintenance therapy, Baron sigmoidoscopic score (231), daily stool frequency, C-reactive protein (CRP) and p-ANCA was recorded.

Measurements of anxiety and stress – psychometric questionnaires:

Within 24 hours of admission each participant completed questionnaires to assess stress levels using the Perceived Stress Questionnaire (Recent, R-PSQ, General, G-PSQ) (115) and also anxiety and depression (Hospital Anxiety & Depression Score (HADS-A and -D)) (232).

The perceived stress questionnaire is a validated questionnaire, devised by Susan Levenstein et al (233), to measure psychological stress. It consists of two identical 30 question questionnaires: recent, in which the statements used apply to the *last month*, and general, in which used statements apply to the *last two years* (Appendix 1.3). The score for both recent and general stress levels were stated as the PSQ index ranging from 0 (non-stressed) to 0.99 (highly stressed). In a study of outpatients with quiescent UC, those in the upper tertile on the basis of their general perceived stress questionnaire (G-PSQ) score, had a greater rate of subsequent relapse (115).

The widely used HADS questionnaire consists of a 14 question validated questionnaire, developed to measure anxiety and depression in the hospital setting (Appendix 1.4) (232, 234). The anxiety and depressive subscales are also valid measures of severity of the emotional disorder. Each item is answered by the patient on a four point (0–3) response category so the possible scores range from 0 to 21 for anxiety and 0 to 21 for depression. A score of 0 to 7 is regarded as being in the normal range, a score of 11 or higher indicating probable presence of the mood disorder and a score of 8 to 10 being just suggestive of the presence of the respective state (235).

4.3.2 Inactive UC patients

Inclusion criteria:

Outpatients with UC (aged 16-75) diagnosed by standard clinical, radiological and pathological criteria, with inactive disease. Inactive disease was defined as patients in clinical remission for >3

months together with a Baron's sigmoidoscopic score of < 2 (Table 4.1) (231) and a Simple Clinical Colitis Activity Index (SCCAI) of < 3 (Table 4.2) (236). The Simple Clinical Colitis Activity Index, consisting of scores for five clinical criteria (Table 4.2), has been validated as a measure of clinical activity; a score of < 3 represents clinical remission (236). It has been shown to have a highly significant correlation with the Powell-Tuck Index (r=0.959, p<0.0001) which also incorporates sigmoidoscopy (236, 237).

Exclusion criteria:

Patients were excluded if there was a change in UC medication in the previous 3 months or if they were currently using topical therapy (5-ASA or steroid).

4.3.2 Outcome measures

4.3.2.1 Study 1: ASUC vs Inactive UC

The psychometric scores (HADS-A & D and PSQ-R & G) of the ASUC patients were compared to those of the 27 outpatients with inactive UC.

4.3.2.2 Study 2: ASUC (new diagnosis vs previously diagnosed)

The psychometric scores (HADS-A & D and PSQ-R & G) of the newly diagnosed ASUC patients were compared to those with ASUC previously diagnosed.

4.3.2.3 Study 3: ASUC (clinical outcomes)

Clinical response was assessed after 3 days of intravenous steroids. Non-responders were defined as those patients whose bowel frequency was >8/day or CRP>45 mg/L, according to the Travis' criteria [3]. Use of second line medical therapy (ciclosporine/infliximab) and colectomy rate at day 70 was recorded

Using a similar design to that of Levenstein et al (115), we compared clinical outcomes, using the Travis criteria (day 3) and colectomy rates at day 70, between patients with anxiety, depression and stress scores in the upper and lower tertiles.

Table 4.2 The Simple Clinical Colitis Activity Index

Symptom	Score
Bowel Frequency (day)	
1-3	0
4-6	1
7-9	2
>9	3
Bowel frequency (night)	
1-3	1
4-6	2
Urgency of defaecation	
Hurry	1
Immediately	2
Incontinence	3
Blood in stool	
Trace	1
Occasionally frank	2
Usually frank	3
General well being	
Very well	0
Slightly below par	1
Poor	2
Very poor	3
Terrible	4
Extracolonic features	1 per manifestation
Total Score	

4.3.3 Statistics

The study population was divided into three tertiles on the basis of their Perceived Stress Questionnaire (PSQ-R &G) results. The proportions of patients who responded to intravenous steroid therapy in the most 'stressed' upper tertile was compared with the response rate in the lower tertile and analysed by chi-squared analysis. Similar analyses were undertaken for the HADS-A and HADS-D questionnaires.

We calculated that a sample size of 69 patients (23 in the low-stress tertile and 23 in the high-stress tertile, with the middle tertile being excluded in this analysis) would enable us to detect a clinically important difference of 40% (estimating an 80% response rate in the low-stress group and 40% in the highly stressed group) in the response rate to intravenous steroids, with power 80% and P=0.05 (238).

Differences between the ASUC patients according to psychological tertiles and between their inactive UC controls were sought in categorical data using Chi squared test or Fisher exact test and in continuous data using Mann Whitney U test. All P values were 2-tailed. Outcome measures are shown as median values (ranges). Analysis was performed using GraphPad Prism (version 5.0, San Diego, California) and SPSS (version 17.0) statistical software.

4.3.4 Ethical considerations

This study received formal ethical approval from the UK National Research Ethics Service (reference no: 08/H0703/23).

4.4 RESULTS

Studies 1-3: Patients recruited

39 ASUC patients (aged 28 (18-74) yrs (median (range)); disease duration 10 (0-240) months) and 27 patients with inactive disease (aged 36 (22-65) yrs (median (range)); disease duration 121 (22-370) months) were recruited (Table 4.3).

Table 4.3 Baseline demographics of ASUC and inactive UC patients. There was no significant difference in age, gender nor disease extent between those with ASUC compared to those with inactive UC. Those in the ASUC group had a shorter disease duration, higher Baron's sigmoidoscopic score and CRP (mg/L) compared to those with inactive disease.

	ASUC (n=39)	Inactive UC (n=27)	P value
Age	28 (18-74)	36 (22-65)	0.09
Male	23 (59%)	16 (59%)	1.0
Disease extent			
Proctitis	0 (0%)	0 (0%)	0.58
Left	12 (31%)	6 (22%)	
Extensive	27 (69%)	21 (78%)	
Disease duration (months)	10 (0-240)	121 (22-370)	<0.0001
Baron's Score	2 (2-3)	1 (0-1)	<0.0001
CRP (mg/l)	64 (6-248)	<5 (1.1-11.7)	<0.0001

4.4.1 Stress, Anxiety and Depression

Study 1: ASUC vs Inactive UC

Patients with ASUC had higher stress levels (R-PSQ Index 0.52 (0.18-0.94) (median (range)), G-PSQ 0.48 (0.10-0.93)) and higher depression scores (HADS-D 6 (0-17)) than patients with inactive UC (R-PSQ 0.36 (0.12-03.66), p= 0.001, G-PSQ 0.38 (0.18-0.76), p=0.046, HADS-D 3 (0-9) p=0.046 respectively) [Figures 4.1 and 4.2] but there was no difference in anxiety scores between the 2 groups (HADS-A: 10 (0-21), 8.0 (0-15), p=0.18, respectively) [Figure 4.2].

In patients with ASUC, there was a positive correlation between stress and both anxiety scores (R-PSQ, r2=0.27, p=0.001; G-PSQ, r2= 0.14, p=0.02)) [Figure 4.3(i)] and depression scores (R-PSQ, r2=0.29, p=0.0004; G-PSQ, r2= 0.11, p=0.036)) [Figure 4.3(ii)]. The positive correlation between stress and anxiety (R-PSQ, r2=0.33, p=0.002; G-PSQ, r2= 0.30, p=0.004)) [Figure 4.3(iii)] was also seen in the inactive UC patients in this group but there was no correlation with depression (R-PSQ, r2=0.01, p=0.71; G-PSQ, r2= 0.05, p=0.29)) [Figure 4.3(iv)].

Study 2: Previously diagnosed vs new diagnosis UC

Although stress and depression scores were similar, anxiety levels were higher in the 11 newly presenting ASUC patients (12 (3-18)) (median(range)) than in those previously diagnosed (9 (0-21), p=0.049) [Fig 4.4].

Figure 4.1 Study 1: Stress levels in ASUC compared to inactive UC. Patients with ASUC had higher stress levels than in patients with inactive UC. Median values shown.

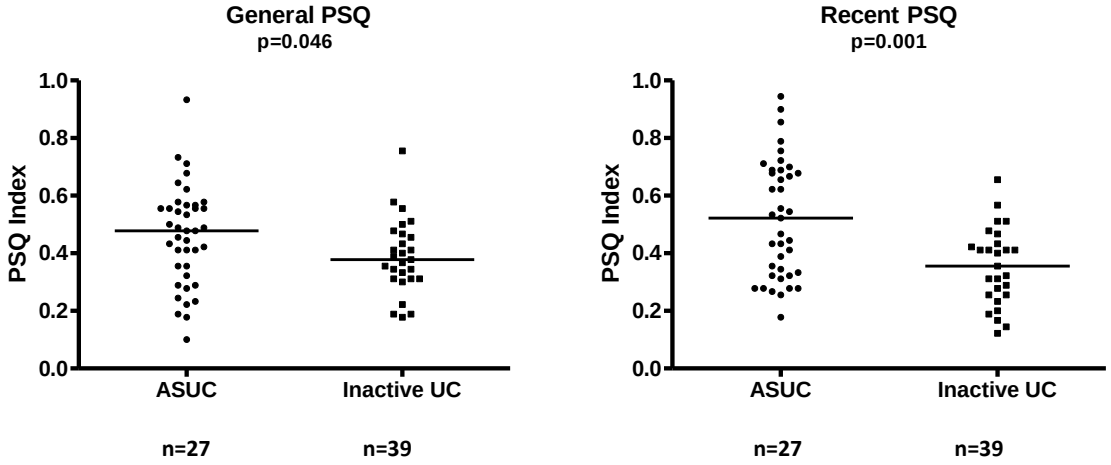


Figure 4.2 Study 1: Anxiety and depression levels in ASUC compared to inactive UC. Patients with ASUC had similar anxiety scores but higher levels of depression than patients with inactive UC. Median values shown.

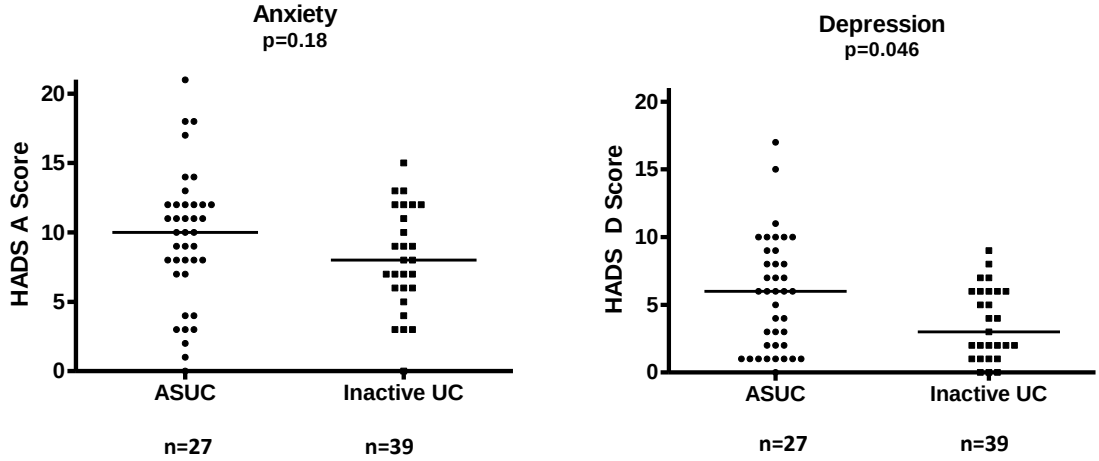


Figure 4.3(i) Correlation of (A) recent stress and (B) general stress with anxiety in ASUC. In patients with ASUC, there was a positive correlation between stress and anxiety.

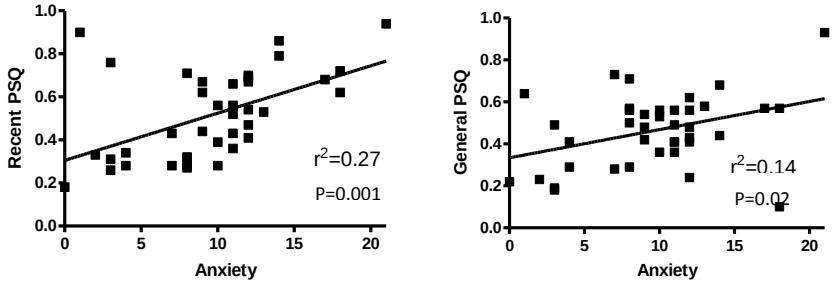


Figure 4.3(ii) Correlation of (A) recent stress and (B) general stress with depression in ASUC. In patients with ASUC, there was a positive correlation between stress and depression.

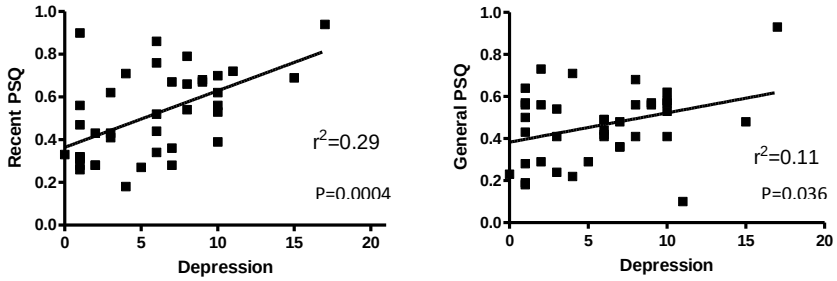


Figure 4.3(iii) Correlation of (A) recent stress and (B) general stress with anxiety in inactive UC patients. In patients with inactive UC, there was a positive correlation between stress and anxiety.

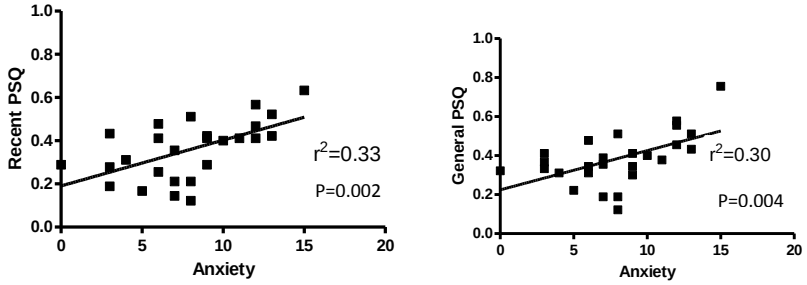


Figure 4.3(iv) Correlation of (A) recent stress and (B) general stress with depression in inactive UC patients. In patients with inactive UC, there was no correlation between stress and depression.

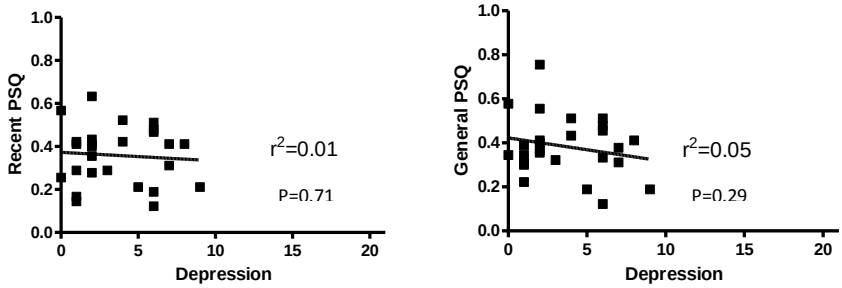
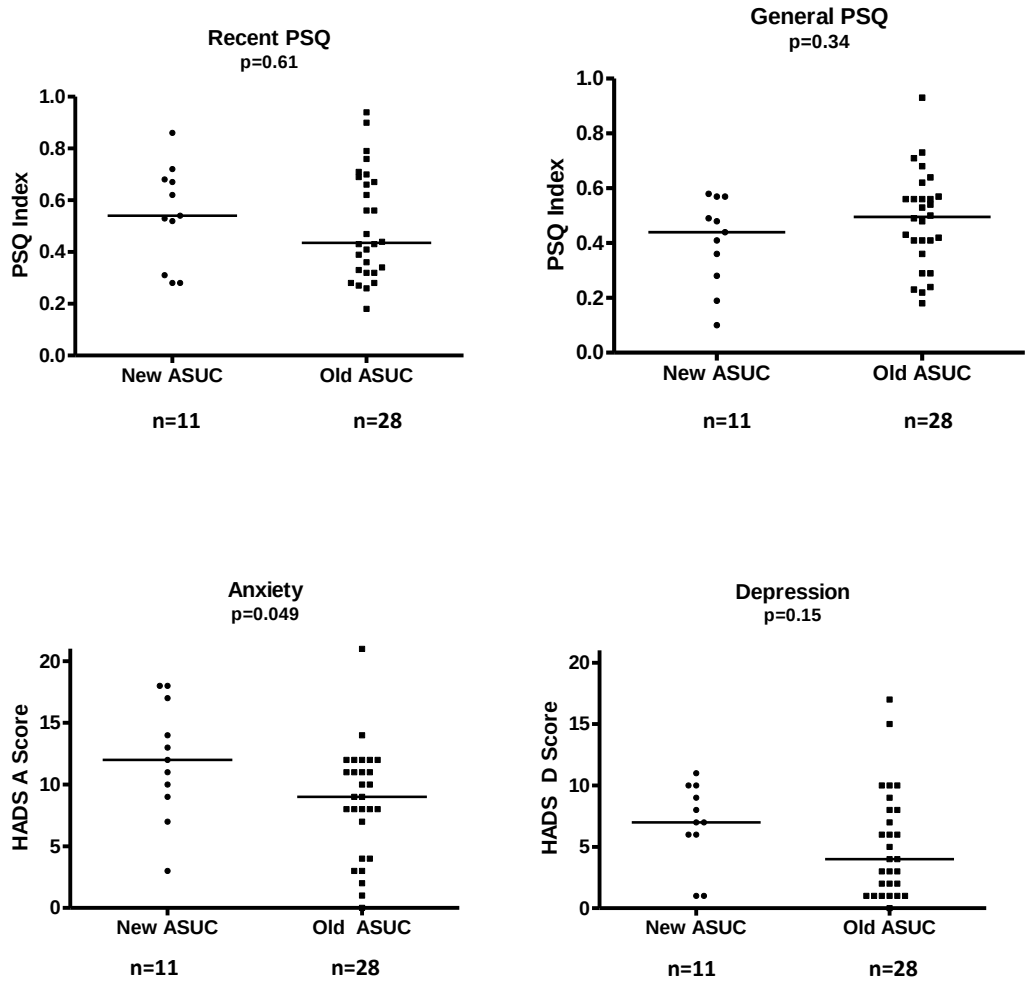


Figure 4.4 Perceived stress, anxiety and depression scores in newly diagnosed ASUC compared to previously diagnosed UC. Although stress and depression scores were similar, anxiety levels were higher in the newly presenting ASUC patients than in those UC patients previously diagnosed. Median values shown.



4.4.2 Study 3: Clinical outcomes

Overall clinical outcome

16/39 (41%) patients did not respond to iv hydrocortisone by Travis criteria (day 3). 11/39 (28%) commenced on 2nd line medical therapy and 9/39 (23%) needed colectomy by day 70. All patients had were given 2nd line medical therapy prior to colectomy. Overall colectomy rates for the ASUC group independent of their psychological state at baseline is shown in Figure 4.5.

ASUC outcome according to psychological state

There was no significant difference in those responding to iv hydrocortisone (by Travis criteria) or in day 70 colectomy rates (Fig 4.6) between patients who were highly (upper tertile) anxious (Travis response 8/13, colectomy rate 2/13), highly (upper tertile) depressed (Travis response 6/13, colectomy rate 3/12) or highly (upper tertile) stressed (R-PSQ: Travis response 8/12, colectomy rate 6/13; G-PSQ Travis response 5/13, colectomy rate 4/13) compared to those less (lower tertile) anxious (5/13 (p=1.0), 3/13 (p=1.0), respectively), depressed (lower tertile) (Travis response 7/13 (p=1.0), 1/13 (p=0.59) or stressed (lower tertile) (R-PSQ, 5/13 (p=0.44), 1/13 (p=0.08); G-PSQ 5/12 (p=1.0), 1/13 (p=0.32), respectively) (n=12 represents incomplete questionnaire completion by one individual).

Figure 4.5 Kaplan Meier survival curve to colectomy in patients with ASUC (n=39). At day 70, 9/39 (23%) of the ASUC patients needed colectomy (day 70).

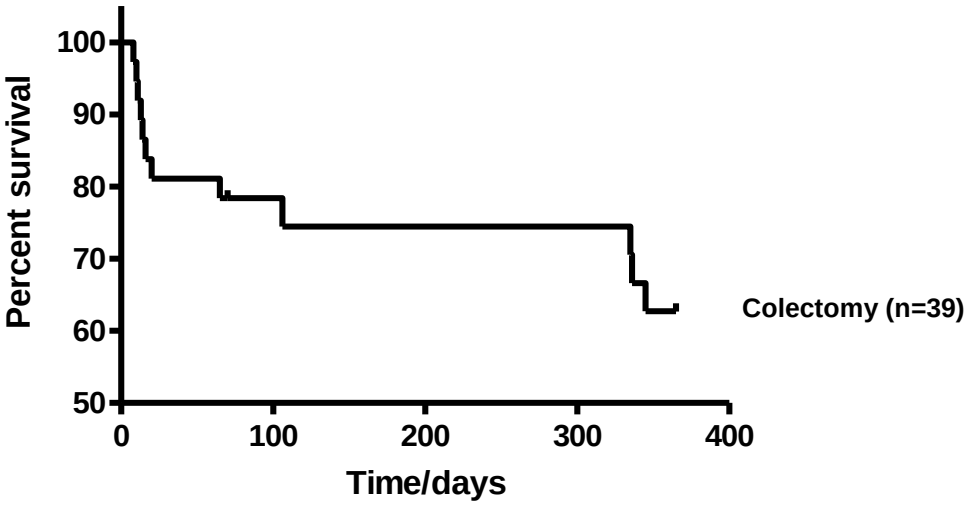
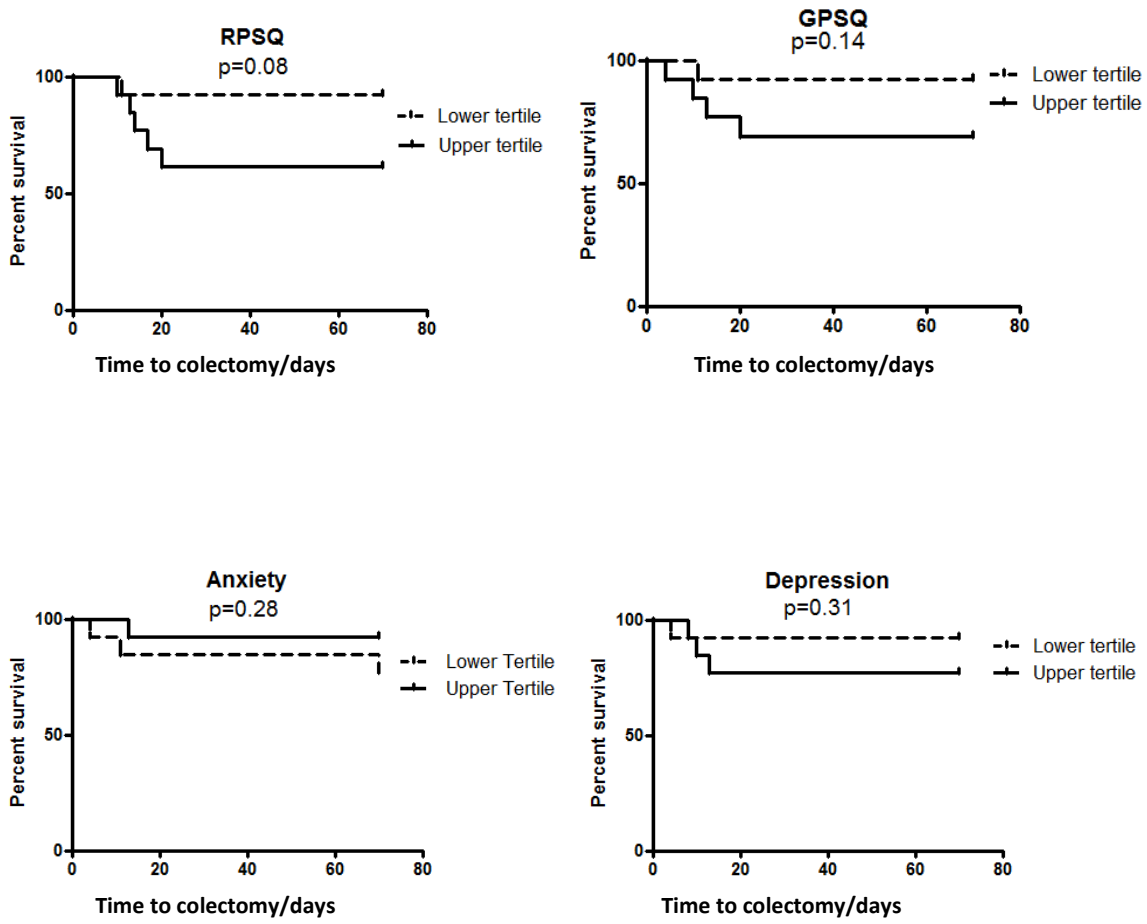


Figure 4.6 Kaplan Meier survival curves to colectomy in patients with ASUC according to upper and lower tertiles of stress, anxiety and depression. There was no difference in colectomy rates at day 70 between patients who were highly (upper tertile) stressed, anxious or depressed stressed compared to those less so (lower tertile).



4.5 DISCUSSION

In recent years, there has been increasing recognition by doctors and patients that psychological distress and depression are common in, and can worsen the course of IBD (see Chapter 1).

Study 1: ASUC vs Inactive UC

This study has shown that perceived stress levels and depression scores are greater in patients admitted with ASUC than in those in remission. It may be as a result of hospital admission that these patients appeared to be more stressed and depressed than those with inactive disease. However it could also be argued that it was the effect of being more stressed and depressed that caused severe active disease. Furthermore, anxiety was associated with perceived stress (in both inactive and active disease), whereas depression was associated with perceived stress in patients admitted with active disease (ASUC group). Although we did not study this, in a separate cross sectional survey of mood disturbances from our unit, anxiety and depression were significantly more common in patients with IBD than in healthy controls (239).

Study 2: Previously diagnosed vs new diagnosis UC

Our results in study 2 show that although stress scores were similar, anxiety levels were higher in the newly presenting ASUC patients than those with longstanding disease; this is a perhaps not unsurprising consequence of 'fear of the unknown'. As discussed in chapter 1, Maunder and Esplen (see Table 1.4) (149) suggest that the process of normal adjustment to IBD depends on the interaction of a triad of illness uncertainty, loss and change, and suffering. They suggest that maladaptive coping leads to anxiety and depression and propose a step-wise escalation of psychological interventions appropriate for each stage of adjustment.

Study 3: Clinical outcomes

As far as we are aware, study 3 (longitudinal) is the first study to assess clinical outcome in patients admitted with ASUC according to psychological status. Our study design was based on a that of a previous study by Levenstein et al, in which patients with quiescent UC, in the upper tertile on the basis of their perceived stress questionnaire (PSQ R or G) score, had a greater rate of subsequent relapse (115).

We found that neither stress nor mood significantly influence outcome of acute severe UC. There was no difference in those responding to iv hydrocortisone (by Travis criteria) or in day 70 colectomy rates between patients who were highly anxious, depressed or highly stressed compared to those minimally anxious, depressed or stressed. Although there was no significant difference in day 70 colectomy rates (Fig 4.6) between patients who were highly (upper tertile) stressed (RPSQ) to those who were less stressed (lower tertile) there was a trend to a higher proportion of those highly stressed needing colectomy. This failure to reach statistical significance may reflect a type 2 error due to the small numbers of patients recruited in study 3 (longitudinal study), despite attempted recruitment over 2 years at four IBD centres.

4.5.1Limitations

There are a number of limitations to this study. Firstly, to further assess the effect of hospital admission on stress and mood in IBD, it would have been useful to compare the stress and mood in ASUC patients with a further control group, for example, general gastroenterology in-patients, which was not assessed in this study.

We acknowledge the small numbers of patients recruited in study 3 (longitudinal study); this could have been increased by the incorporation of further centres and a longer recruitment period, which was not feasible in the study. Lastly, this study did not assess patients' personality, resilience nor the coping strategies they employ (81, 127).

In summary, clinicians should consider providing a more holistic approach, screening their admitted IBD patients for stress and related mood disorders. There is some evidence that cognitive behavioural therapy of various types, antidepressants, and possibly exercise, can improve IBD-associated mood disorders (see Chapter 1). Because of the difficulties inherent in undertaking appropriately targeted and blinded studies, good data about the effects on IBD of interventions aimed to ameliorate stress and its associated mood disorders are limited. As a next step, we would suggest conducting appropriately designed clinical trials to evaluate the effects of stress management and other psychologically-orientated therapies in patients with ASUC, assessing not only patients' psychological well-being and stress resolution but also the impact on the course of their colitis itself.

4.6 CONCLUSION

Perceived stress and depression levels are greater in patients with ASUC than in those in remission and anxiety scores are highest in patients newly presenting with UC. Although further controlled studies are needed to assess whether psychological interventions can influence outcome in acute severe UC, psychological support should be available for patients with ASUC, particularly those newly presenting to help them cope with their disease.

CHAPTER 5: DOES PSYCHOLOGICAL COUNSELLING ALTER THE NATURAL HISTORY OF INFLAMMATORY BOWEL DISEASE?

SUMMARY

- There is increasing evidence that psychological stress can increase mucosal inflammation and worsen the course of inflammatory bowel disease (IBD). To assess whether psychotherapy by a counsellor specially trained in management of IBD can influence the course of disease, a case controlled study was designed to compare the course of IBD in 24 patients (13 ulcerative colitis; 11 Crohn's), during the year before (year 1) and the year after referral (year 2) for supportive outpatient psychotherapy to an IBD counsellor, to that of 24 IBD controls.

- Patients were referred for counselling because of disease-related stress, work problems, concerns about surgery and bereavement.

- In the year after starting counselling (year 2), patients had significantly fewer relapses and outpatient attendances than in the year before referral (year 1); furthermore, steroid usage and relapse-related use of other IBD medications was lower during psychotherapy. Patients also informally reported improvements in their well-being and perception of stress

- There were no differences in any of these measures between years 1 and 2 in the control group.

- The findings suggest that IBD-focussed counselling may improve not only psychological well-being, but also the course of IBD in individuals with psychosocial stress.

5.1 INTRODUCTION

As discussed in chapter 1 psychological stress has long been anecdotally reported as adversely affecting disease activity in IBD, and there have been substantial recent advances in both proving this relationship and in elucidating the mechanisms by which it occurs (82, 124, 125). To date there have been very few reports, however, of the effects of attempts to ameliorate stress on disease course in patients with IBD.

5.2 HYPOTHESIS AND AIMS

We hypothesised that the natural history of IBD could be altered by psychotherapy given by a counsellor specially trained in the management of IBD-related psychological problems.

To do this, comparisons were made of the course of IBD in the year before and the year after patients with psychological symptoms started supportive psychotherapy, with that of a case-matched group of patients with IBD not receiving psychotherapy, and with that of a number of patients who were referred for psychotherapy but failed to attend.

5.3 METHODS

5.3.1 Patient group

Using retrospective case note review, the course of IBD was assessed during the year before (year 1) and after referral (year 2) of patients with an established diagnosis of IBD (218), confirmed by conventional endoscopic, histological and radiological features referred for supportive outpatient psychotherapy to an IBD counsellor (Meg Corser (MC)) between 2000-2007 at Barts and The London NHS Trust. 34 patients were referred for outpatient supportive therapy. Of these, 24 patients had psychotherapy sessions (Table 5.1) and 10 failed to attend. Of the 10 patients who failed to attend after referral for counselling, the clinical course of 6 was evaluated; the remaining 4 patients who failed to attend could not be evaluated: 2 were lost to follow up from the IBD clinic within a few weeks of referral and 2 were referred within 6 months of their diagnosis of IBD, so that data for the year prior to referral (year 1) was not obtainable. Each year about 2000 IBD patients attend the outpatient the

specialist outpatient clinic at this tertiary centre. Patients referred for psychotherapy had psychological difficulties related to their IBD or had suffered recent major life events, which were raised by them in discussion with the physician in the outpatient clinic, and were open to the idea of psychological counselling. None of the patients had received IBD-focussed counselling previously.

5.3.2 Controls

From our IBD database, we obtained 24 control patients each matched to one of the group of counselled patients for age, sex, diagnosis, disease duration, medication at baseline and for relapse rate in year 1 (Table 5.1). None had problems for which they requested psychological support. Details of their disease course in year 2 were subsequently obtained by case note review.

In addition, the course of disease before referral (year 1) and after referral (year 2) was assessed in the 6 evaluable patients who were referred for psychotherapy but failed to attend (see above).

5.3.3 Outcome measures

The outcome measures assessed in years 1 and 2 were: the number of relapses documented in the notes by the physician, numbers of outpatient attendances, numbers of hospital admissions, numbers of courses of steroids, and relapse-related use of other IBD medication, i.e. an increase in 5-aminosalicylate dosage or introduction of antibiotics, immunosuppression (thiopurine or methotrexate), or anti-TNF therapy. Relapse was defined by the physician's global assessment: in UC as the presence of diarrhoea and rectal bleeding with a step-up in their IBD medication; and for CD as the presence of abdominal pain and/or diarrhoea also with a step up in their IBD medication.

5.3.4 Psychotherapy

All psychotherapy sessions were carried out by the same counsellor (MC). She had had previous experience in relationship and bereavement counselling and had undergone a training programme organised by Crohn's and Colitis UK in 1997-8 at St Mark's Hospital, London, UK. This programme included training in both IBD itself and aspects of counselling and psychotherapy relating to IBD.

Each patient was provided with a verbal working contract which adhered to the British Association of Counselling and Psychotherapy regulations, with no ceiling set for the number of sessions he/she received. Sessions were person-centered and used both cognitive behavioural therapy and solution focused-therapy, to provide continuous psychological support to deal with IBD-related and external

events. The counsellor aimed to enable the patient to seek internal resources to develop resilience; she made no special recommendations about smoking cessation. Patients' psychological response to therapy was assessed by the counsellor, as part of the chart review process, using a visual analogue scale 0-6 (0 denotes poor, 6 excellent response to counselling), consisting of: commitment to the sessions; resolution of stress-related difficulties; and overall psychological well-being.

5.3.5 Statistical analysis

Statistical analyses were undertaken Graphpad Prism (Version 5, San Diego California) software. Comparison between the counselled patients and their controls at baseline was made using Wilcoxon's signed ranks test, Fisher exact test and chi squared test for continuous and discrete variables respectively. Outcome measures are shown as median values (ranges), and comparisons between year 1 and 2 within and between the case-matched groups were made using Wilcoxon's signed ranks test. All analyses were two-tailed and p-values were considered significant if less than 0.05.

5.3.6 Ethical Considerations

This study was designed to assess the value of our clinical counselling service and thus did not require formal ethical approval, according to UK National Research Ethics Service (NRES) guidelines (221).

5.4 RESULTS

5.4.1 Reasons for referral

34 patients were referred for counselling at least a year after diagnosis of IBD. Of these, 24 underwent counselling. The reasons for referral were disease-related stress (14 patients), work problems (3), concerns about surgery (5) and bereavement (2). The patients received 6 (1-13) 1 hour counselling sessions during year 2. 15 patients completed their counselling during year 2, while 9 continued for up to a further 5 years.

5.4.2 Demographics

There were no significant differences between the 24 counselled patients and their matched controls in terms of age, sex, IBD type, disease duration or medication at baseline (Table 5.1). In addition, 19 of the 24 controls were matched identically to 19 of the 24 counselled patients in terms of the number of relapses in year 1. However, there were more smokers in the counselled group (7 CD, 3UC) than control group (3 CD) ($p=0.049$) at baseline.

Table 5.1 Baseline demographics of patients in counselled group and matched controls. There were no significant differences between the groups for any of the baseline variables except for smoking (p=0.049 Fisher exact test).

Characteristic		**Counselled patients (n=24)**	**Control patients (n=24)**
Age (median (range)) yrs		38 (18-67)	37 (20-64)
Male		11 (46%)	11 (46%)
Smoker		10 (42%)	3 (12.5%)
Duration of disease (median (range)) yrs		5 (1-40)	4 (1-33)
Ulcerative Colitis		**13**	**13**
Extensive		9 (69%)	9 (69%)
Left-sided		4 (31%)	4 (31%)
Crohn's disease		**11**	**11**
Location	Ileal	1 (9%)	1 (9%)
	Ileocolonic	6 (54%)	6 (54%)
	Colonic	4 (36%)	4 (36%)
Behaviour	Inflammatory	5 (45%)	3 (28%)
	Stricturing	4 (36%)	4 (36%)
	Penetrating	2 (18%)	4 (36%)
+ Perianal		1 (9%)	3 (28%)
Medication			
5-aminosalicylate		18 (75%)	20 (83%)
Immunosuppressant (azathioprine/methotrexate)		13 (54%)	12 (50%)
Steroids (oral)		5 (21%)	6 (25%)
Infliximab		1 (4%)	1 (4%)

5.4.3 Clinical outcomes

As shown in Table 5.2 and Fig 5.1, in the year after starting it (year 2), counselled patients had fewer relapses (0 (0-2)) and outpatient attendances (3.5 (1-10)) than in the year before referral (year 1) (2 (0-5), P=0.0008; and 6.5 (1-17), P=0.0006, respectively). There were no significant differences in these variables between years 1 and 2 in the control group (Table 5.2 and Figures 5.1 and 5.2), and the differences between the changes seen in each variable in the two groups were statistically significant (P=0.006 and P=0.03 respectively). The numbers of hospital admissions did not change between year 1 and 2 in either group (Figure 5.3). However, steroid usage (1 course (0-4) in year 1, 0 (0-2) in year 2, P=0.005) (Figure 5.4) and relapse-related use of other IBD medications (5 ASA/antibiotics) declined during psychotherapy (1 drug (0-5) in year 1, 0 (0-2) in year 2, P=0.002) but did not change in the control group (p=0.01 and P=0.0006 for differences from counselled group). No patients in the counselled group were commenced on an immunomodulator or anti-TNF therapy in either year 1 or 2. In the control group, there was no significant overall change in the use of immunomodulator or anti-TNF between year 1 and 2. Furthermore, sub-analysis of the key outcome measures when limited to the 19 subject pairs that were well matched in year 1 on all variables, including relapse rates, confirmed the results obtained for the complete set of 24 patient-pairs (data not shown).

In the 6 evaluable patients who were referred for counselling but did not attend any sessions, there were no differences in the numbers of relapse (2 (0-3)) and outpatient attendances (5.5 (2-9)) in the year before referral (year 1) compared with those in the year after (year 2) (1.5 (1-3), p=0.75 and 5.5 (3-10), p=0.75, respectively) (Figures 5.1 and 5.2). Similarly, there were no differences in steroid use (Figure 5.3) or hospital admissions (Figure 5.4).

Table 5.2 Effects of counselling on IBD activity. In the year after starting it (year 2), counselled patients had fewer relapses and outpatient attendances than in the year before referral. There were no significant differences in these variables between years 1 and 2 in the control group. Steroid usage and relapse-related use of other IBD medications (5 ASA/antibiotics) declined during psychotherapy 1 but did not change in the control group. The numbers of hospital admissions did not change between year 1 and 2 in either group. Median values are shown (range).

Outcome variable	**Counselled patients (n=24)**			**Control patients (n=24)**			**Changes in counselled vs control pts' results**
	Year 1	Year 2	P value†	Year 1	Year 2	P value††	P value†††
No of relapses*	2 (0-5)*	0 (0-2)	0.0008	1 (0-3)*	2 (0-2)	0.64	0.0006
No of out-patient attendances	6.5 (1-17)	3.5 (1-10)	0.0006	5 (2-9)	5 (2-11)	0.99	0.03
Courses of steroids	1 (0-4)	0 (0-2)	0.005	1 (0-3)	1 (0-2)	0.62	0.01
Changes in 5ASA/antibiotics	1 (0-5)	0 (0-2)	0.002	0 (0-2)	0 (0-2)	0.81	0.0006
Changes in Immunosuppression	0 (0-0)	0 (0-0)	-	0 (0-2)	0 (0-2)	0.57	-
New infliximab	0 (0-0)	0 (0-0)	-	0 (0-1)	0 (0-3)	0.50	-
No of hospital of admissions	0 (0-2)	0 (0-2)	0.33	0 (0-2)	0 (0-1)	0.43	0.21

† P value for the difference between year 1 and year 2 for counselled group (Wilcoxon signed rank test). †† P value for the difference between year 1 and year 2 for control group (Wilcoxon signed rank test). ††† P value for differences between changes in variables for counselled versus control groups (Wilcoxon signed rank test)

* The number of relapses in year 1 in the counselled group (prior to intervention) was not significantly different to that of the control group in year 1, p = 0.08 (Wilcoxon signed rank test),

Figure 5.1 Relapse rates in years 1 and 2 in the three patient groups, counselled patients (n=24), case-matched controls (n=24) and patients who were referred for counselling but failed to attend (n=6). In the year after starting it (year 2), counselled patients had fewer relapses than in the year before referral. There were no significant differences in the control or referred but failed to attend groups. Individual data points are shown; the horizontal lines indicate median values.

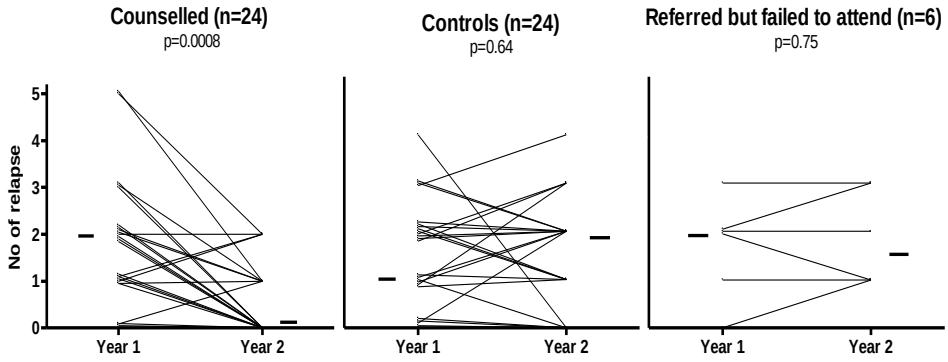


Figure 5.2 Outpatient attendances in years 1 and 2 in the three patient groups, counselled patients (n=24), case-matched controls (n=24) and patients who were referred for counselling but failed to attend (n=6). In the year after starting it (year 2), counselled patients had fewer outpatient attendances than in the year before referral. There were no significant differences in the control or referred but failed to attend groups. Individual data points are shown; the horizontal lines indicate median values.

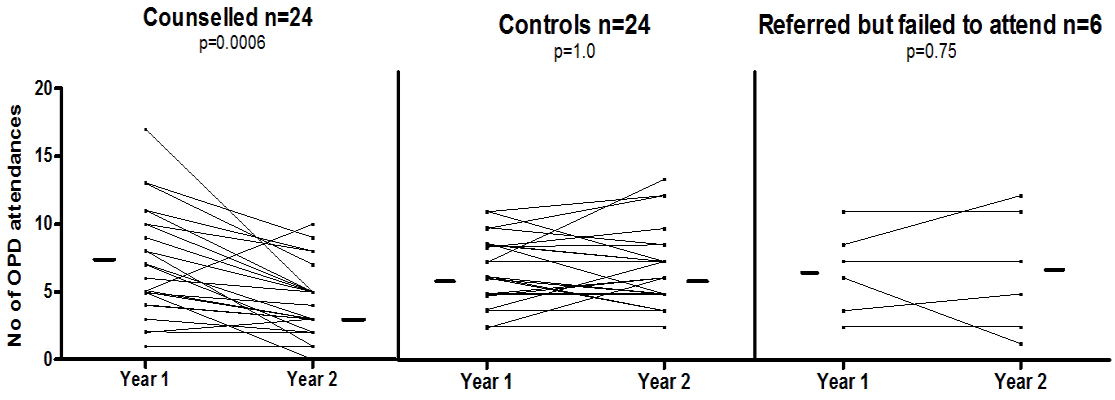


Figure 5.3 Hospital admissions in years 1 and 2 in the three patient groups, counselled patients (n=24), case-matched controls (n=24 and patients who were referred for counselling but failed to attend (n=6). The numbers of hospital admissions did not change between year 1 and 2 in any of the groups. Individual data points are shown; the horizontal lines indicate median values.

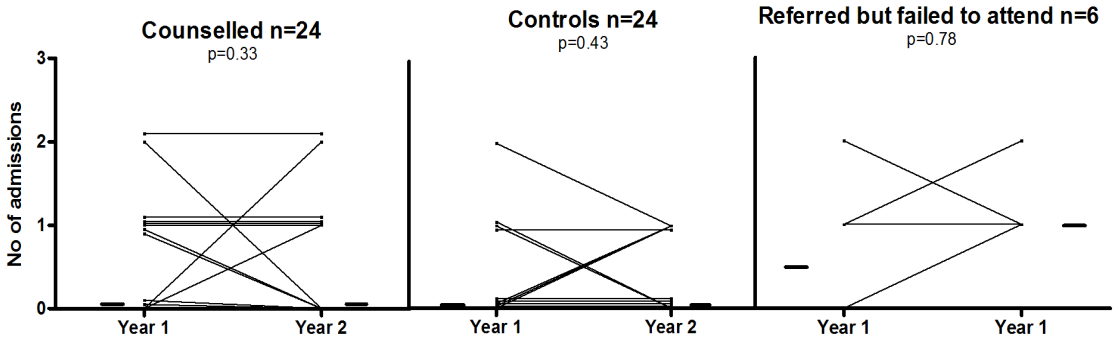
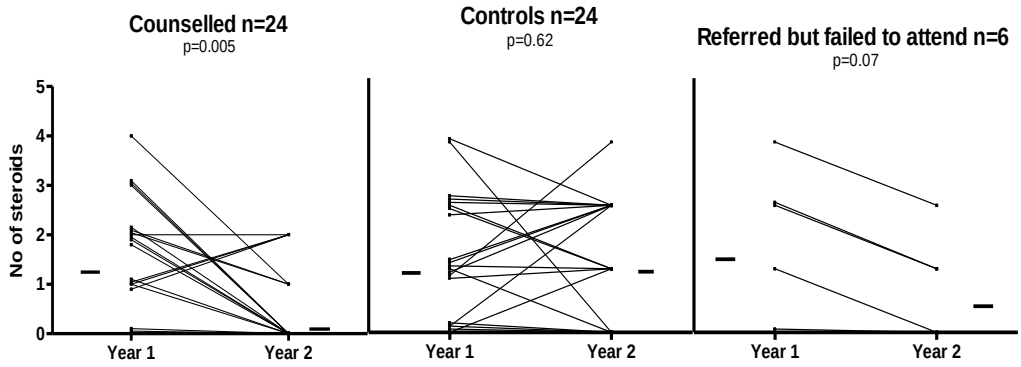


Figure 5.4 Steroid use in years 1 and 2 in the three patient groups, counselled patients (n=24), case-matched controls (n=24) and patients who were referred for counselling but failed to attend (n=6). In the year after starting it (year 2), counselled patients had fewer steroid courses than in the year before referral. There were no significant differences in the control or referred but failed to attend groups. Individual data points are shown; the horizontal lines indicate median values.



Duration of counselling

The effect of duration of counselling on IBD course was also assessed. The 12 patients who had therapy for < 6 months had a tendency towards improvement in relapse rates between year 1 (1.5 (0-5)) and year 2 (0.5 (0-2)) (p=0.07) ; the changes in their outcome variables were all still statistically significant when compared with those of their matched controls (year 1: 1 (0-3); year 2: 1 (0-4)) (p=0.03 for changes in counselled vs control patients' results). In patients receiving counselling for > 6 months, there was a significant reduction in the relapse rate between years 1 (2 (0-5)) and year 2 (0 (0-1)) (p=0.002), and the differences between the changes seen in them and their matched controls (year 1: 1.5 (0-4); year 2: 2 (0-3)) was also significant (p=0.004).

Effect of smoking cessation

Of the 10 smokers in the counselled group, 4 stopped in year 2 (3CD, 1 UC), compared to 1 out of the 3 patients with CD in the control group. Sub–analysis of the data without the 3 CD smokers in the counselled group who stopped, and their matched controls, did not influence the results found after psychotherapy; the counselled patients had fewer relapses (0 (0-2)) and outpatient attendances (4 (0-9)) than in the year before referral (year 1) (2 (0-5), P=0.0009; and 7(1-17), P=0.0001, respectively). There were no significant differences in these variables between years 1 and 2 in the control group (relapses year 1 (2 (0-4)), year 2 (2 (0-4)) (p=0.70), outpatient attendances year 1 (6 (2-9)), year 2 (5 (2-11)) (p=0.84)), and the differences between the changes seen in each variable in the two groups were statistically significant (P=0.001 and P=0.001 respectively).

5.4.4 Counsellor assessment

The counsellor's assessment of the 20 patients who attended >1 session showed that patients were committed to the sessions (median score 4 (4-6)). Counselling was felt to help solve stress-related difficulties (4 (3-5)) and patients were scored 4 (3-6) overall in psychological well-being after the counselling sessions. Patients also informally reported improvements in their well-being and perception of stress level. The 4 patients who attended only the first counselling session felt that counselling was unlikely to be of benefit to them, but continued to be followed up in the IBD clinic.

5.5 DISCUSSION

As discussed in chapter 1, in recent years, there has been increasing recognition by doctors as well as patients that psychological stress and other psychological disorders such as depression can worsen the course of IBD (82, 124, 125, 136).

Interestingly the baseline demographics revealed more smokers in the counselled group compared to their matched controls in keeping with the suggestion that IBD patients who are more stressed are more likely to be smokers.

This study has shown that counselling in patients identified to have psychological difficulties related to their IBD or to recent major life events, benefited them both in relation to the activity of their IBD and to their psychological well being. The improvement in IBD activity associated with psychotherapy was demonstrated by reductions in relapse rates, in use of steroids and other medications, and in outpatient attendances in the counselled compared to the control patient group. Two of our patients had counselling because of recent bereavement; this is of interest in relation to the use in two previous studies reporting a positive association between IBD activity and life events of questionnaires (Holmes Recent Life Change and Psychiatric Epidemiology Research Interview Life Events Scales) which incorporate bereavement as a major factor in life event scores (128, 131).

5.5.1 Limitations

There are a number of limitations to this study, the first being that it is a retrospective case-note review. We acknowledge that the study size is small, and that the numbers counselled represent a small proportion of patients seen in the IBD clinic when viewed in relation to the findings of the ADAPT study discussed in chapter 1 (150). The psychological support service in our IBD service has limited capacity: our one part-time counsellor (MC) can see only a limited number of referrals. Patients seen in the IBD clinic can also gain access to psychological support through their general practitioners, but we have no figures for the numbers of patients given counselling outside the hospital setting. There was no formal assessment of the psychological state of the counselled patients beyond the therapist's overall judgment. The tiny minority of very disturbed patients are normally referred to a psychiatrist rather than our counsellor: the apparently disproportionately low number of

patients referred to the counsellor in relation to the ADAPT findings (150) does not imply that the counselled patients in the present study were particularly distressed individuals.

There was no objective documentation of IBD activity in this study, for example using colonoscopy, blood tests (C-reactive protein) and/or faecal calprotectin given that disease activity may improve as a result of the direct effect of stress reduction on bowel frequency rather than through its effects on mucosal inflammation.

To decrease the possibility that the results in the counselled patients could have been explained by regression to the mean, we compared them with both individual case-matched controls who did not have psychological difficulties leading to referral for counselling (Tables 5.1 and 5.2), and with a small number of patients referred for counselling but who did not attend (Figure 5.1): in both these control groups, disease activity variables were unaltered in year 2. The relapse rate in year 1 showed a non-significant trend to being higher in the counselled patients than in the controls, suggesting that the counselled patients may have been sicker; however sub-analysis of the 19 patient-pairs in whom all variables were matched in year 1 revealed no differences in the outcome measures between the two groups. Re-analysis of the data after removal of the patients who stopped smoking in year 2 did not alter our results, so that smoking cessation in the patients with CD, whether or not a consequence of psychotherapy, did not account for its beneficial effects.

It is conceivable that counselling may have improved the course of patients' IBD by increasing their adherence to medication (240), but we were unable to collect data about treatment adherence. Lastly, this study gives no indication of the mechanisms by which counselling works, whether directly through psychoneuroimmunological pathways (82, 124, 125), or indirectly, for example by improving drug adherence.

5.6 CONCLUSIONS

This retrospective study of IBD patients with psychosocial stress demonstrates that IBD-focussed counselling may improve not only patients' psychological well-being and stress resolution but also the activity of their IBD, as indicated by reductions in relapse rate, use of steroids and other medications,

and outpatient attendances during the year after it was started. These findings suggest that counselling could also reduce healthcare utilisation and costs in patients with IBD complicated by psychological stress.

CHAPTER 6: HYPNOTHERAPY FOR THE PREVENTION OF RELAPSE IN ULCERATIVE COLITIS: A MULTI-CENTRE, RANDOMISED, SINGLE-BLIND, CONTROLLED CLINICAL TRIAL

SUMMARY

- There are anecdotal reports of the use of hypnotherapy in IBD and we hypothesised that it could be used for the maintenance of remission in UC.

- A multi-centre, randomised, single-blind, controlled trial was conducted to compare relapse rates in patients with quiescent UC treated either with gut-focussed hypnotherapy (GFH) or control educational sessions (CES) after withdrawal from a thiopurine. Patients with inactive UC treated for ≥1 year with azathioprine or mercaptopurine were asked to stop it. Patients were randomised 2:1 to receive GFH or CES over 13 weeks. The primary outcome was relapse rate at week 52. Psychological status and quality of life were assessed at weeks 0 and 13 and at relapse using the HADS, perceived stress (PSQ) and IBDQ questionnaires. 16 patients were randomised to GFH and 10 to CES.

- At week 52, there was no difference in relapse rates between those patients who had received GFH and the CES-treated patients. At week 13, GFH did not alter psychological or quality of life scores in patients still in remission.

- This trial did not suggest that gut-focussed hypnotherapy has a major effect in preventing relapse or altering psychological status in patients with UC withdrawing from thiopurines.

6.1 INTRODUCTION

As indicated in chapter 1, hypnotherapy can be defined as the intentional induction of a trance-like state without the loss of will or consciousness. It has been used successfully for many years as a treatment for psychological disorders. It has also been used in a variety of medical disorders including irritable bowel syndrome, which are believed to have a psychosomatic component and to be worsened by psychological stress.

6.2 AIMS

We hypothesized, because of existing anecdotal data in IBD, that by reducing the systemic and/or mucosal response to psychological stress or by other pathways, hypnotherapy would reduce the relapse rate in patients with inactive UC. To test this hypothesis we selected a population of patients with UC who are at substantial risk of relapse. Many patients with UC need to take a thiopurine, azathioprine or mercaptopurine (MP), in addition to a 5ASA, to keep their disease in remission: in these, withdrawal of the drug has been associated with a relapse rate at 1 year of 60% (241).

Therefore, to test whether hypnotherapy has a clinically useful prophylactic role, we conducted a multi-centre, randomised, single-blind, controlled trial to compare relapse rates in patients with quiescent UC treated either with gut-focussed hypnotherapy (GFH) or control educational sessions (CES) after withdrawal from a thiopurine.

6.3 METHODS

6.3.1 Patients

Patients for recruitment were sought from 6 centres in London, UK (Barts and the London NHS Trust, University College London Hospitals NHS Trust, Guy's and St Thomas' Hospitals NHS Trust, Imperial Healthcare NHS Trust, West Middlesex University Hospital NHS Trust and North-West London NHS Trust (St.Marks Hospital)) during the period October 2007 – April 2010.

6.3.2 Inclusion criteria

UC was confirmed by standard clinical, radiological, endoscopic and/or histological criteria. Patients aged 16-75 years with inactive UC who had been treated with azathioprine or mercaptopurine for a minimum of 1 year were considered for inclusion. Inactive disease was defined by a Simple Colitis Activity Index (SCCAI) score <3 (236) and Baron's sigmoidoscopic score <2 (231). Patients were required to be in clinical remission for at least 3 months prior to recruitment and on unaltered maintenance therapy (including 5ASA) for at least 4 months.

6.3.3 Exclusion criteria

Exclusion criteria were: use of prednisolone orally or topically, or of topical 5ASA in the preceding 3 months, antibiotics, warfarin, anti-diarrhoeal drugs, NSAIDs, aspirin at a dose of greater than 75 mg/day, herbal remedies; alcohol or drug abuse; pregnancy or breast feeding; female of child-bearing age not taking adequate contraception; participation in another drug trial in the previous three months; serious liver, renal, cardiac, respiratory, endocrine, neurological or psychiatric illness. Patients were also excluded if they already used relaxation techniques.

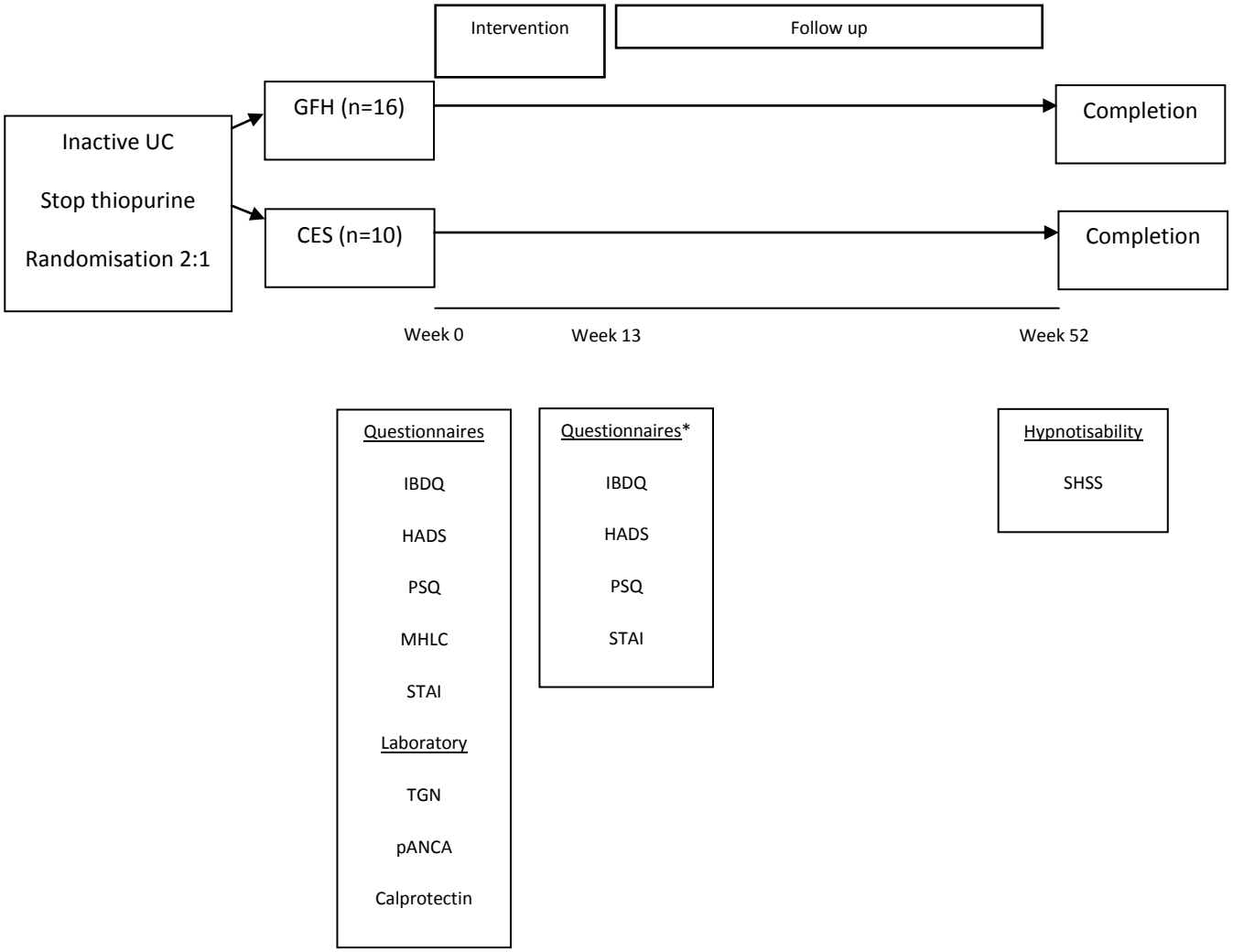
6.3.4 Protocol

An overview of the study protocol is shown in Figure 6.1. The study was registered with ClinicalTrials.gov (Ref: NCT00553163). At recruitment patients were asked to stop taking azathioprine or mercaptopurine. Patients underwent separately arranged sessions with the therapist (MS) and for clinical assessment (MW), including sigmoidoscopy, which precluded them from meeting each other, for example in waiting rooms, to compare treatments.

Patients were randomized on a 2:1 basis to gut-focused hypnotherapy (GFH) or control educational sessions (CES) at each participating site using a computer-generated code. The interventions took place over the first 13 week after randomization. Patients were subsequently assessed every 3 months by the clinician until 1 year or relapse, if earlier.

Figure 6.1 Study protocol: Hypnotherapy for the prevention of relapse in UC. UC, ulcerative colitis, GFH, gut focused hypnotherapy, CES, Control education sessions, HADS, Hospital Anxiety and Depression score, PSQ, Perceived Stress, MHLC, Multidimensional Health Locus of Control, STAI, State Trait Anxiety Inventory, TGN, thioguanine nucleotide levels, SHSS, Stanford Hypnotisability Susceptibility Score.

Protocol



6.3.5 Thiopurine withdrawal

It was decided to use patients withdrawing from use of a thiopurine for this trial for several practical and ethical reasons. At the time of this study design, there was good data about relapse rates on azathioprine withdrawal (241) and therefore a base for power calculations (see below). Thiopurines, while effective therapy, carry a substantial risk of side-effects (e.g. bone marrow suppression, liver damage, infection, lymphoma) and require regular blood checks, so that patients and doctors would welcome their discontinuation if feasible. If hypnotherapy proved effective, it would be a safe alternative to azathioprine or mercaptopurine.

6.3.6 Interventions

Gut-focussed hypnotherapy (GFH)

All sessions were performed by the same medically qualified hypnotherapist (MS), who was not involved in undertaking the end-point assessments. Subjects first underwent a preliminary 20 min interview with the therapist to establish rapport and to ask about their conceptualisation of UC. Subjects were then given instruction about relaxation techniques. They were instructed on how hypnosis may influence gut function. Hypnosis was induced by eye closure, followed by progressive muscular relaxation and standard deepening techniques.

Session one was spent familiarising the patient with the process. In subsequent sessions, abdominally focused suggestions were introduced, centred around reducing inflammation and normalising colonic motility and sensitivity using both patient-centred imagery and conditioning techniques. More direct suggestions about reduction of pain and improvement of health were made on a repetitive basis at each session. Patients were informed that the effects of hypnosis are not necessarily immediate. The emphasis was on the patient developing control over their gut rather than being controlled by their gut. This was part of promoting an internal locus of control (242), which is known to be important for successful outcome with biofeedback (243) and self management of diabetes (244). Subjects were seen at 6 face-to-face visits in the 13 week treatment period (weeks 1, 2, 3, 5, 9 and 13). Subjects also received a CD with instructions for self-hypnosis and were encouraged to practise at home on at least a daily basis; they received a phone call at weekly intervals from the therapist to monitor progress and compliance. After the end of the initial 13 week period, patients were asked to continue to practise self-hypnosis, and were phoned monthly by the therapist.

Control educational sessions (CES)

The control interventions were undertaken by the same therapist (MS) who undertook the hypnotherapy sessions. Subjects first underwent a preliminary 20 min interview with the therapist to establish rapport and to ask about their knowledge of UC.

Subjects were seen at 4-weekly intervals (a total of 4 face-to-face visits in the 13 week treatment, at weeks 1, 5, 9 and 13), and received a phone call at weekly intervals from the therapist to monitor progress and field questions. After the end of the initial 13 week period, patients were phoned monthly by the therapist. No attempt was made to offer any form of relaxation techniques to these patients.

The content of the educational sessions was standardised, to cover the following: (a) what is the nature and prognosis of UC?; (b) what is the cause of UC?; (c) what are the implications of UC for family life (covering inheritance risk, sexual function, pregnancy and childbirth) ?; (d) the medical and surgical treatment of UC (see Appendix 2).

6.3.7 Outcome measures

Primary end-point: The proportion of patients suffering a relapse at 1 year. Relapse was defined symptomatically by SCCAI >2, recorded from a diary card completed daily by each patient, and confirmed sigmoidoscopically (Baron score >1).

Secondary end-points:

i) Psychological status: To assess whether GFH improved patients' mood they were asked to complete the Hospital Anxiety Depression Score (HADS), Perceived Stress Questionnaire (PSQ) (115) and State Trait Anxiety Inventory (form Y) (STAI) at entry and week 13. Furthermore, to assess the relation between disease activity and mood, subjects also completed these questionnaires at relapse.

The STAI Form Y is also a validated questionnaire for measuring anxiety in adults. It differentiates between the temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety". It comprises two twenty item scales (for copyright reasons only part, STAI Y-1, is shown in Appendix 1.5) with a range of scores between 20-80; higher scores indicating greater anxiety (245).

In addition, patients were asked to complete the multidimensional health locus of control questionnaire (form C) (MHLC) (246) at entry (Appendix 1.6). The MHLC is an 18 item, area-specific measure of expectancies regarding locus of control developed for prediction of health-related behaviour. An internal locus of control (score range 6-36) is known to be important for successful outcome with biofeedback (243) and self-management of diabetes (244).

The Stanford Hypnotic Susceptibility Scale (247) was carried out after the final intervention to ensure no differences between the 2 groups. This scale measures how easily a person can be hypnotized; and results range from 0 (not susceptible) to 12 (highly susceptible) (summary of scale in Appendix 1.7).

Other tests measured at baseline included the measurement of thioguanine nucleotide (TGNs) concentrations to assess adherence to thiopurines, and faecal calprotectin (248) to confirm inactive disease. In addition, pANCA was also measured at baseline; a negative pANCA has been shown to increase the risk of anxiety- or depression-related flare of UC (116).

ii) Quality of life: Patients were asked to complete the Inflammatory Bowel Disease Questionnaire (IBDQ) at recruitment, at week 13 and at relapse (249). The IBDQ is a validated and reliable tool to measure of health-related quality of life in adult patients with IBD. The questionnaire consists of 32 questions scored in four domains: bowel symptoms, emotional health, systemic systems and social function.

iii) Faecal calprotectin: This was used to confirm inactive disease at baseline (248). This was undertaken by myself, with samples run in duplicate, using PhiCAL enzyme linked immunoassay (Firefly Scientific, UK).

6.3.8 Blinding

All psychometric and laboratory results were withheld from the clinical assessor and hypnotherapist until the trial was complete so as to maintain blinding. The clinical assessor (MW) was also blind to each patient's treatment arm.

6.3.9 Statistical analysis

The primary parameter was relapse rate at 12 months. With azathioprine withdrawal the 12 month relapse rate was reported as 60% at the time this study was devised (241). The minimum clinically useful difference in relapse rate at 12 months with hypnotherapy compared to control was considered to be 35%. At a power of 80%, using 2:1 randomisation, we calculated that we would need 60 patients in total (40 patients for GFH and 20 for CES) to detect a 35% absolute difference between groups at $p<0.05$. Assuming a 10% drop-out rate we intended to recruit 66 patients in all.

Time-to-relapse curves were calculated using the Kaplan–Meier method, and statistical significance determined using the log rank test. Differences between the IBD patients and their controls were sought in categorical data using Chi squared test or Fisher exact test and in continuous data using Wilcoxon signed rank (for comparing paired data) or Mann Whitney U (for comparing unpaired data). All P values were 2-tailed. Outcome measures are shown as median values (ranges).

Data was analysed on an intention-to-treat basis. Analysis was performed using GraphPad Prism (version 4.0) and SPSS (version 17.0) statistical software.

6.3.10 Ethical Considerations

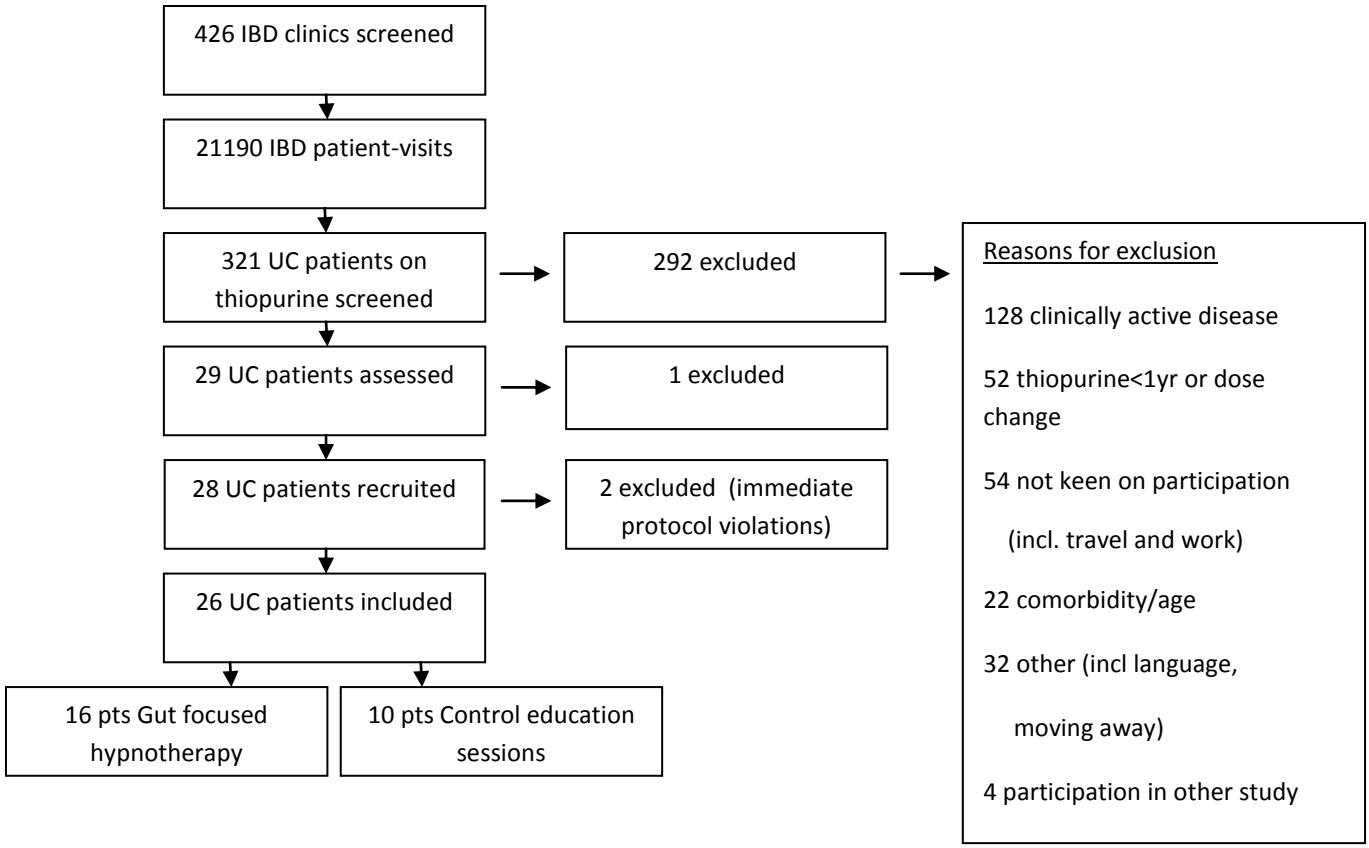
This study received formal ethical approval from the UK National Research Ethics Service (reference no: 07/H0705/60).

6.4 RESULTS

6.4.1 Recruitment

21190 IBD patient visits were screened at 426 clinics over 30 months producing 321 patients with UC on a thiopurine: 292 declined enrolment or did not meet inclusion criteria. Of 29 potential participants, 1 was excluded for active UC and 2 for protocol violations at baseline. Thus, 16 patients were randomised to GFH and 10 to CES (Figure 6.2).

Figure 6.2 CONSORT (250) diagram of recruitment: Hypnotherapy for the prevention of relapse in UC. IBD, denotes inflammatory bowel disease, UC, ulcerative colitis



6.4.2 Demographics and other baseline data

As shown in Table 6.1, the phenotype of UC differed with regards to age with those receiving CES being significantly older than those receiving GFH. At baseline, there were no differences between treatment groups in disease extent or duration, time since last relapse, 5ASA use, duration of thiopurine use, faecal calprotectin, TGN levels, pANCA status nor IBDQ (Table 6.2). All but one of the patients were thiopurines adherent as judged by their baseline 6 TGN level. Those receiving CES appeared more stressed at baseline (recent PSQ) but there were no differences between in anxiety or depression scores (HADS and STAI) between the groups (Table 6.2).

Table 6.1 Demographics and other baseline data for both the Gut Focussed Hypnotherapy (GFH) and Control Education Session (CES) groups. There were no differences between treatment groups in disease extent or duration, time since last relapse, 5ASA use, duration of thiopurine use, faecal calprotectin, TGN levels, pANCA status nor IBDQ. Those receiving CES appeared more stressed at baseline (recent PSQ) but there were no differences in anxiety or depression scores (HADS and STAI) between the groups.

P value for the differences calculated using the Chi squared test and Mann-Whitney U test. SCCAI, simple clinical colitis activity index, TGN, thioguanine nucleotide level (pmol/8 x108erythrocytes), MHLC, Multidimensional Health Locus of Control (Internal) Form C, R-PSQ, recent perceived stress questionnaire, HADS A, hospital and anxiety depression score – anxiety, HADS D, hospital and anxiety depression score – depression, STAI, State Trait Anxiety Inventory, IBDQ, inflammatory bowel disease questionnaire . *CRP values were given values <5 by certain laboratories.

	Hypnotherapy (n=16)	**Education (n=10)**	*P value*
Age (median (range) yrs)	31 (22-65)	48.5 (29-63)	*0.03*
Male (no of patients)	8 (50%)	7 (70%)	*0.42*
Disease extent			
Left	2 (12.5%)	4 (40%)	
Total	14 (87.5%)	6 (60%)	*0.16*
Disease Activity ((median (range))			
SCCAI	0 (0-2)	0.5 (0-2)	*0.1*
Baron's score	0.5 (0-1)	1(0-1)	*0.2*
Duration of thiopurine (months (range))	66 (18-282)	82 (12-94)	*0.42*
Maintenance 5ASA	14 (87.5%)	9 (90%)	*1.0*
Time to previous flare (months (range))	34 (7-117)	20 (4-94)	*0.47*

TGN (median (range))	240 (0-817)	230 (75-574)	*0.96*
MHLC (median (range))	22 (10-28)	18.5 (9-27)	*0.27*
Laboratory			
Hb	13.5 (10.8-15.6)	14.3(13.1-16.0)	*0.39*
WBC	5.62 (4-8.1)	5.51 (3.7-7.1)	*0.37*
MCV	94.7 (67.7-104.3)	92.7 (86-107.1)	*0.50*
PLT	261 (195-860)	279(207-380)	*0.70*
CRP	<5 (1-11.7)*	<5 (1.7-5)*	*0.71*
Faecal calprotectin	8.5 (<5-198)	<5 (<5-210)	*0.78*
pANCA +ve	4 (25%)	4 (40%)	*0.66*
Psychological status			
R-PSQ	0.30 (0.12-0.57)	0.42 (0.28-0.63)	*0.03*
G-PSQ	0.34 (0.24-0.58)	0.42 (0.32-0.76)	*0.054*
HADS – Anxiety	7 (3-12)	10 (0-15)	*0.15*
HADS – Depression	2 (1-8)	5.5 (0-9)	*0.61*
STAI – State	37 (24-58)	45 (28-63) (n=9)	*0.12*
STAI – Trait	25.5 (28-53)	47 (25-54) (n=9)	*0.17*
Quality of life: IBDQ	192 (172-210) (n=15)	190.5 (149-215)	*0.42*

6.4.3 Primary outcome

Eight of 16 (50%) GFH and 7 of 10 (70%) CES-treated patients had relapsed by week 52 (p=0.42) (Figure 6.3).

6.4.4 Secondary outcomes

Psychological status and quality of life.

At week 13 following the final therapy session, neither GFH nor CES altered psychological (HADS-A, HADS-D, R-PSQ, and STAI) or IBDQ scores in patients still in remission (Table 6.2).

At relapse, patients in both groups showed deteriorations in IBDQ (GFH: week 0, 193 (172-210) (n=15), relapse 133 (97-144) (n=5), p=0.002; CES: week 0, 190 (190 (149-215), relapse 148 (122-166) (n=6), p=0.002 (Mann Whitney U)) and those given GFH had higher scores for depression (table 6.3).

Figure 6.3. Kaplan Meier survival curve of UC patients remaining in remission after gut-focused hypnotherapy or control education sessions. Relapse was defined by SCCAI>2, Baron's score >1. There was no difference in relapse rates between the groups at week 52. GFH, gut-focused hypnotherapy, CES, control education session. P value was calculated using log rank test.

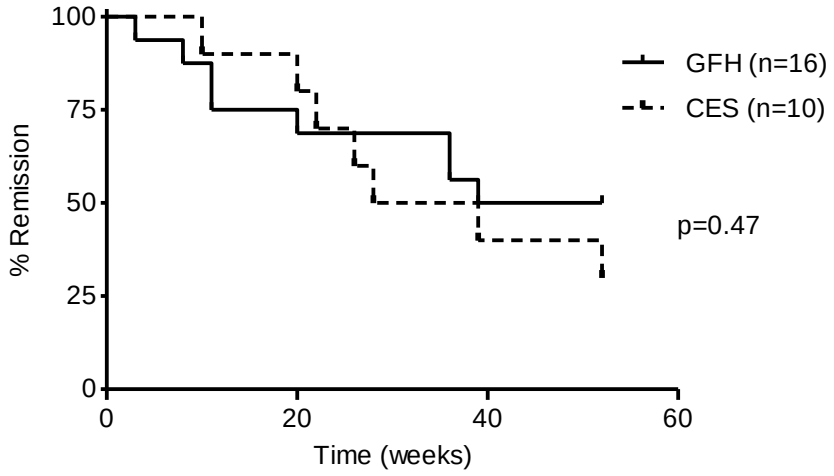


Table 6.2. Psychological status and quality of life scores between baseline and week 13 in those patients who remained in remission (at week 13) in both the GFH and CES groups. Neither GFH nor CES altered psychological (HADS-A, HADS-D, R-PSQ, and STAI) or IBDQ scores in patients still in remission. R-PSQ, recent perceived stress questionnaire, HADS A, hospital and anxiety depression score – anxiety, HADS D, hospital and anxiety depression score – depression, STAI, State Trait Anxiety Inventory, IBDQ, inflammatory bowel disease questionnaire. *P values were calculated using Wilcoxon signed rank test.

Questionnaire	Hypnotherapy (n=12)			Education (n=9)		
	Week 0	Week 13	*P value*	Week 0	Week 13	*P value*
R-PSQ	0.29 (0.12-0.57) (n=11)	0.31 (0.11-0.59) (n=11)	*0.50*	0.44 (0.29-0.63)	0.45 (0.07-0.68)	*0.29*
HADS A	7.5 (3-12)	7 (4-11)	*0.92*	11 (0-15)	10 (4-14)	*1.0*
HADS D	2 (1-8)	1.5 (0-8)	*0.71*	5 (0-7)	4 (0-8)	*0.82*
STAI - STATE	33 (24-48) (n=11)	34 (21-54) (n=11)	*1.0*	46 (28-63) (n=8)	39.5 (22-53) (n=8)	*0.09*
STAI - TRAIT	36 (28-51) (n=11)	38 (25-49) (n=11)	*0.21*	48.5 (25-54) (n=8)	45.5 (28-55) (n=8)	*0.34*
IBDQ	192 (172-210) (n=11)	195 (114-212) (n=11)	*0.93*	188 (149-215)	192 (170-212)	*0.23*

Table 6.3 Psychological status and quality of life scores between baseline, week 13 (in those patients who remained in remission), and at relapse in both the GFH and CES groups. R-PSQ, recent perceived stress questionnaire, HADS A, hospital and anxiety depression score – anxiety, HADS D, hospital and anxiety depression score – depression, STAI – State Trait Anxiety Inventory, IBDQ, inflammatory bowel disease questionnaire. *P values were calculated using Kruskal-Wallis test.

Questionnaire	**Hypnotherapy (n=16)**				**Education (n=10)**			
	Week 0 (n=16)	Week 13 (n=12)	Relapse (n=8)	*P value**	Week 0 (n=10)	Week 13 (n=9)	Relapse (n=7)	*P value**
R-PSQ	0.30 (0.12-0.56)	0.31 (0.11-0.59) (n=11)	0.48 (0.29-0.58) (n=5)	*0.13*	0.42 (0.28-0.63)	0.45 (0.07-0.68) (n=8)	0.47 (0.34-0.73) (n=6)	*0.62*
HADS - Anxiety	7 (3-12)	7 (4-11)	10 (2-15) (n=5)	*0.49*	10 (0-15)	10 (4-14)	9.5 (7-12) (n=6)	*0.95*
HADS - Depression	2 (1-8)	1.5 (0-8)	7 (5-10) (n=5)	*0.03*	5.5 (0-9)	4 (0-8)	6 (1-10) (n=6)	*0.53*
IBDQ	193 (172-210) (n=15)	194 (114-212)	133 (97-144) (n=5)	*0.004*	190 (149-215)	192 (170-166)	148 (122-166) (n=6)	*0.002*

6.4.5 Compliance

14/16 (87.5%) patients given GFH attended all the therapists' sessions compared to all 10 of those receiving CES. In addition, 14/16 (87.5%) of the GFH patients reported using self-hypnosis daily for the first 3 months and 10/12 (83%) did so at least weekly until week 52 or relapse.

6.4.6 Susceptibility to hypnotherapy

In 11 of the 16 patients who completed the SHSS in the GFH group, the SHSS score was (median (range) 8 (3-12). There was no difference in SHSS within the GFH group in those who remained in remission ((11 (4.5-11) (n=5)) compared to those who relapsed ((8 (3-12) (n=6), (p=0.45))

6.4.7 Outcome according to pANCA, locus of control and psychological status in the GFH treated group

In patients receiving GFH there was no difference in pANCA status between those who remained in remission (4 out 7: pANCA –ve) and those who relapsed (6 out of 7: PANCA -ve) (p=0.55, Fisher exact test) (Table 6.4).

In patients receiving GFH there was no difference in baseline MHLC (Internal) scores between those who remained in remission (22 (10-28)) (median (range)) and those who relapsed (18.5 (9-27)).

Furthermore, relapse in these patients was not influenced by baseline R-PSQ, HADS-A, HADS-D or STAI scores (Table 6.5).

Table 6.4 Comparison of those patients who received GFH remaining in remission compared to those who received GFH and relapsed according to pANCA status at baseline. pANCA –ve status did not predict relapse ((p=0.55) *P values were calculated using Mann Whitney U test). (In 2 patients, pANCA status was not checked).

	GFH remission (n=7)	GFH relapse (n=7)
P ANCA -ve	4	6
P ANCA +ve	3	1

Table 6.5 Comparison of those patients who received GFH remaining in remission compared to those who received GFH and relapsed according to psychological status at baseline. Relapse in these patients was not influenced by baseline R-PSQ, HADS-A, HADS-D, or STAI scores. R-PSQ, recent perceived stress questionnaire, HADS A, hospital and anxiety depression score – anxiety, HADS D, hospital and anxiety depression score – depression, STAI – State Trait Anxiety Inventory, IBDQ, inflammatory bowel disease questionnaire. *n=7 in both groups as 2 patients failed to complete the STAI questionnaire, **P values were calculated using Mann Whitney U test.

Questionnaire	**Hypnotherapy (n=16)**		
	Remission (n=8)	Relapse (n=8)	*P value***
R-PSQ	0.27 (0.12-0.43)	0.40 (0.16-0.57)	*0.34*
HADS - Anxiety	6 (0-7)	6 (3-12)	*0.60*
HADS- Depression	1 (0-6)	2 (1-8)	*0.28*
STAI - STATE	33 (25-45) (n=7)*	42.5 (31-48) (n=7)*	*0.18*
STAI -TRAIT	35 (28-50) (n=7)*	50.5 (32-51) (n=7)*	*0.18*

6.5 DISCUSSION

While small uncontrolled studies have suggested that hypnotherapy could have a beneficial effect both on disease activity and quality of life in patients with IBD (207-209), this trial, which as far as we are aware is the first randomised controlled study of hypnotherapy in IBD, failed to show any improvement in relapse rate or psychological status in patients with UC who had discontinued treatment with a thiopurine. Furthermore, we did not find any relationship between response to hypnotherapy and either the Stanford Hypnotisability Susceptibility Score, or psychometric assessments of mood and stress perception at recruitment.

6.5.1 Trial design

Gut-focussed hypnotherapy (GFH)

The hypnotherapy technique we used was selected in part to mimic the type of hypnosis used in the previous study in our unit, since this had shown that a single session of hypnosis reduced systemic and rectal mucosal measures of inflammation (204). In addition, we asked subjects to practise self-hypnosis daily, since it has the advantage of being more practicable and cheaper than asking patients, who are often in full time employment, to attend the hospital on a weekly (or even daily) basis: we used these arguments both in relation to the trial itself and to clinical use of hypnotherapy should it have proved effective in this study. There is also evidence that self-hypnosis is effective in children with abdominal symptoms (251).

Control procedure (educational session, CES)

Any form of relaxation therapy, such as breathing advice or non-gut-focussed hypnotherapy, could conceivably have had a beneficial effect and therefore have reduced differences in outcome between the GFH and control groups. We therefore chose as our control procedure a non-emotive question and answer educational interview about the nature of UC, previous studies having not suggested that education about IBD improves its natural history, as discussed in chapter 1 (section 1.5.3) (171, 251); indeed, the relapse rate after thiopurine withdrawal in our control group (70%) proved to be similar at 1 year to that reported by Hawthorne et al (241). A more recent study, which was published after we

begun our trial, a third of UC patients relapsed within 12 months after withdrawal of azathioprine (252).

6.5.2 Stratification for psychological state and other factors

Recognising that the response to hypnotherapy might be influenced by their pre-treatment psychological state, we considered either recruiting only patients with pre-existing psychological or stress-related 'vulnerability', or stratifying at recruitment the patients into two groups, for example on the basis of their Perceived Stress Questionnaire (PSQ) score and/or pANCA status, previous work having shown that a high PSQ is associated with an increased risk of relapse (115), and that a negative pANCA increases the risk of anxiety or depression-related flare of UC (116).

However, such an approach would have produced several problems. First, fewer patients would have been eligible for the study. Second, in UC, perhaps unlike in irritable bowel syndrome, hypnotherapy may act more through its effects on autonomic balance and augmentation of vagal tone (204) than by reducing psychological stress. In the event, retrospective analysis showed no obvious relation between psychometric scores or pANCA and the effect of hypnotherapy on relapse rate, although this conclusion is of course compromised by a possible Type 2 statistical error as a result of small numbers of patients in each subgroup.

6.5.3 Limitations of trial

Difficulties in recruitment.

The main limitation of this study, as implied above, is the small numbers of patients recruited, despite intensive efforts at six large IBD centres. Although our negative results may therefore reflect a type 2 error, they do not suggest that hypnotherapy has a very major effect in reducing the relapse rate of UC or improving patients' quality of life.

The reasons given for our inability to complete recruitment for the trial are shown in Figure 6.1: many highlight the difficulty in recruiting patients with inactive UC to a study involving multiple time-consuming hospital visits. They also suggest that even if hypnotherapy had been shown to be an effective option, it might not be popular with the majority of potentially appropriate patients. By actually targeting the correct patient may make the treatment more acceptable.

'*Floor' effect*

Although our failure to detect any effect of GFH on IBDQ or the psychometric scores of these patients with UC could also be due to a type 2 statistical error, another explanation could be a floor effect, since baseline scores indicated a low prevalence of psychological disturbance in the patients recruited (Table 6.2).

Randomization and blinding

In order to maximise the potential generalisability of our results, we opted to randomize our patients to hypnotherapy or the educational sessions, rather than allow them to choose which arm to participate in. In retrospect, it seems possible that this decision may have had an adverse effect on our ability to recruit patients, as well as, conceivably, on the outcome of the hypnotherapy arm. Conversely, the single-blind design is likely to have tilted the outcome in favour of those patients having hypnotherapy.

6.6 CONCLUSIONS

This trial did not suggest that gut-focussed hypnotherapy has a major effect in preventing relapse of altering psychological status in patients with UC withdrawing from thiopurines. Whether hypnotherapy would be valuable as an adjunctive therapy, for example in patients with mild-moderately active IBD, or whether it would benefit carefully selected patients, for example those with marked sympathetic overactivity (253) such as during severe flares (254) or high hypnotisability scores, merits further investigation.

CHAPTER 7: SUMMARY AND CONCLUSIONS

Here, I will outline the main results arising from this thesis, indicate some future directions and finally conclude with some unifying thoughts.

Chapter 3: Tobacco dependence and awareness of health risks of smoking in patients with inflammatory bowel disease.

This study of IBD patients' smoking habits demonstrates that a smaller proportion of CD patients continue to smoke than has been reported previously. However, contrary to our hypothesis, patients with CD who smoke do so despite recognising the detrimental effects of smoking on their disease. This is not explained by nicotine dependence which in our IBD patients is lower than in smokers' clinic clients and comparable to that of the general population

Unfortunately, we did not have data on our patients' educational level and cannot therefore draw any conclusions about the relation between this factor and their knowledge about smoking and Crohns'; this could be incorporated into future studies. Furthermore, our interrogation of patients about their knowledge of its effects on IBD was limited, and could be done more fully in the future.

Why patients who know the risks incurred by smoking, but who are not highly nicotine dependent continue to smoke is unclear. One possible explanation might be that psychological stress contributes to their smoking habit (67), but unfortunately we did not assess this, or other mood characteristics, in this study. Again, it would be extremely useful if future studies to assess smoking in IBD, were designed to assess both psychological stress and mood disorders, which in turn could be potential targets to assist CD patients to give up smoking.

Chapter 4: Anxiety and psychological stress in ASUC: prevalence and effect on outcome

Our study showed that perceived stress levels are greater in patients with ASUC than in those in remission and anxiety scores are highest in patients newly presenting with UC, but neither stress nor anxiety appeared to influence disease outcome.

The next step would be to conduct appropriately designed clinical trials to evaluate the effects of stress management and other psychologically-orientated therapies in inpatients with ASUC, assessing their impact not only on patients' psychological well-being and stress resolution but also on the course of their IBD itself. For example, in a study of rheumatology inpatients and diabetic outpatients, a multifaceted psychiatric intervention (conducted by a psychiatric liaison nurse and/or using referral to a liaison psychiatrist followed by advice to the treating physician) was targeted at the complex medically ill (255). The prevalence of major depression was reduced from 61% to 28% in the intervention group with no change in those receiving standard care (57% to 50%). A similar study design could conceivably be used in patients with ASUC or indeed inpatients active Crohn's disease.

Chapter 5: Does psychological counselling alter the natural history of IBD?

We have shown that in IBD outpatients with psychosocial stress, IBD-focussed counselling may improve not only patients' psychological well-being and stress resolution but also the activity and course of their IBD. .

A third of patients would like access to psychological support, though not all of these patients had a mood disorder (150). As a first step to meeting their needs, gastroenterologists should consider routinely screening their patients during clinic visits in an effort to identify those suffering from stress and related mood disorders: the quality of life of these individuals may improve most with a psychological approach.

A limitation of the published studies of psychological interventions as well as our own, is the poor characterization of the study subjects in terms of the type and severity of their psychological disorder. Common sense dictates that IBD patients with associated mood disorders have different needs from those who are distressed by their disease (adjustment disorder), and from those who cope effectively. Thus, the essential clinical question is what psychological intervention should be offered, when and to whom?

There is a wide range of other factors likely to influence response to, and therefore choice of therapy. These include the patient's perception of their stress, its severity and duration; their resilience and coping strategies; their mood and personality; their age and social support. This highlights the

importance of offering individualised psychological therapy tailored to the stage of adjustment either to their disease (149) or to an external chronic stress; all factors which need to be taken into account in future trials. Because of the difficulties inherent in undertaking appropriately targeted and blinded studies, large patient numbers are needed for multiple stratifications.

Chapter 6: Hypnotherapy for the prevention of relapse in UC: A multi-centre, randomised, single-blind, controlled clinical trial.

Gut-focussed hypnotherapy does not appear to have a major clinically useful effect in preventing relapse or altering psychological status in patients with ulcerative colitis who are withdrawing from treatment with thiopurines. At week 52, there was no difference in relapse rates between those patients who had received gut-focussed hypnotherapy and the control education sessions treated patients. At week 13, gut-focussed hypnotherapy did not alter psychological or quality of life scores in patients still in remission.

Our failure to detect any effect of gut-focussed hypnotherapy on quality of life or the psychometric scores of these patients with UC could have been due a floor effect, since baseline scores indicated a low prevalence of psychological disturbance in the patients recruited. Further studies would need to be designed to ensure recruitment of enough patients to provide sufficient statistical power to enable detection of change in disease activity and/or mood status. Whether hypnotherapy would be valuable as an adjunctive therapy merits further investigation.

SUMMARY

There is now good evidence of an association between psychological stress and the course of IBD. Importantly, current investigations in both man and animals of the mechanisms by which stress induces relapse may open up new therapeutic targets acting at a range of specific points in the relevant psychoneuroimmunological pathway. In animal models, for example, probiotics (256, 257), inhibitors of mast cell degranulation (99, 258) , beta-blockers (96) and a PPARγ agonist (93) have each been shown to reduce the adverse effects of stress on intestinal mucosal inflammation.

Subsequent clinical trials will be needed to determine whether conclusions derived from relatively acute animal experiments are comparable and applicable to humans with IBD.

Trials of psychotherapy and other ways of addressing psychological stress and mood disorders are fraught with difficulty. Attempts to conduct further therapeutic studies in the future will need to take these into account if they are to provide results of clinical value. Areas which are worthy of specific attention include:-

- The need for careful and objective documentation of IBD activity, for example using colonoscopy, blood tests and/or faecal calprotectin (259) given that disease activity scores such as the CDAI may improve as a result of the direct effect of stress reduction on bowel frequency rather than through its effects on mucosal inflammation.
- Stratification of patients with IBD by disease diagnosis, site, extent, activity, smoking habit and conventional treatment. There may be, for example, differences in the associations between stress and UC, on the one hand, and depression and Crohn's disease on the other.
- Stratification of patients by genotype, since patients with different genotypes may respond differently to different psychological interventions.
- Stratification of patients with UC by pANCA status, in view of the apparently greater psychobiological responsiveness of pANCA-negative patients compared with their pANCA-positive counterparts (116).
- Stratification of patients by severity and type of psychological stress or mood disturbance.
- Stratification of patients to take into account their personality, resilience and the coping strategies they employ (81, 127),
- Design of trials with sufficient statistical power to enable detection of change in disease activity and/or mood status. For example, having included a substantial proportion of subjects whose disease was inactive at recruitment, several trials to date have sought a beneficial effect of the test intervention on disease activity: equivocal or negative results were almost inevitable.
- Individualization of therapy by stage of adjustment to IBD (149).

- Differences in therapeutic approach and response for different age groups. Adults, for example, may well respond to interventions ineffective or inappropriate in children or adolescents.
- In future studies of antidepressants and other pharmacological approaches, avoidance, where possible, of drugs which themselves can directly influence IBD symptom scores, for example by reducing stool frequency (181). If use of such agents is unavoidable, careful account of their intestinal effects needs to be taken in trial design and analysis.
- Assessment of the value of training in the use of specific coping techniques (127) .
- The impracticality, given current health cost restrictions in most countries, of certain potential therapeutic approaches. Despite the likely importance of individualization of therapy, attention should be given to assessing the efficacy of group as opposed to single person-to-person therapies.

The evaluation of the effects of psychological stress and mood disorders on the course of IBD remains in its infancy, particularly as it relates to useful therapeutic applications. The points listed above indicate that trial design needs to be improved if we are to gain a clearer idea of the possible benefit to the course of IBD of approaches aimed at modifying psychoneuroimmunological pathways (125, 126).

Patients suffering with IBD vary dramatically in their psychological response to the illness: despite significant morbidity from their IBD, many appear heroically resilient. For those who develop or already have associated psychological stress or other mood disturbances, management should be holistic and, as far as possible, individualized.

Nevertheless, it is clear that at the same time as optimizing conventional treatment of their IBD, physicians should look out, and even formally screen for psychological stress and mood disorders in their patients. They should be ready and able to offer patients therapies directed at improving their psychological state, even if such approaches have not yet been shown to reduce IBD activity. At the very least, physicians should ensure that they have in place routes for prompt referral of their patients to colleagues with expertise in the management of psychological disorders. What remains unclear is which of the wide range of available interventions is most appropriate for individual patients with IBD

who have associated psychological illness. Further formal well-designed randomized controlled trials of psychological interventions are urgently needed, and should focus in particular on their effects on objectively assessed activity of the associated bowel disease.

CHAPTER 8: REFERENCES

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APPENDICES

APPENDIX 1: QUESTIONNAIRES

The following questionnaires were used in the thesis:

A1.1 Smoking study: Beliefs about smoking in patients with inflammatory bowel disease

A1.2 Montreal Classification of IBD

A1.3 Perceived Stress Questionnaire (General and Recent)

A1.4 Hospital Anxiety & Depression Score

A1.5 State Trait Anxiety Inventory

A1.6 Multidimensional health locus of control (MHLC) scales (Form C)

A1.7 Stanford Hypnotisability Susceptibility Score

A1.1: SMOKING STUDY

BELIEFS ABOUT SMOKING IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Please complete this form, if you have any problems with the questions we will help you if necessary. The information is strictly confidential.

1) What condition do you suffer?

Crohn's Disease		Ulcerative Colitis	

2) Will smoking worsen your condition?

Yes		No	

3) Are you a smoker?

Yes		No	

If yes, please complete the following questions:

4) How many cigarettes do you smoke per day?

_____per day

5) Have you ever been advised to stop smoking

a) By you GP

Yes		No	

b) By your Gastroenterologist

Yes		No	

6) Have you ever tried to stop smoking?

Yes		No	

7) Have you been to a smoking cessation clinic

Yes		No	

8) Are you aware there is a smoking cessation clinic in the hospital?

Yes		No	

9) Would you consider attending the smoking cessation?

Yes		No	

10) Do you smoke more when your disease is active?

Yes		No	

11) Do you smoke more when you are stressed?

Yes		No	

Please turn over

How soon after you wake up do you smoke your first cigarette?	Within 5 mins	3
	6-30 mins	2
	31-60 mins	1
	> 60mins	0
Do you find it difficult to stop smoking in no smoking areas?	Yes	1
	No	0
Which cigarette would you hate most to give up?	The first of the morning	1
	Any other	0
How many cigarettes per day do you usually smoke?	10 or less	0
	11-20	1
	21-30	2
	30 or more	3
Do you smoke more frequently in the first hours after waking than during the rest of the day?	No	0
	Yes	1
Do you smoke if you are so ill that you are in bed most of the day?	No	0
	Yes	1

Thank you for completing this questionnaire

A1.2: MONTREAL CLASSIFICATION OF IBD

Crohn's Disease		
Age at diagnosis	A1: <16	
	A2: 17-40	
	A3: >40	
Location	L1: Ileal	
	L2: Colonic	
	L3: Ileo-colonic	
	L4: Upper GI	
Behaviour	B1: Inflammatory	
	B2: Stricturing	
	B3: Penetrating	
	P: Perianal	
Ulcerative Colitis		
Age at diagnosis	A1: <16	
	A2: 17-40	
	A3: >40	
Location	Extensive	
	Left sided	
	Proctitis	

A1.3: PERCEIVED STRESS QUESTIONNAIRE

General PS Questionnaire

Name: _____ Age: _____ Date: _____

Sex: _____ Marital status: _____ Occupation: _____

Instructions: For each sentence, mark the number that describes how often it applies to you *in general, during the last two years*. Work quickly, without bothering to check your answers, and be careful to describe your life *in the long run*.

	Almost never	Some-times	Often	Usually
1. You feel rested	1	2	3	4
2. You feel that too many demands are being made on you	1	2	3	4
3. You are irritable or grouchy	1	2	3	4
4. You have too many things to do	1	2	3	4
5. You feel lonely or isolated	1	2	3	4
6. You find yourself in situations of conflict	1	2	3	4
7. You feel you're doing things you really like	1	2	3	4
8. You feel tired	1	2	3	4
9. You fear you may not manage to attain your goals	1	2	3	4
10. You feel calm	1	2	3	4
11. You have too many decisions to make	1	2	3	4
12. You feel frustrated	1	2	3	4
13. You are full of energy	1	2	3	4
14. You feel tense	1	2	3	4
15. Your problems seem to be piling up	1	2	3	4
16. You feel you're in a hurry	1	2	3	4
17. You feel safe and protected	1	2	3	4
18. You have many worries	1	2	3	4
19. You are under pressure from other people	1	2	3	4
20. You feel discouraged	1	2	3	4
21. You enjoy yourself	1	2	3	4
22. You are afraid for the future	1	2	3	4
23. You feel you're doing things because you have to, not because you want to	1	2	3	4
24. You feel criticized or judged	1	2	3	4
25. You are lighthearted	1	2	3	4
26. You feel mentally exhausted	1	2	3	4
27. You have trouble relaxing	1	2	3	4
28. You feel loaded down with responsibility	1	2	3	4
29. You have enough time for yourself	1	2	3	4
30. You feel under pressure from deadlines	1	2	3	4

Recent PS Questionnaire

Name: _____ Age: _____ Date: _____

Sex: _____ Marital status: _____ Occupation: _____

Instructions: For each sentence, mark the number that describes how often it applies to you *during the last month*. Work quickly, without bothering to check your answers, and be careful to consider *only the last month*.

	Almost never	Some-times	Often	Usually
1. You feel rested	1	2	3	4
2. You feel that too many demands are being made on you	1	2	3	4
3. You are irritable or grouchy	1	2	3	4
4. You have too many things to do	1	2	3	4
5. You feel lonely or isolated	1	2	3	4
6. You find yourself in situations of conflict	1	2	3	4
7. You feel you're doing things you really like	1	2	3	4
8. You feel tired	1	2	3	4
9. You fear you may not manage to attain your goals	1	2	3	4
10. You feel calm	1	2	3	4
11. You have too many decisions to make	1	2	3	4
12. You feel frustrated	1	2	3	4
13. You are full of energy	1	2	3	4
14. You feel tense	1	2	3	4
15. Your problems seem to be piling up	1	2	3	4
16. You feel you're in a hurry	1	2	3	4
17. You feel safe and protected	1	2	3	4
18. You have many worries	1	2	3	4
19. You are under pressure from other people	1	2	3	4
20. You feel discouraged	1	2	3	4
21. You enjoy yourself	1	2	3	4
22. You are afraid for the future	1	2	3	4
23. You feel you're doing things because you have to, not because you want to	1	2	3	4
24. You feel criticized or judged	1	2	3	4
25. You are lighthearted	1	2	3	4
26. You feel mentally exhausted	1	2	3	4
27. You have trouble relaxing	1	2	3	4
28. You feel loaded down with responsibility	1	2	3	4
29. You have enough time for yourself	1	2	3	4
30. You feel under pressure from deadlines	1	2	3	4

A1.4: HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

Name: _____ Date: _____

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.
This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.
Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

	FOLD HERE			FOLD HERE	
A	**D**			**A**	**D**
		I feel tense or .wound up.	**I feel as if I am slowed down**		
3		Most of the time	Nearly all the time		**3**
2		A lot of the time	Very often		**2**
1		From time to time, occasionally	Sometimes		**1**
0		Not at all	Not at all		**0**
		I still enjoy the things I used to enjoy	**I get a sort of frightened feeling like .butterflies. in the stomach**		
	0	Definitely as much			
	1	Not quite so much	Not at all	**0**	
	2	Only a little	Occasionally	**1**	
	3	Hardly at all	Quite often	**2**	
			Very often	**3**	
		I get a sort of frightened feeling as if something awful is about to happen	**I have lost interest in my appearance**		
			Definitely		**3**
3		Very definitely and quite badly	I don't take as much care as I should		**2**
2		Yes, but not too badly	I may not take quite as much care		**1**
1		A little, but it doesn't worry me	I take just as much care as ever		**0**
0		Not at all			
		I can laugh and see the funny side of things	**I feel restless as if I have to be on the move**		
	0	As much as I always could	Very much indeed		**3**
	1	Not quite so much now	Quite a lot		**2**
	2	Definitely not so much now	Not very much		**1**
	3	Not at all	Not at all		**0**
		Worrying thoughts go through my mind	**I look forward with enjoyment to things**		
3		A great deal of the time	As much as I ever did	**0**	
2		A lot of the time	Rather less than I used to	**1**	
1		Not too often	Definitely less than I used to	**2**	
0		Very little	Hardly at all	**3**	
		I feel cheerful	**I get sudden feelings of panic**		
	3	Never	Very often indeed		**3**
	2	Not often	Quite often		**2**
	1	Sometimes	Not very often		**1**
	0	Most of the time	Not at all		**0**
		I can sit at ease and feel relaxed	**I can enjoy a good book or radio or television programme**		
0		Definitely			
1		Usually	Often	**0**	
2		Not often	Sometimes	**1**	
3		Not at all	Not often	**2**	
			Very seldom	**3**	
		Now check that you have answered all the questions			
				A	**D**
			TOTAL		

A1.5: STATE-TRAIT ANXIETY INVENTORY FOR ADULTS

(For use by Mahmood Wahed only. Received from Mind Garden, Inc. on December 13, 2007)

To whom it may concern,

This letter is to grant permission for the above named person to use the following copyright material;

Instrument: **State-Trait Anxiety Inventory for Adults**;
Authors: *Charles D. Spielberger, in collaboration with R.L. Gorsuch, G.A. Jacobs, R. Lushene, and P.R. Vagg*. Copyright: 1968, 1977 by Charles D. Spielberger

for his/her thesis research.

Five sample items from this instrument may be reproduced for inclusion in a proposal, thesis, or dissertation. The entire instrument may not be included or reproduced at any time in any other published material.

Sincerely,
Vicki Jaimez
Mind Garden, Inc.
www.mindgarden.com

DIRECTIONS:

A number of statements which people have used to describe themselves are given below. Read each statement and then blacken the appropriate circle to the right of the statement to indicate how you feel *right* now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

SELF-EVALUATION QUESTIONNAIRE STAI Form Y-1

Please provide the following information:

Name Date S____

Age Gender (*Circle*) **M F** T____

			NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1.	*I feel calm*	.....	**1**	**2**	**3**	**4**
2.	*I feel secure*	.....	**1**	**2**	**3**	**4**
3.	*I am tense*	.....	**1**	**2**	**3**	**4**
4.	*I feel strained*	.....	**1**	**2**	**3**	**4**
5.	*I feel at ease*	.....	**1**	**2**	**3**	**4**

A1.6: MULTIDIMENSIONAL HEALTH LOCUS OF CONTROL (MHLC) SCALES (Form C)

Instructions: Each item below is a belief statement about your medical condition with which you may agree or disagree. Beside each statement is a scale which ranges from strongly disagree (1) to strongly agree (6). For each item we would like you to circle the number that represents the extent to which you agree or disagree with that statement. The more you agree with a statement, the higher will be the number you circle. The more you disagree with a statement, the lower will be the number you circle. Please make sure that you answer EVERY ITEM and that you circle ONLY ONE number per item. This is a measure of your personal beliefs; obviously, there are no right or wrong answers.

1=STRONGLY DISAGREE **(SD)** 2=MODERATELY DISAGREE **(MD)** 3=SLIGHTLY DISAGREE **(D)**	4=SLIGHTLY AGREE **(A)** 5=MODERATELY AGREE **(MA)** 6=STRONGLY AGREE **(SA)**

		SD	MD	D	A	MA	SA
1	If my condition worsens, it is my own behaviour which determines how soon I will feel better again.	1	2	3	4	5	6
2	As to my condition, what will be will be.	1	2	3	4	5	6
3	If I see my doctor regularly, I am less likely to have problems with my condition.	1	2	3	4	5	6
4	Most things that affect my condition happen to me by chance.	1	2	3	4	5	6
5	Whenever my condition worsens, I should consult a medically trained professional.	1	2	3	4	5	6
6	I am directly responsible for my condition getting better or worse.	1	2	3	4	5	6
7	Other people play a big role in whether my condition improves, stays the same, or gets worse.	1	2	3	4	5	6
8	Whatever goes wrong with my condition is my own fault.	1	2	3	4	5	6
9	Luck plays a big part in determining how my condition improves.	1	2	3	4	5	6
10	In order for my condition to improve, it is up to other people to see that the right things happen.	1	2	3	4	5	6
11	Whatever improvement occurs with my condition is largely a matter of good fortune.	1	2	3	4	5	6
12	The main thing which affects my condition is what I myself do.	1	2	3	4	5	6
13	I deserve the credit when my condition improves and the blame when it gets worse.	1	2	3	4	5	6
14	Following doctor's orders to the letter is the best way to keep my condition from getting any worse.	1	2	3	4	5	6
15	If my condition worsens, it's a matter of fate.	1	2	3	4	5	6
16	If I am lucky, my condition will get better.	1	2	3	4	5	6
17	If my condition takes a turn for the worse, it is because I have not been taking proper care of myself.	1	2	3	4	5	6
18	The type of help I receive from other people determines how soon my condition improves.	1	2	3	4	5	6

A1.7 STANFORD HYPNOTIC SUSCEPTIBILITY SCALE, FORM C (Summary)

Andre M. Weitzenhoffer & Ernest R. Hilgard

Stanford University

Modified by John F. Kihlstrom

Summary of protocol:

Establishing Rapport

ITEM 0 INDUCTION BY EYE CLOSURE

ITEM 1 HAND LOWERING.

ITEM 2 MOVING HANDS APART.

ITEM 3 MOSQUITO HALLUCINATION.

ITEM 4 TASTE HALLUCINATION.

ITEM 5 ARM RIGIDITY

ITEM 6 DREAM

ITEM 7 AGE REGRESSION

ITEM 8 ARM IMMOBILIZATION

ITEM 9 ANOSMIA

ITEM 10 HALLUCINATED VOICE

ITEM 11. NEGATIVE VISUAL HALLUCINATION

ITEMS 12/13 POSTHYPNOTIC SUGGESTION AND AMNESIA

POST-EXPERIMENTAL INTERVIEW

Note on the Modifications

The various Stanford scales of hypnotic susceptibility have served the field of hypnosis extremely well for more than 30 years. Nonetheless, over the years certain modifications seemed desirable. Very quickly, for example, the original authors sanctioned a group version of the Stanford Hypnotic Susceptibility Scale, Form A, known as the Harvard Group Scale of Hypnotic Susceptibility, Form A (a Form B is also in existence, roughly paralleling the Stanford Form B); later, Arlene H. Morgan and Josephine R. Hilgard adapted the Stanford scales for clinical testing of adults and children, and E.R.

Hilgard proposed that the Stanford Hypnotic Susceptibility Scale, Form C be tailored for special purposes, so that some of the screening purposes of the Stanford Profile Scales of Hypnotic Susceptibility, Forms I and II, could be accomplished without additional testing.

There are five principal modifications in the present version of SHSS:C. (1) The wording of the Induction by Eye Closure (Item #0) has been altered slightly to reduce unintended connotations of authoritarian control present in the original. (2) Age Regression (Item #7) permits the subject to choose between two target ages within each epoch. (3) Anosmia (Item #9) substitutes oil of peppermint for ammonia. (4) Posthypnotic Amnesia (Item #12) is assessed in terms of a joint criterion considering both initial amnesia and subsequent reversibility, and the instructions for the reversibility test now ask subjects to report *all* items they remember; in addition, an optional recognition test of amnesia has been included, following procedures developed by John J. Allen at the University of Minnesota (the recognition test does not compromise the standard amnesia test of SHSS: C). (5) Finally, a test of Posthypnotic Suggestion (Item #13) modified from SHSS:A has been added to reflect the special interests of the laboratory, although it does not enter into the scoring of the scale. John F. Kihlstrom

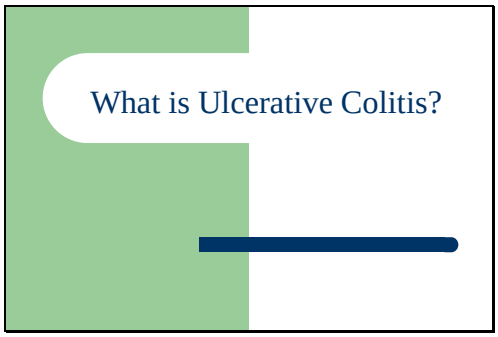
Note: If a subject fails to respond to *three consecutive suggestions*, the experimenter should terminate the scale with Item #12 (Posthypnotic Amnesia), including Item #13 (Posthypnotic Suggestion).

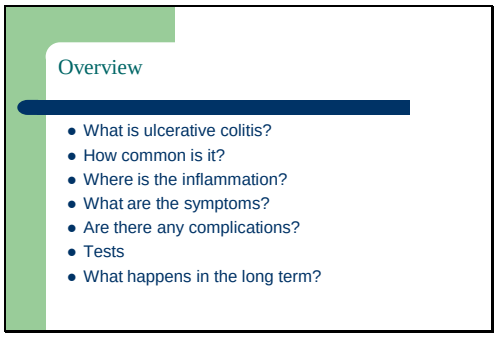
APPENDIX 2: HYPNOTHERAPY STUDY - EDUCATION SESSIONS

The following are the control education sessions in the randomised study of hypnotherapy for the prevention of relapse in ulcerative colitis study (written by MW).

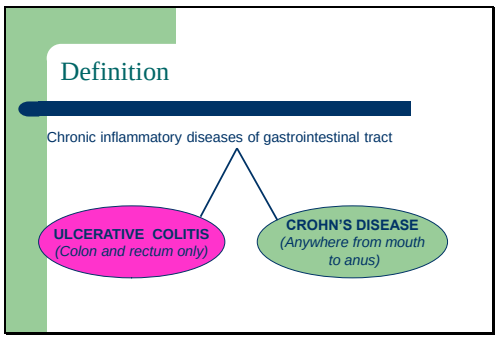
Education session 1: What is ulcerative colitis?

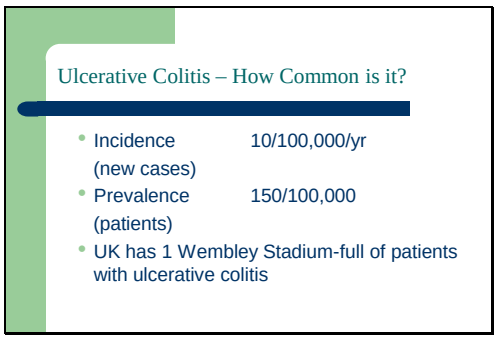
Slide 1+2





Slide 3+4





Slide 5+6

Age of Onset

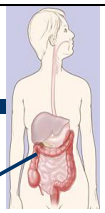
- 2 age peaks
  - 20 – 40 years old
  - 60 – 80 years old
- Not much difference between men and women

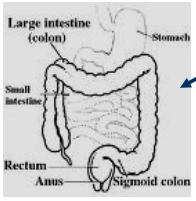
Epidemiology

- Can affect up to 5% of immediate family (mum, dad, brother, sister)
- Related to
  - Non-smoking

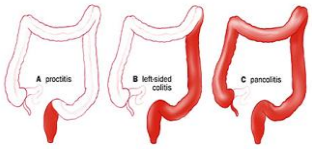
Slide 7+8

Structure of the colon?





Which part of the colon is affected ?

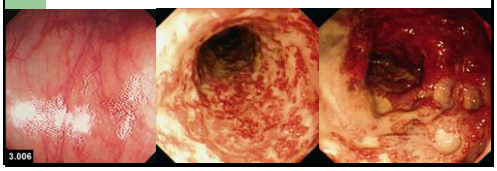


- Rectum – Proctitis
- Left sided colitis
- Total colitis

Slide 9+10

Endoscopic Appearances

normal *ulcerative colitis*



What are the symptoms ?

- diarrhoea, often bloody
- urgency to empty bowel
- abdominal pain
- weight loss
- feeling generally unwell

Slide 11+12

When do symptoms occur ?

- relapses & remissions

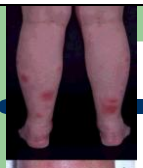
- onset any age
- life-long

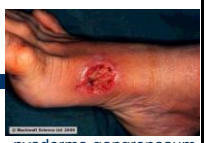
Other symptoms – outside the bowel

- Skin
- Eyes
- Joints
- Liver

Slide 13+14

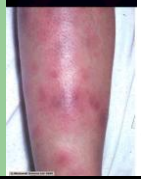
Skin





pyoderma gangrenosum

(this is very rare)



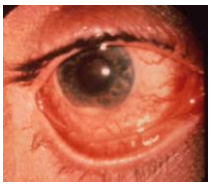
erythema nodosum

(this is rare)

Eyes

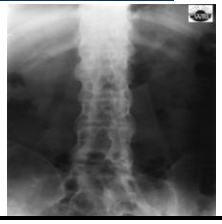
Iritis

(rare)



Slide 15+16

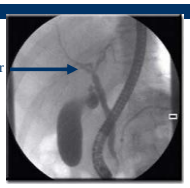
Ankylosing Spondylitis (again rare)



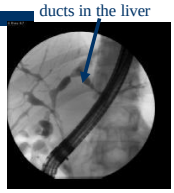
Sclerosing cholangitis

Scarring of the bile ducts in the liver

Liver



normal



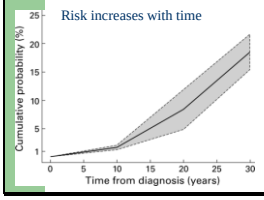
sclerosing cholangitis

Slide 17+18

Complications

- In the bowel:
  - Bleeding from ulceration
  - Perforation
  - Cancer

Colorectal Cancer



Other risk factors

- extent of disease
- sclerosing cholangitis
- other family members with bowel cancer
- poorly controlled disease

Slide 19+20

Tests

- To make the diagnosis of ulcerative colitis
- To find out how much of the colon is affected
- To assess current disease activity
- To look for any complications

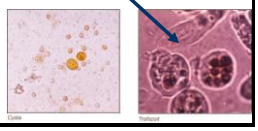
Investigations – Blood tests

- Diagnosis and disease activity
  - Haemoglobin
  - Inflammatory markers
- If anaemia present, check iron levels
- Complications
  - Liver function tests

Slide 21+22

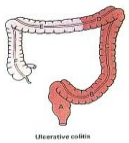
Investigations – Exclude infection

- Infection complicates/initiates 10% UC relapses
- Hot fresh stool
  - Microscopy for amoebae in travellers
  - Clostridium difficile toxin



Investigation - Endoscopy

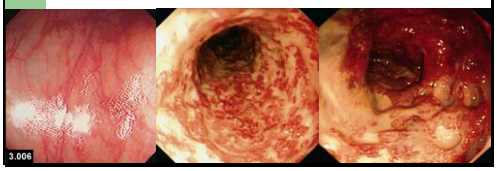
- Sigmoidoscopy with biopsies
- Colonoscopy with biopsies



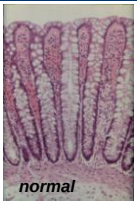
Slide 23+24

Endoscopic Appearances

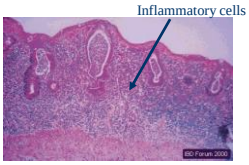
normal *ulcerative colitis*



Biopsies appearances (under the microscope)



normal



ulcerative colitis

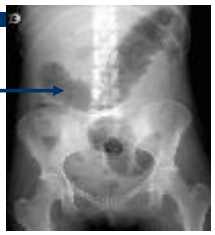
Slide 25+26

Xray tests

- Abdominal X ray
- CT scan
- WBC Scan

Abdominal X ray in acute ulcerative colitis

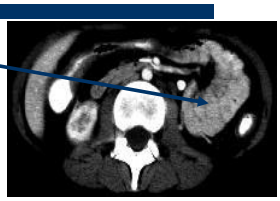
- Transverse colon dilation, mucosal islands and "thumb-printing"



Slide 27+28

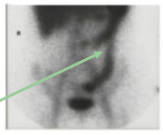
CT scan

- Inflammed colon

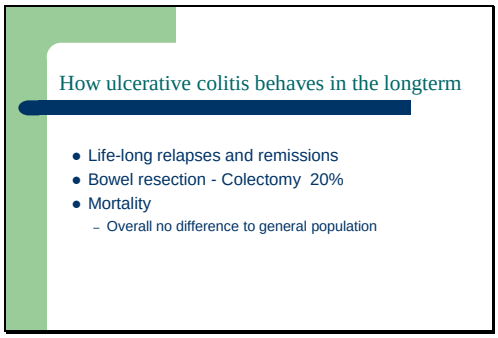


Assessing disease extent in ulcerative colitis with radiolabelled white cell scan

- This involves giving a blood sample. The white cells are then labelled with a small amount of a tracer and then blood is replaced back. The images taken with camera
- 99-Tc HMPAO scan
- UC extending to mid-transverse colon

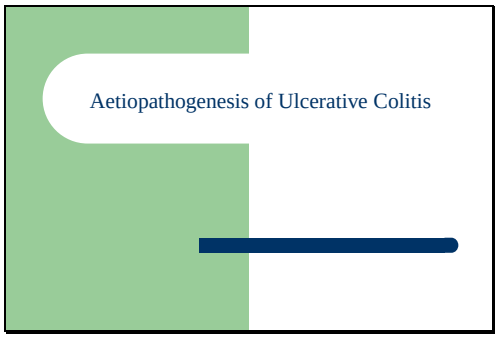


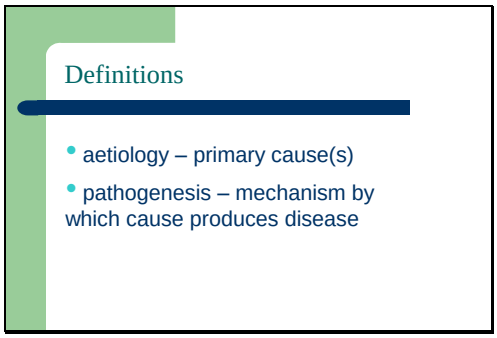
Slide 29


How ulcerative colitis behaves in the longterm
Life-long relapses and remissions
Bowel resection - Colectomy 20%
Mortality
Overall no difference to general population

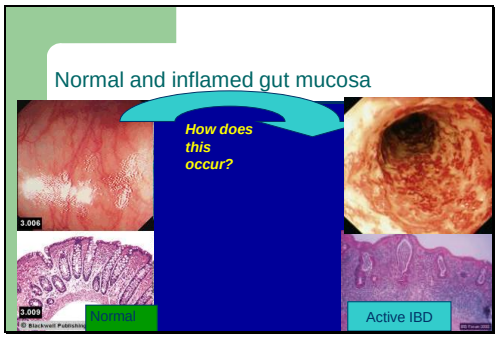
Education session 2: The aetiopathogenesis of ulcerative colitis.

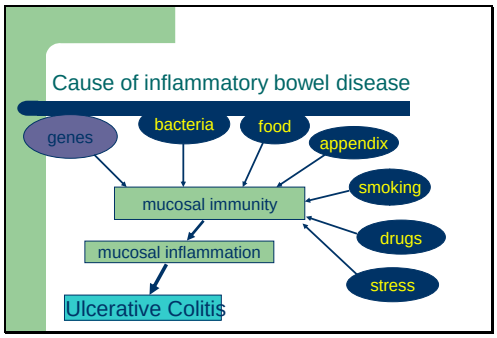
Slide 1+2



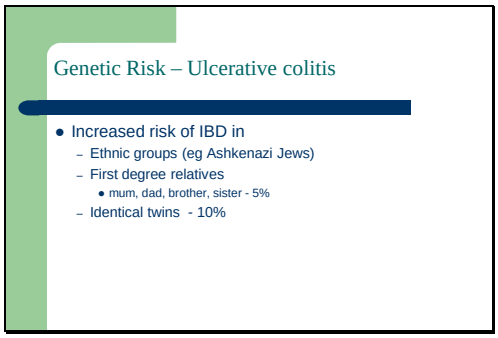


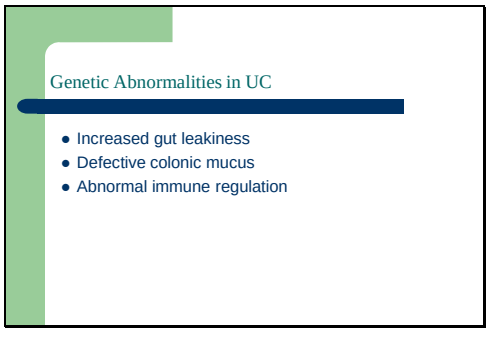
Slide 3+4





Slide 5+6





Slide 7+8

Intestinal bugs (bacteria)

- UC symptoms and pathology look like those caused by bacterial infection
- Onset and relapse of UC may be triggered by infections (C diff, salmonella, amoebae….)

Gut bugs (bacteria) in IBD

- More bugs in the colon than cells in the body!
- Resident gut bugs are likely to be a major environmental factor in IBD
- Balance of “good” and “bad” bugs changes
- Mucosal immunity influenced by gut bugs
- Some patients with IBD respond to antibiotics and probiotics

Slide 9+10

Diet in UC

- Cows’ milk intolerance (Up to 5%)
- No other dietary factors are known

- **What is this?**

Slide 11+12

Appendix in UC

- Risk of UC is reduced in people with appendicectomy at age less than 20
- The appendix is often in inflamed in patients with UC

Non smoking and UC

- UC commoner in non- and ex-smokers
- Nicotine patches have some effect in treating active UC
- Why smoking is good for UC but bad for Crohn’s is unknown

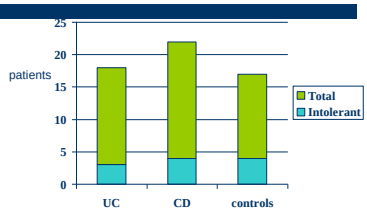
Slide 13+14

Can drugs initiate relapse in UC

- NSAIDs - bad for all IBD
- Opioids (loperamide, codeine) – cause bowel distension in acute severe UC
- Antibiotics - unproven
- Iron - unproven

Slide 15+16

Oral iron well tolerated and effective in UC



- Ferrous sulphate also as effective in restoring Hb in IBD as in controls

Psychological stress

Hockney 1962

Slide 17+18

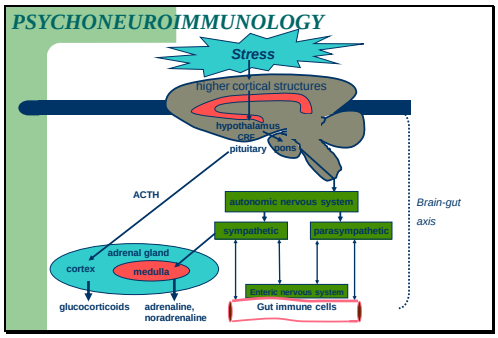
What is stress?

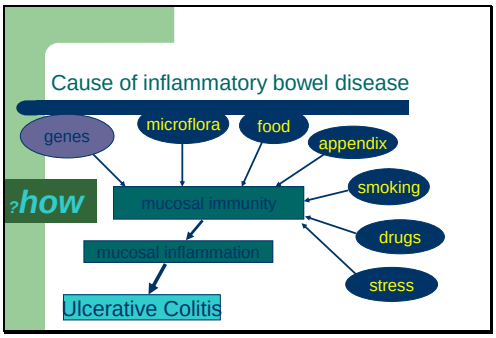
- A (real or perceived) threat to an organism's homeostasis
  - physical
  - psychological
- Function of stress response is to maintain individual's physical or psychological stability

Stress - UC

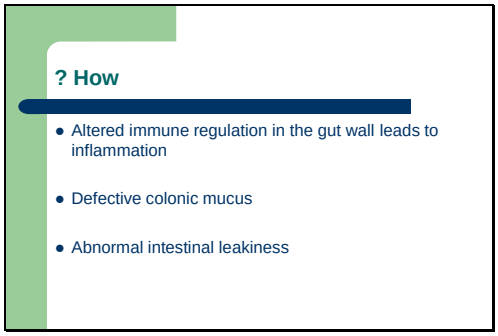
- Psychological stress is common in patients with IBD
- Stress may trigger flare of UC
- This may be mediated by
  - Brain - Gut interactions
  - Brain – Adrenal gland interactions

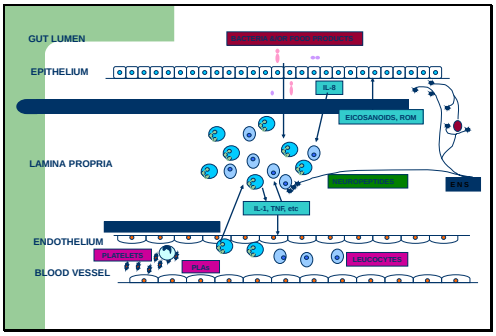
Slide 19+20





Slide 21+22





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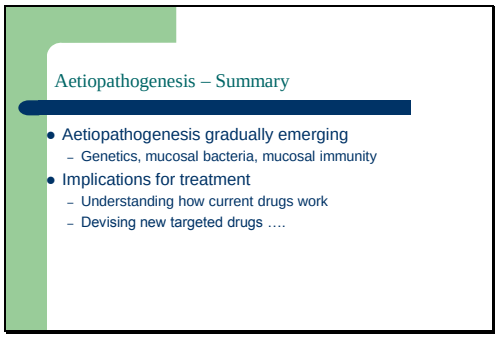
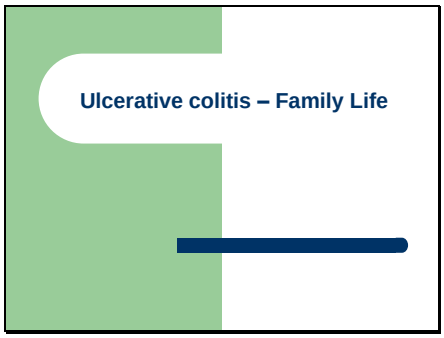
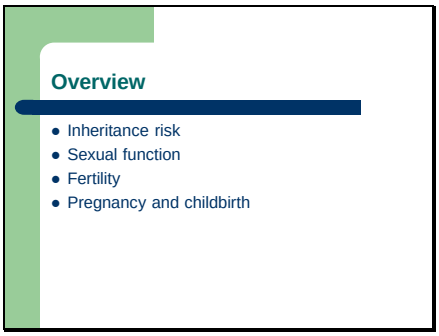


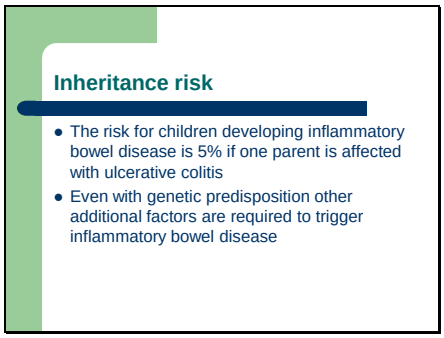
Education session 3: Ulcerative colitis – implications for family life

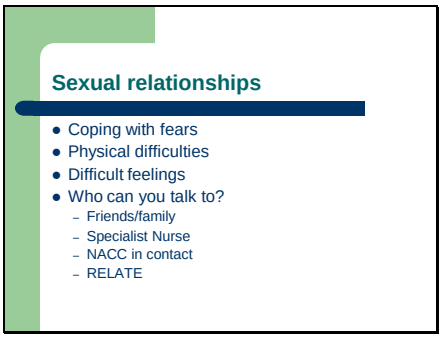
Slide 1+2



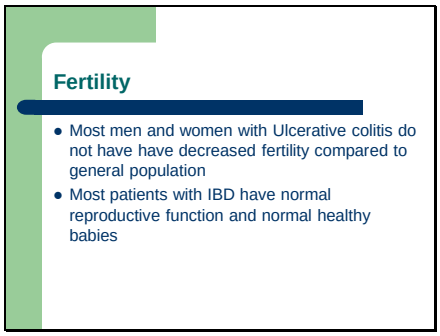


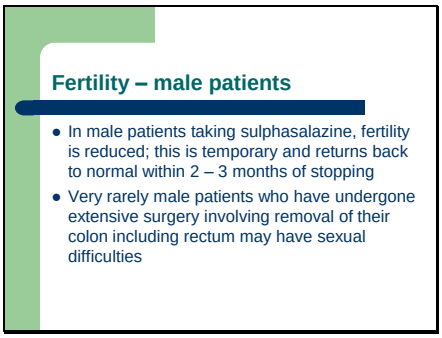
Slide 3+4





Slide 5+6





Slide 7+8

Fertility – female patients

- Females who have undergone pouch surgery for UC have a risk of reduced fertility
- Oral contraceptive pill
  - Important to remember that severe diarrhoea may reduce the protective effect of the pill

Pregnancy

- Does pregnancy affect the activity of the disease?
- Does ulcerative colitis affect the outcome of pregnancy?

Slide 9+10

Does pregnancy affect the activity of the disease?

- Pregnancy itself has no consistent effect on the activity of ulcerative colitis

Does ulcerative colitis affect the outcome of pregnancy?

- If disease is inactive at the time of conception, the chances of having a healthy baby are the same as the general population
- If disease is active at the time of conception there is an increased risk to baby (premature delivery, abortion) and other pregnancy complications are increased

Slide 11+12

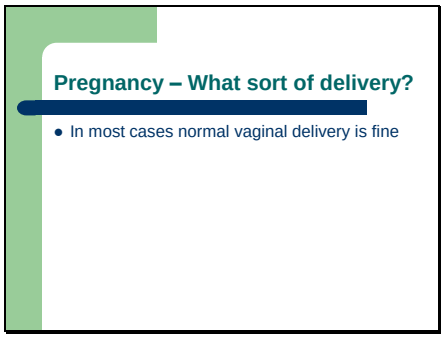
Does medication for ulcerative colitis taken in pregnancy affect the foetus?

- Important to keep disease under control
- Most of the drugs including azathioprine are safe during conception and pregnancy
- **Methotrexate** should **NOT** be taken by either partner as there is a risk of congenital birth defects

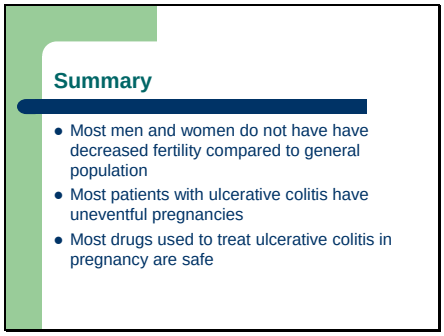
Pregnancy - Diet

- Patients do not require a special diet
- Balanced diet with adequate intake of calories, vitamins and minerals

Slide 13+14

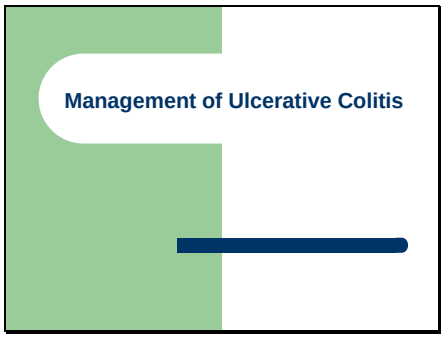


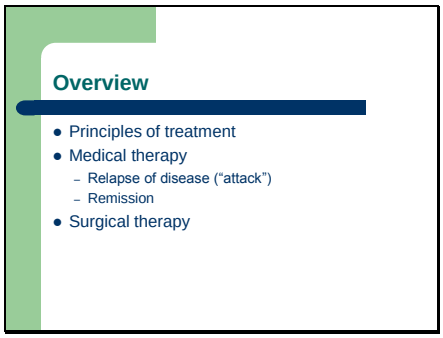
Slide 15



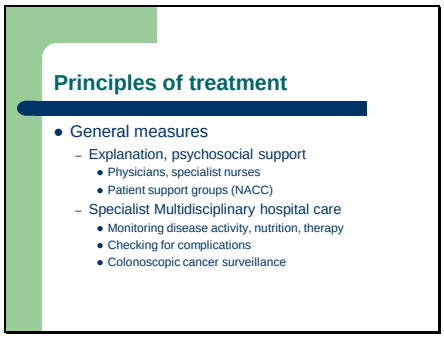
Education session 4: Management of Ulcerative Colitis

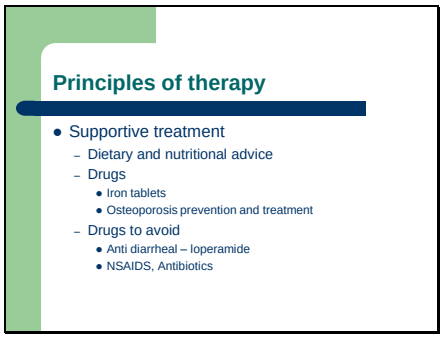
Slide 1+2



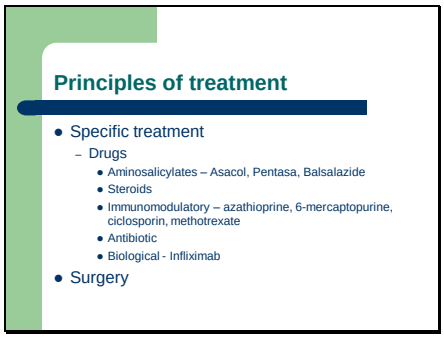


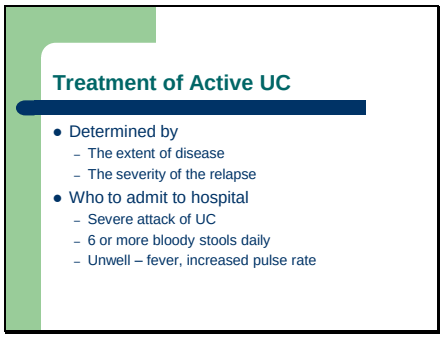
Slide 3+4





Slide 5+6





Slide 7+8

Mild attack

- 5 ASA orally (asacol/pentasa/balsalazide/sulphasalazine)
  - Dose up to 4.8g daily (12 tablets/sachets)
- Topically (directly into rectum)
  - Proctitis – suppositories
    - Asacol,pentasa
    - Predsol
  - Left sided disease – foam or retention enema
    - Asacol, pentasa
    - predfoam

Moderate attack

- As mild plus
- Oral Prednisolone (steroids)
  - 40mg daily – weekly reduction of dose
- Calcium supplements (Calcichew D3 Forte) to protect bones

Slide 9+10

Severe attack

- Intravenous (hydrocortisone or methylprednisolone) then oral prednisolone
- Continue with 5 ASA (asacol/pentasa/sulphasalazine/balsalazide)
- Antibiotics if infection is suspected
- If no response to steroids at 3-7 days consider
  - Ciclosporin
  - Infliximab
- Surgery for non responders at 5-7 days, dilated colon, perforation or major haemorrhage

Keeping UC inactive (in remission)

- 5 ASA drugs (asacol/pentasa/suphasalazine/balsalazide)
  - 2g-2.4g daily
  - Reduces risk of bowel cancer
  - Blood test every 6 months – 1year
- Azathioprine, mercatopurine
  - Patients who have repeated attacks
  - Careful monitoring required – blood tests every 3 months

Slide 11+12

Medical treatment - summary

- Depends on disease extent and severity
- Active UC is treated primarily with steroids and 5 ASA
- Maintenance of remission achieved with 5ASA, although azathioprine/mercaptopurine required for patients in whom 5ASA (asacol/pentasa/suphasalazine/balsalazide) are ineffective

Surgery for ulcerative colitis

Slide 13+14

Surgery for Ulcerative Colitis

- Who is involved in the decision?
- Reasons for surgery
- Types of operation

Surgery – who is involved?

- The patient will be closely involved in the decision
- Requires close liaison with physicians and surgeons
- Specialist nursing care
- Stoma therapist
- Dietician
- Counsellor

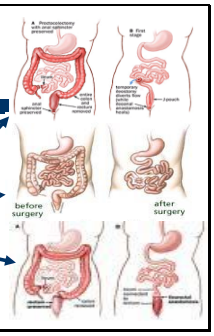
Slide 15+16

Reasons for surgery

- Emergency
  - Colonic perforation
  - Major colonic bleeding
- Urgent
  - Non response to medical treatment of bad attack of ulcerative colitis in 5-8 days
  - Dilating colon
- Elective
  - Chronic active UC despite medical treatment
  - Dysplasia (abnormal cells) on colon biopsy / Cancer

Types of operation

- Restorative protocolectomy with ileoanal pouch
  - Most people
- Protocolectomy with ileostomy
  - Older people
- Colectomy with ileorectal anastomosis
  - Young people



Slide 17

Surgery - summary

- Surgery offers a cure for ulcerative colitis
- The patient should be closely involved in the decision to have surgery

APPENDIX 3: PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

Published papers:

1. Wahed M, Goodhand JR, West O, McDermott A, Hajek P, Rampton DS. Tobacco dependence and awareness of health risks of smoking in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2011;23(1):90-4.
2. Goodhand, JR, Giles, CL, Wahed, M et al. (2011). Poster presentations at medical conferences: an effective way of disseminating research?. Clin Med vol. 11, (2) 138-141
3. Wahed M & Emmanuel A. Does hypnotherapy have a role in the management of IBD? Gastrointestinal Nursing 2010; 8(4): 42-47
4. Wahed M, Corser M, Goodhand JR, Rampton DS. Does psychological counselling alter the natural history of Inflammatory bowel disease? Inflam Bowel Dis 2009; 16 (4):664-9
5. Goodhand JR* & Wahed M &, Rampton DS. Management of stress in inflammatory bowel disease: a therapeutic option? Expert Rev Gastro Hep 2009; 3: 661-79.
   *Equal contribution by both authors
6. Wahed M & Rampton DS. The impact of counselling and other psychological treatments on IBD. Practical Gastro 2009

Abstracts:

1. Wahed M, Goodhand JR, Irving PM, Sanderson J, Bloom SL, McCartney S, Mawdsley J, Rampton DS. Anxiety and psychological stress in acute severe ulcerative colitis: Prevalence and effect on outcome. Gastroenterology 2011; 140 (5) Suppl 1, S60-S61

2. Wahed M, Smith M, Langmead L, J. Mawdsley J, Goodhand JR, Emmanuel AV, Rampton DS. Hypnotherapy for the prevention of relapse in ulcerative colitis: a multi-centred, randomised, single-blind, controlled clinical trial. P0944: UEGW 2011

Oral Presentations:

1. Digestives Disorders Week 2011, Chicago

   Wahed M, Goodhand JR, Irving PM, Sanderson J, Bloom SL, McCartney S, Mawdsley J, Rampton DS. Anxiety and psychological stress in acute severe ulcerative colitis: Prevalence and effect on outcome.

2. Broad Medical Research Program 2011, Los Angeles

   Wahed M, Smith M, Langmead L, J. Mawdsley J, Goodhand JR, Emmanuel AV, Rampton DS. Hypnotherapy for the prevention of relapse in ulcerative colitis: a multi-centred, randomised, single-blind, controlled clinical trial