Six studies pointing to the need for a biopsychosocial approach to treating common gastrointestinal and hepatologic disorders

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Table of Contents

List of Figures

List of Appendices

Appendix 1: Features of 17 studies describing the co-morbidity of psychological problems with IBD in alphabetical order

Appendix 2: Information sheet for research participants

Appendix 3: Royal Adelaide Hospital consent form

Appendix 4: A letter to treating gastroenterologist

Appendix 5: Survey for inflammatory bowel disease patients

Appendix 6: Survey for irritable bowel syndrome patients

Appendix 7: Survey for hepatitis C patients

Appendix 8: Crohn's Disease Activity Index (CDAI)

Appendix 9: Simple Clinical Colitis Activity Index

Appendix 10: Hospital Anxiety and Depression Scale

Appendix 11: Bowel Disease Questionnaire (BDQ)

Appendix 12: Information sheet for doctors

Appendix 13: Royal Adelaide Hospital consent form for doctors

Appendix 14: An Interview's script

Appendix 15: Transcripts of interviews

Appendix 16: Features of 12 studies describing the effect of antidepressants on the course of inflammatory bowel disease in order of the quality significance

Appendix 17: Quality assessment of 12 studies describing the effect of antidepressants on the course of inflammatory bowel disease in order of the quality significance

Abstract

Background and aims

This interdisciplinary thesis was designed to deepen understanding of the co-morbidity of anxiety and depression with chronic diseases of the digestive tract, and inflammatory bowel disease (IBD) in particular. The first part of the thesis aimed to explore the prevalence of psychological problems in IBD compared to irritable bowel syndrome (IBS) and chronic hepatitis C (HCV) groups. It also explored the relationship between the number of co-morbid functional gastrointestinal disorders and the severity of psychological problems in IBD and IBS. It also aimed to determine whether there is a relationship between psychological problems and the response to standard medical treatment/physical outcomes in patients with IBD, IBS and HCV. Furthermore, it aimed to explore whether disclosure of the psychological status of depressed and/or anxious IBD patients to their gastroenterologists influences doctors' behaviour and affects patients' responses to treatment/physical outcomes. The second part of the thesis aimed to investigate the potential role of antidepressants in IBD and to determine the feasibility of future randomised controlled trials on the role of antidepressants in IBD.

Methods

Overall, a cohort of 139 outpatients (64 IBD, 41 HCV, and 34 IBS) and 18 gastroenterologists participated in the six studies comprising this thesis. A mixed methods design was applied. Two cross-sectional studies, an observational cohort prospective management study, a randomised controlled trial, a systematic review and an exploratory interview study were conducted. Differences between the groups for continuous variables were assesed with one way analysis of variance (ANOVA) and independent samples t-tests. Differences in categorical variables were assessed with contingency tables with the

Chi-Square test and the Fisher's Exact Test. Propsective analyses were conducted with repeated measures ANOVA, logistic regression and Poisson regression. Qualitative data were analysed using content analysis.

Results

Overall, 42% of participants were anxious and 19% were depressed. Participants with HCV had higher levels of psychological impairment compared with the IBS, the IBD group and the general population ($p<0.05$). Those IBD participants with fewer co-morbid functional disorders had better physical quality of life than participants with a greater number of these disorders ($p=0.025$). Moreover, depression/anxiety at baseline did not explain medical outcomes after 12 months in this cohort of patients with chronic diseases of the digestive tract. Doctors' knowledge of patients' psychological status was found to have no impact on IBD patients' outcomes after 12 months. However, interestingly, the level of anxiety in IBD participants significantly dropped between the baseline and nine months indicating a possible benefit from participating in the study. In the literature review, insufficient evidence was found to conclude that antidepressants are efficacious for treatment of psychological co-morbidities or somatic complaints in IBD. However, the qualitative interview study indicated a potential positive impact of treatment with antidepressants on coping with disease symptoms and general wellbeing in patients with IBD.

Conclusion

The thesis confirms that there is a significant burden of psychological co-morbidity in patients with chronic gastroenterological diseases. Interdisciplinary approaches to the management of these diseases are therefore warranted in Australian gastroenterology clinics. Anxiety targeted interventions and research in this setting are urgently needed,

especially with respect to patients with HCV. Larger studies exploring the gastroenterologists' role in treatment of co-morbid psychological problems in their patients are recommended. Longer prospective studies on homogenous samples of patients are also needed to clarify the nature of the relationship between psychological problems and relapse of somatic symptoms. Finally, randomised controlled trials exploring the efficacy of antidepressants in IBD are warranted.

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List of publications arising from this thesis at the moment of submission

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2. Mikocka-Walus, A., Turnbull, D., Andrews, J., Moulding, N., Wilson, I., Harley, H., Hetzel, D., Holtmann, G. (2008). Psychological problems in gastroenterology outpatients: A South Australian experience. *Clinical Practice and Epidemiology in Mental Health* [in press].

3. Mikocka-Walus, A., Turnbull, D., Moulding, N., Wilson, I., Andrews, J., Holtmann, G. (2007). Psychological co-morbidity and the complexity of gastrointestinal (GI) symptoms in clinically diagnosed irritable bowel syndrome (IBS) patients, *Journal of Gastroenterology and Hepatology* [in press].

4. Mikocka-Walus, A., Turnbull, D., Moulding, N., Wilson, I., Andrews, J., Holtmann, G. (2007). "It doesn't do any harm, but patients feel better": a qualitative exploratory study on gastroenterologists' perspectives on the role of antidepressants in inflammatory bowel disease, *BMC Gastroenterology*, 7(1):38.

5. Mikocka-Walus, A., Turnbull, D., Moulding, N., Wilson, I., Andrews, J., Holtmann, G.(2007). Controversies surrounding the co-morbidity of depression and anxiety in inflammatory bowel disease patients: a literature review, *Inflammatory Bowel Diseases*, 13 *(2)*: 225-234.

6. Mikocka-Walus, A., Turnbull, D., Moulding, N., Wilson, I., Andrews, J., Holtmann, G. (2006). Antidepressants and inflammatory bowel disease: a systematic review, *Clinical Practice and Epidemiology in Mental Health*, 2(1):24.

List of studies and hypotheses/research questions

Part 1

Study 1: A cross-sectional study comparing the prevalence of psychological problems and the level of quality of life in patients with IBD, IBS and HCV.

- Hypothesis 1: Patients with IBD are most affected by psychological problems compared to patients with IBS and HCV.

Study 2: A cross-sectional investigation into the prevalence of functional gastrointestinal disorders in IBD and IBS patients and exploring the relationship between the number of these disorders and the severity of psychological problems.

- Hypothesis 2: Patients with IBD and patients with IBS with the greater number of functional gastrointestinal disorders have higher levels of depression and anxiety and poorer quality of life than those with smaller number of functional disorders.

- Hypothesis 3: Patients with IBD with co-morbid IBS have higher rate of psychological problems and poorer quality of life than patients with IBD without co-morbid IBS.

Study 3: A cohort prospective management study exploring the temporal relationship between psychological co-morbidities and the likelihood of a successful response to standard medical treatment/better physical outcomes in patients with IBD, IBS and HCV.

- Hypothesis 4: Patients with psychological co-morbidities are less likely to have a satisfactory response to standard treatment/good physical outcomes at 12 months.

Study 4: A pilot randomised controlled trial examining whether disclosure of IBD patients' psychological status to their treating doctors influences patients' responses to the clinical treatment/their physical outcomes.

- Hypothesis 5: Physicians' knowledge of patients' psychological status alters physicians' behavior and/or improves patients' clinical outcomes.

Part II

Study 5: A systematic review of the literature designed to quantitatively and qualitatively explore the problem of using antidepressants in IBD.

- Are antidepressants effective in maintaining or inducing remission of inflammatory bowel disease?

Study 6: Standardised semi-structured interviews enabling in-depth exploration of gastroenterologists' experiences, opinions and attitudes about treating IBD patients with antidepressants.

- What are the gastroenterologists' attitudes and experiences of using antidepressants in patients with inflammatory bowel disease?

Abbreviations

BDI:	Beck Depression Inventory
BMI:	Body Mass Index
CAI:	Colitis Activity Index
cAMP:	Cyclic Adenosine Monophosphate
CBT:	Cognitive-Behavioural Therapy
CD:	Crohn's Disease
CDAI:	Crohn's Disease Activity Index
CES-D:	Center for Epidemiological Studies Depression Scale
CRS:	Clinical Rating Scale
DIS:	Diagnostic Interview Schedule
DSM-III:	Diagnostic and Statistical Manual of Mental Disorders-III
EPI:	Eysenck Personality Inventory
FGIDs:	Functional Gastrointestinal Disorders
GI:	Gastrointestinal
GSI:	Global Severity Index
GSRS:	Gastrointestinal Symptom Rating Scale
HADS:	Hospital Anxiety and Depression Scale
HAM-D:	Hamilton Depression Inventory
HCV:	Hepatitis C
HCVRNA:	Hepatitis C Ribonucleic Acid
IBD:	Inflammatory Bowel Disease
IBDQ:	Inflammatory Bowel Disease Questionnaire
IBS:	Irritable Bowel Syndrome
MAOI:	Monoamine Oxidase Inhibitor

MCS:	Mental Component Summary
PCS:	Physical Component Summary
PGWB:	Psychological General Well-Being Index
POMS:	Profile of Mood States
PSDI:	Positive Symptom Distress Index
PSQ:	Perceived Stress Questionnaire
PST:	Positive Symptom Total
RFIPC:	Rating Form of Inflammatory Bowel Disease Patient Concerns
SADS-L:	Schedule for Affective Disorders and Schizophrenia
SCCAI:	Simple Clinical Colitis Activity Index
sCDAI:	Simplified Crohn's Disease Activity Index
SCL-90:	Symptom Check List 90
SF-12:	Short Form 12 Health Survey
SF-36:	Short Form 36 Health Survey
SIP:	Sickness Impact Profile
SNRI:	Serotonine-Norepinephrine Reuptake Inhibitor
SSRI:	Selective Serotonine Reuptake Inhibitor
STAI:	State and Trait Anxiety Inventory
TNF:	Tumour Necrosis Factor
UC:	Ulcerative Colitis
y.o:	Years Old
Yr:	Year

Preamble

Australians are a healthy nation and a life expectancy at birth of about 80 years places them among the top five nations in the world. In a recent national survey, 56% of Australian adults and young people rated their health as excellent or very good (*Australia's health 2006: The tenth biennial health report of the Australian Institute of Health and Welfare*, 2006). Despite this optimistic figure, the latest National Health Survey showed that an estimated 77% of Australians had a long-term condition (*2004-5 National health Survey: Summary of Results*, February 2006). As would be expected, the proportion increased with age, from 41% of those aged under 15 years to over 95% of persons aged 45 years or over. However, the most commonly reported long term conditions are usually not life threatening and include problems with eyesight, hayfever and allergic rhinitis, arthritis, and back and disc disorders.

Although the death rates associated with cancer, cardiovascular disease and diabetes have declined in recent years, the prevalence of these and other chronic conditions significantly increased. Interestingly, nowadays the leading cause of the non-fatal burden of disease and injury in Australia are mental conditions and it has been estimated that one in 5 Australians will suffer from some form of mental illness at some point of their life (*Australia's health 2006: The tenth biennial health report of the Australian Institute of Health and Welfare*, 2006).

Given longer life expectancy, most people will experience chronic illness (including mental conditions) and disability in their life, and a substantial number of people will

additionally suffer from depression and/or an anxiety disorder. This gloomy vision of the future seems additionally concerning because many health care professionals, especially those who completed their education by 1980s and those beyond the general practice area, are not always prepared to satisfy the needs of the chronically ill. Until the 1980s, medical training was focused primarily on treatment of acute diseases, where for a single cause a single treatment could be offered. Chronic diseases, on the other hand, usually result from multiple causes and treatment approach is typically not as straightforward as in an acute problem. Curiously, as the latter may be effectively treated within the biomedical model, the experience of a chronic condition depends more on biopsychosocial factors such as culture or personality (Sperry, 2006). With only recent changes to the medical curriculum, in many cases the extramedical help to patients remains in the hands of allied health professionals whose training was conducted fully in light of the biopsychosocial paradigm (Engel, 1977). This thesis, being written by a psychologist, is particularly focused on integrating psychological aspects of chronic disease, seen from both a patient's and a doctor's perspective, with its medical characteristics. The author's intent was to draw a multidimensional picture of problems experienced by patients suffering from inflammatory bowel disease and other common chronic gastroenterological and hepatologic disorders: irritable bowel syndrome and chronic hepatitis C.

Importantly, the choice of these disorders to be a main focus of research on the psychological aspect of chronic conditions was not accidental. Gastroenterology has much to offer to behavioural scientists with an interest in the relationship between somatic disease and psychological problems, as the gut, while responding to environmental and physiological factors, also directly cooperates with the brain through the so-called brain-gut axis (Jones, Dilley, Drossman, & Crowell, 2006). There is, therefore, a potential for gastrointestinal (GI) conditions to be associated with mental problems (especially in the

case of functional bowel disorders) (Drossman, 1999; Levy et al., 2006). Because of this, the understanding and treatment of GI disorders must incorporate a psychological perspective. Creating a sub-discipline called "psychogastroenterology", which would link the knowledge from both fields, could improve the standard medical care of GI patients. Furthermore, the co-operation of gastroenterologists with psychologists could contribute to better understanding and more effective treatment of gastrointestinal conditions.

This interdisciplinary thesis aims to be a voice in a discussion on the closer co-existence of gastroenterology and psychology, and on the application of the biopsychosocial model to a deeper understanding of gastrointestinal disorders. Although the thesis explores the issues of interest in the context of the biopsychosocial model and aims to further demonstrate its usefulness in the area of chronic disease, it is important to acknowledge that a variety of other models could be used to better understand psychological co-morbidity in chronic gastroenterological diseases. An example may be the "Stress, appraisal and emotion" model by Lazarus (Lazarus, 1993) that explains responses to stressful situations (e.g. chronic disease) by individual differences in cognition. This thesis, however, has examined the utility of the biopsychosocial model, as it has been effective in describing functional gastrointestinal disorders and thus could be also used to better explain other gastroenterological diseases such as IBD and chronic hepatitis C (Drossman et al., 1999; Drossman, 1998a). Thus, herein, IBD, a chronic, disabling and only rarely life threatening condition, which significantly impacts on patients' quality of life and which has been controversially associated with psychological problems, was compared with: 1) a chronic and potentially life threatening hepatologic disorder with a significant psychological burden present mainly in those sufferers aware of their diagnosis (HCV), and 2) a very common chronic functional and non-life threatening condition of the gastrointestinal tract where the psychological burden is not obviously proportional to the severity of its

presentation (IBS). Exploring the co-morbidity of these three common gastrointestinal conditions with psychological problems such as anxiety and depression can contribute to creating a model of care for GI patients. Comparisons with other chronically ill populations can inform the need for redefining Australian treatment guidelines for these patients in light of the premises of the biopsychosocial model within the newly proposed discipline of "psychogastroenterology".

I. The biomedical and biopsychosocial models

According to archaeological studies, thousands of years ago people believed that mind and body were a part of the same system and that illness, whether physical or mental, was caused by the presence of evil spirits (Kaplan, 1975). Through the centuries, this perspective has changed. The ancient philosophers were the first to separate body from mind. Later, a dualistic view of mind and body was shared by such influential philosophers as Descartes and Malebranche (Marx & Hillix, 1963). Indeed, the works of Descartes laid the foundation for a contemporary medical approach called the biomedical model. For the last 300 years this model explained disease as an affliction of a body caused by a disturbance of physiological processes (Descartes, 1956). Somatic illness was, therefore, completely separated from psychosocial processes of the mind. Consequently, the biomedical model has reduced illness to a single-factor problem of biological malfunction, ignoring the variety of factors that may influence human health (Taylor, 2006). In response to this inadequate approach and as a result of the works of Sigmund Freud (Breuer & Freud, 1936; Freud, 1922), Flanders Dunbar (Dunbar, 1955) and Franz Alexander (Alexander, 1952), in the 20th century, the biomedical concept of illness began to change, albeit faster in the social sciences than in medicine (Taylor, 2006). Fortunately, the last 30 years have brought great changes to the medical curricula worldwide (including Australia) and medical students have been increasingly exposed to the medical humanities

(Benbassat, Baumal, Borkan, & Ber, 2003; Cohen, Krackov, Black, & Holyst, 2000; Eaton, 1980; Gordon, 2005; Jasnoski & Warner, 1991; Satterfield, Mitteness, Tervalon, & Adler, 2004).

The new school of thought to emerge as a result of this process was named the "biopsychosocial model". It implies the interplay of biological, psychological and social factors (including culture) in causation and experience of any illness (Engel, 1977, 1980). It also emphasises the practitioner-patient relationship as an important factor in the therapeutic outcome and a shift in the understanding of health and illness. In particular, the latter involves appreciation that health is not a steady state but rather something that one achieves through multi-level actions (Taylor, 2006). Importantly for the purposes of this thesis, the biopsychosocial model implies an interdisciplinary approach to managing chronic disease in which the practitioner is aware of the social and psychological factors contributing to illness (Engel, 1997) and in which illness behaviour may play a role in chronic illness. However, it is important to stress one more time that the biopsychosocial model was created in response to inadequacies of the previous model. In his works, Engel has indicated the limitations and failings of the biomedical model approach (Engel, 1960, 1977, 1980) demonstrating that its greatest flaw is in ignoring the patient and their attributes as a human being and reducing a person and their psychosocial circumstances to physico-chemical terms (Engel, 1980). Engel has also studied psychological aspects of chronic diseases in the area of gastroenterology (Engel, Walker, & Katon, 1996; Engel, 1955, 1956; Glaser & Engel, 1977); however, he has never fully applied the biopsychosocial model to deepen understanding of chronic gastroenterological diseases. Nevertheless, this has been done by Douglass Drossman who used Engels' concept to explain the aetiology and course of functional gastrointestinal disorders (Drossman et al., 1999; Drossman, 1998a). Drossman has emphasized that that the relationship between

psychosocial events and gastrointestinal functions is best explained by the reciprocal interaction of physiologic and psychosocial processes. Thus, factors important in understanding functional gut disorders include: early life genetics and environment; psychosocial aspects such as life stressors, coping or social support; and physiology (motility and sensation). The presented studies aimed to bring the Drossman's observations one step further and to enrich gastroenterologists' and psychologists' knowledge of the psychosocial elements of managing not only functional gastrointestinal disorders (such as irritable bowel syndrome) but also other chronic diseases of the digestive tract such as inflammatory bowel disease and chronic hepatitis C.

II. Patients' experiences of chronic disease

Chronic diseases carry a physical, economic and social burden for sufferers but, perhaps most importantly, they also have serious psychological implications. The specific features of many chronic diseases are their "uncertain aetiology, multiple risk factors, a long latency period, a prolonged course, functional impairment or disability, and incurability" (Brownson, Remington, & Davis, 1998). The complexity of each of these features as well as the variety of individual circumstances leads to the fact that each person affected by a chronic condition perceives and copes with their disease in a slightly different way. However, despite this variability of chronic illness experiences, researchers have established that some elements of adjustment to illness are common for the majority of people (a comprehensive analysis of psychological adjustment to chronic disease can be found elsewhere (Stanton, Revenson, & Tennen, 2006)).

Fennell (Fennell, 2001, 2003) created a four-phased model of chronic disease experience. The researcher noted, however, that not all individuals go through the four stages. Many, especially if socio-economically disadvantaged, never manage to go beyond the first phase,

called Crisis. This phase takes place at the onset of the disease. It leads the individual to seek help for symptoms through medical treatment, spiritual help or substance abuse. The second phase, Stabilization, happens when the individual becomes familiar with the illness (through periods of relapses and remissions) and has to restructure life patterns and self-perception. In the next, the Resolution phase, the individual reaches the acceptance that the pre-illness sense of self will not fully come back and develops a new self. In the final phase of Integration, the sufferer is able to put the old and the new self together. In this phase social contacts and the re-establishment of employment are important. Moreover, the individual who manages to reach this phase no longer treats the disease as an ultimate tragedy and is able to perceive it as an only one of many facets of life.

As can be seen in this model, sufferers adjusting to chronic illness may potentially encounter many psychological difficulties. Problems usually arise from the fact that patients' lives become restricted; they live in social isolation; they experience problems with establishing a new self; and they perceive themselves as having become a burden (Charmaz, 1983). Surprisingly, many people cope quite well with the adverse psychological reactions they experience. This occurs because of internal resources for solving problems called coping. Coping is defined as a process of managing demands that are perceived as exceeding the resources of the person (Lazarus & Folkman, 1984). According to Taylor (2006), coping strategies applied by the chronically ill are not significantly different to those used by the healthy population to manage stress. There are two main types of coping strategy: problem-based, implying doing something constructive about difficulties; and emotion-based, implying reduction of emotional impact through adopting a particular attitude. Some types of coping might not facilitate psychological adjustment as well as others, an example being avoidant coping (Siegel, Gluhoski, & Karus, 1997). Those people who cannot successfully cope with chronic illness are

therefore prone to more serious psychological problems such as anxiety and/or depression than those who cope well (Taylor, 2006).

According to Taylor (2006) and others (Stewart & Shields, 1985), common reactions to being diagnosed with a chronic illness are denial, anxiety and depression. Thus, anxiety and depression may be the result of an ineffective coping style as well as the result of a diagnosis or of the disease itself. Through denial, people try to contradict the implications of their condition and this defence mechanism may lead to avoidance of medical treatment. It can, however, be helpful in the early period of illness, for example, when a patient is being hospitalised and does not have to think about problems associated with illness that are difficult to solve at this stage. Moreover, in the terminally ill, denial has been found to be a good predictor of higher survival rates (Moorey & Greer, 2002).

Anxiety is also a typical response to the disease. In contrast to denial, it does not appear to have any positive impact on the sufferers. Anxious patients have worse outcomes in many chronic diseases (Barbour, Blumenthal, & Palmer, 2006; Graydon, 1988) and while anxiety related to the disease itself decreases with time (i.e. proportionally to the growth of knowledge about the disease), anticipatory anxiety of the disease's future impact on different aspects of life increases. Quite often anxiety becomes a permanent element of the life of chronically ill people and, in some cases, it may lead to an anxiety disorder. According to the ICD-10, anxiety disorders are disorders where anxiety is not restricted to any environmental situation (*ICD-10-AM: Tabular list of diseases*, 2000). There are many types of anxiety disorders, for example phobic anxiety disorder, agoraphobia, social phobia, obsessive-compulsive disorder. The symptoms of the anxiety disorder vary but may include persistent nervousness, trembling, muscular tension, sweating, light-headedness, and feeling of unreality, fear of dying, palpitations, dizziness and epigastric

discomfort. Therefore, regular assessment and treatment of anxiety may be needed in the chronically-ill populations in order to prevent anxiety disorders.

Depression usually appears after denial and/or anxiety, being a delayed reaction to the severe stressor of a diagnosis. Somewhat like anxiety, it may have a detrimental effect on the medical outcome of a patient (Lavoie et al., 2006; Sobel & Markov, 2005), but unlike anxiety that periodically comes and goes, it can be a long-term problem. Similarly to anxiety, depressive symptoms may become permanent and may lead to depressive disorders such as major depressive disorder, dysthymic disorder or bipolar disorder ("Diagnostic and statistical manual of mental disorders [electronic resource] : DSM-IV-TR," 2000). Common symptoms of depression are: lower mood, reduction of energy, decrease in activity, reduced capacity for enjoyment and interest, lower self-esteem, tiredness and disturbed sleep (*ICD-10-AM: Tabular list of diseases*, 2000). Moreover, depressed patients are more difficult to detect within the chronically ill population, as symptoms of depression may be similar to the disease symptoms and medication side effects. As will be discussed later in this chapter in relation to treatment for hepatitis C and inflammatory bowel disease, some types of medication may lead to depression.

Furthermore, the anecdotal view of many medical practitioners and the wider community is that low mood in the chronically ill is something to be expected and unavoidable, whereas depression can and should be treated as quickly as possible to avoid further consequences such as suicide. There is good evidence of the strong association between both depression and medical illness (Harris & Barraclough, 1997, 1998) and suicide (Harris & Barraclough, 1994). Some researchers have claimed that as many as 15% of depressed patients will eventually commit suicide (Guze & Robins, 1970). However, a more recent study has not confirmed this high suicide risk showing a rate of 3.4% in

depressed patients (Blair-West & Mellsop, 2001). Nevertheless, due to the well-recognised co-morbidity of depression with chronic illness (Derogatis & Wise, 1989), the risk of suicide and because depression impairs quality of life in people suffering from various medical conditions (Dickens et al., 2006; Oguzturk et al., 2005; Regula et al., 2005; Sullivan, Levy, Russo, & Spertus, 2004), regular screening for depression and anxiety is warranted. It should therefore become a part of standard treatment, particularly in light of the availability of simple and cost-free anxiety and depression screening measures such as the Depression Anxiety Stress Scales (DASS) or the Hospital Anxiety and Depression Scale (HADS). It is, however, important to acknowledge that these questionnaires can only show sub-threshold levels of anxiety and depression, and serious presentations have to be diagnosed by a specialist using a psychiatric structured interview based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) classification ("Diagnostic and statistical manual of mental disorders [electronic resource] : DSM-IV-TR," 2000).

Such measures are also available to evaluate another important aspect of the lives of chronically ill people: their quality of life. Quality of life was not considered important in the management of medical conditions until the mid-1980s and was not regularly assessed in a standard measure. Previously, the construct was used solely by medical practitioners to measure morbidity and mortality (Taylor, 2006). Now, it is thought to be a crucial health outcome measure in management of the chronically ill (Naughton & Shumaker, 1998). Quality of life may be differently defined depending on whether the term is used in the field of psychology, sociology, medicine, economics or other social sciences (Gerson, 1976; Naughton & Shumaker, 1998). It is also a very subjective construct and because of that, some investigators argue that it is difficult to measure (Goodinson & Singleton, 1989; Naughton & Shumaker, 1998). Therefore, in order to avoid a too broad understanding of the term and make measuring more reliable, medical researchers have introduced the more

specific term, *health-related quality of life* (HRQOL), which describes quality of life from a medical perspective only. HRQOL is considered to have several dimensions, of which the most basic are: physical functioning; social functioning; psychological functioning; overall life satisfaction; and perceptions of health status (Naughton & Shumaker, 1998).

Despite the controversy associated with the term's definition and measurement, most contemporary health researchers find the construct useful and consider it an essential component in overall assessment of the health status of chronically ill people (Alonso et al., 2004; Ferrucci et al., 2000; Sherbourne, Meredith, Rogers, & Ware, 1992). In particular, regular measurement of HRQOL is necessary in the chronically ill to unmask and quantify unsuspected problems encountered by certain patient groups, to compare the impact of treatments, especially those causing severe side effects, and to compare different management approaches. It can also be used in assisting policy-making to more fully evaluate the cost-effectiveness of interventions (Taylor, 2006).

Anxiety, depression and poor quality of life are all predictors of poorer medical outcomes in many chronic conditions (Lavoie et al., 2006; Mittermaier et al., 2004; Sobel & Markov, 2005; Yates et al., 2004). Moreover, they can interact with each other. Psychological status is known to independently impact on HRQOL (Henning, Turk, Mennin, Fresco, & Heimberg, 2006). Furthermore, there is a positive relationship between the presence of anxiety and depression (Kessler et al., 1996). All these associations are also common among people suffering from chronic gastrointestinal and hepatologic disorders. Indeed, there is good evidence that psychological problems such as anxiety, depression and panic disorder frequently coexist with gastrointestinal disorders (Folks & Kinney, 1992; Maunder, 1998; Mayer, Craske, & Naliboff, 2001). As this thesis is focused on the relationship between patients' psychological problems and physical outcomes/response to

medical treatment (defined by remission/relapse status) in these conditions, and in inflammatory bowel disease in particular, the next section will focus on the background literature on the three diseases and their psychological aspects. However, as the main focus of this thesis is on inflammatory bowel disease, the relevant background section will be much broader than the respective sections on irritable bowel syndrome and chronic hepatitis C.

III. Inflammatory bowel disease

Background

Inflammatory bowel disease (IBD) is a generic term used to describe a group of chronic and usually relapsing inflammatory disorders of the gastrointestinal tract, of which Crohn's disease (CD) and ulcerative colitis (UC) are the most common.

History

Both diseases are not new to the 20th century, as there are historical reviews indicating that the ancient Greeks and Chinese described cases of abdominal pain and diarrhoea that resembled IBD (Gitnick, 1991). UC and CD were, however, not officially named until the 19th and the 20th century, respectively. The term *ulcerative colitis* was used by British physicians, the first being Samuel Wilks of London, a pathologist who described the disorder (Gitnick, 1991; Janowitz, 2003; Wilks, 1859). Crohn's disease was not officially named until 1931, when Burrill Crohn wrote of the discovery of a new intestinal disease, *Terminal (Regional) Ileitis*, in his letter to the American Gastroenterological Association and later used the term during various presentations (Crohn, Ginzburg, & Oppenheimer, 1952; Janowitz, 2003). In order to honour the discoverer, surgeon Brian Brooke renamed

the disease and the term *Crohn's disease* entered common use. A detailed historical review pertinent to IBD has been presented elsewhere (Gitnick, 1991; Hawkins, 1990).

Epidemiology

The prevalence of IBD ranges from 37 to 246 cases per 100,000 persons for UC and from 26 to 199 cases per 100,000 persons for CD depending on the region of the world (Loftus, 2004), with an estimated total of 61,000 sufferers in Australia (*The economic costs of Crohn's disease and ulcerative colitis*, 2007 June), and a peak incidence at around 20 years of age. The increase in annual incidence of IBD observed since the 1940s has reached a plateau in recent years and is now estimated at 1.3 to 5.3 per 100,000 people (Loftus et al., 2006; Sandler & Golden, 1986). The disease is most common in developed countries such as the United States, the United Kingdom and Scandinavia. Incidence is moderate in Central Europe, and relatively low in South America, Asia and Africa (Whelan, 1990). However, recent research has indicated the rising trend of incidence in Asia and Eastern Europe (Lakatos, 2006; Loftus, 2004). In Australia, the relative frequency of IBD has been found to be similar to rates reported in Northern Europe and the United States (McDermott et al., 1987). However, it needs to be acknowledged that there are no true population-based data on prevalence and incidence of IBD in Australia. The disease's prevalence is not equally distributed among races, with the Jewish and Caucasian populations at highest risk (Karlinger, Gyorke, Mako, Mester, & Tarjan, 2000). Both sexes have been observed to be equally affected by IBD, however, UC is slightly more common in men, and CD in women (Ekbom, Helmick, Zack, & Adami, 1991; Stonnington, Phillips, Melton, & Zinsmeister, 1987).

Presentation and aetiology

Inflammatory bowel disease is characterised by an inappropriate immune response that causes characteristic inflammatory lesions in the gut wall. Both Crohn's disease and ulcerative colitis involve inflammation of the bowel wall and both have a relapsing course. Crohn's disease causes inflammation of the full thickness of the bowel wall anywhere along the digestive tract (from mouth to anus) in a discontinuous fashion, whereas ulcerative colitis affects the colon only, causing inflammation which is continuous, commencing in the rectum and extending proximally along the bowel for a variable distance. In UC, only the mucosal layer of the bowel is inflamed. Although CD may involve the gut anywhere along its length, it mainly affects the distal small intestine (ileum) and colon. Common symptoms of CD include: abdominal pain; diarrhoea; urgency; fever; weight loss and anaemia of a chronic disease. Ulcerative colitis similarly involves symptoms such as diarrhoea and abdominal pain; however, rectal bleeding and the passage of mucous per rectum are also commonly experienced, with weight loss and anaemia being less common than in CD (Feldman, Friedman, & Brandt, 2006; Rampton, 2000).

The aetiology of IBD is unknown. Nonetheless, genetic, immune and environmental factors have all been implicated in its causation (Lashner, 2005; Rampton, 2000). Some researchers have also controversially proposed that IBD may be partly a psychosomatic disease (Engel, 1955; Lieberz, 1991; Scheib & Wirsching, 1991; Sheffield & Carney, 1976; Tocchi et al., 1997). However, the editors of major handbooks on gastroenterology do not share this view, claiming that psychological factors are a result, rather than a cause of IBD, and that most probably they do not contribute to aetiology (Feldman et al., 2006; Shearman, Finlayson, & Camilleri, 1997). Although the possible psychosomatic origin of IBD is disputed, most studies report that stressful life events exacerbate the disease (Anton,

1999; Drossman, 1998b; Duffy et al., 1991; Levenstein et al., 1994). More specifically, it has been conceptualised that psychological stress may be linked to the exacerbation of IBD, and UC in particular, by inducing systemic and mucosal proinflammatory responses (Mawdsley, Macey, Feakins, Langmead, & Rampton, 2006).

Treatment

Common treatment options for inflammatory bowel disease include aminosalicylates (e.g. sulfasalazine, mesalazine), glucocorticoids (e.g. predisolone), immunomodulators (e.g. azathioprine 6MP, methotrexate), and antibiotics (e.g. metronidazole, ciprosolxacin). Less common treatments for severe disease include cyclosporine and monoclonal antibodies (e.g. infliximab) (Allan et al., 1997; Domenech, 2006; Panaccione, Ferraz, & Beck, 2005). Aminosalicylates and immunomodulators are mainly used to maintain remission of IBD; however, they can also be used to control mild to moderately active disease. Immunomodulators become effective after 10-12 weeks of treatment whereas corticosteroids are used when the quick response is required and they are typically a first-line treatment to induce remission. However, it should be acknowledged that corticosteroids cannot be used as a maintenance therapy as they have been commonly associated with many serious side effects when taken for a long time (Domenech, 2006). However, obviously, all listed treatment options are associated with the risk of side effects and, importantly for the purpose of this thesis, some of these side effects may be of psychological nature (e.g. mood changes, mania, depression and psychoses induced by corticosteroids) (Gitnick, 1991).

IBD and psychosocial functioning

Inflammatory bowel disease is at present an incurable condition and its course is unpredictable (Feldman et al., 2006). Although IBD only rarely decreases survival, it may still be life threatening at times (Prior, Gyde, Cooke, Waterhouse, & Allan, 1981; Winther, Jess, Langholz, Munkholm, & Binder, 2003). However, as the disease is usually diagnosed in young adults, sufferers must cope with their disease for many years. Their quality of life and psychosocial wellbeing may thus be profoundly impaired as a consequence of systemic symptoms, surgery (such as installing a stoma) and medication side effects (particularly in the case of corticosteroids). Older patients with IBD have also been reported as feeling stigmatized (de Rooy et al., 2001) and having problems with constant thinking about toilets, which restricts their social activities and limits their family life (Mukherjee, Sloper, & Turnbull, 2002). Consistently, both CD and UC have a significant impact on patients' self-image, social relationships and sexual functioning (Moody, Probert, Srivastava, Rhodes, & Mayberry, 1992; Rampton, 2000). Moreover, IBD in remission is often associated with functional gastrointestinal disorders such as irritable bowel syndrome (IBS) (there will be further discussion on IBS later in this chapter) (Farrokhyar, Marshall, Easterbrook, & Irvine, 2006). According to researchers, in remission, 42% - 62% of patients with Crohn's disease and 33% of patients with ulcerative colitis concurrently suffer from IBS (Barratt, Kalantzis, Polymeros, & Forbes, 2005; Minderhoud, Oldenburg, Wismeijer, van Berge Henegouwen, & Smout, 2004; Simren et al., 2002). Therefore, these patients' quality of life and psychosocial well-being remain impaired regardless of whether IBD is active or quiescent (Tanaka & Kazuma, 2005). Furthermore, as many as 93% of patients with IBS have been found to have a lifetime history of some psychological disorder (Walker et al., 1990). Thus, anxiety and depression appearing in patients with IBD may be partly explained by co-existent IBS.

In view of the above findings, it is not surprising that patients with IBD experience some psychological disturbances more commonly than healthy people. The rate of psychological problems in patients with IBD has been estimated at about 29%-35% during remission (Andrews, Barczak, & Allan, 1987; Mittermaier et al., 2004) and, according to some investigators, at as much as 80% for anxiety and 60% for depression during relapse (Addolorato, Capristo, Stefanini, & Gasbarrini, 1997). In general, the rate of common psychological problems, such as anxiety and depression, is higher in chronically ill people than in the wider population. Moreover, the prevalence of depression in the chronically ill has increased during the last forty years, from approximately 20% in the late 1960s (Schwab, Bialow, Brown, & Holzer, 1967) to around 30% in the 1980s and 1990s (Cavanaugh, Clark, & Gibbons, 1983; Rodin, Craven, & Littlefield, 1991). This increase might be the result of better understanding of depressive symptoms among medical practitioners, more common use of good quality screening questionnaires, or the fact that people live longer and, because of that, are more likely to become depressed. It can also be a consequence of the high prevalence of chronic conditions in the general population and the well recognised co-morbidity of chronic diseases with psychological problems. It is, however, important to acknowledge that the prevalence of psychological problems in the chronically ill and in the healthy population may vary depending on the method they are measured with and thus, many more people will be classified as cases by the screening questionnaires than by a psychiatric interview based on the DSM-IV criteria.

Interestingly, the prevalence of anxiety in the medically ill is fairly stable and has been estimated at about 20% for the last 50 years (Rodin et al., 1991). However, in some medical conditions such as hyperthyroidism, respiratory disease and hypoglycaemia, the level of anxiety increases to as much as 47% and depression to 44% (Derogatis & Wise, 1989). In line with this, the prevalence of anxiety and depression is also noticeably higher

in people suffering from gastrointestinal problems than in the wider population, and is estimated at about 30% (Derogatis & Wise, 1989; Härter, Conway, & Merikangas, 2003). In light of these published data, the high rate of anxiety and depression present during relapses of IBD (Addolorato et al., 1997) appears to be unique to these patients, even among the medically ill, and has been interpreted as supporting the view that a patient's psychology perhaps plays a role in the aetiology and the course of IBD. However, it can also lend support to the concept that the relationship between a chronic disease and psychological problems is circular. Thus, depression impacts on the chronic disease and the chronic disease impacts on depression. It is therefore difficult to say which arises first. Moreover, it may result from the fact that IBD is both a chronic and acute disease, and the prevalence of anxiety and depression in acute diseases has been found to be higher than in the normal healthy population. For example, 21% of acute coronary syndrome patients have been noted to be moderately or highly anxious (Whitehead, Strike, Perkins-Porras, & Steptoe, 2005) and 59% of acute lower back pain patients have been found to have some form of anxiety or depression (Edwards, Gatchel, Adams, & Stowell, 2006). Forty-four percent of patients experiencing acute pain have been reported as being moderately or severely anxious before the surgery and 30% were still anxious after the surgery (Carr, Nicky Thomas, & Wilson-Barnet, 2005). In the same group of patients, 30% were depressed before the surgery and 21% after the surgery.

Notwithstanding this controversy, the high rate of psychological problems in patients with IBD should attract the attention of researchers interested in reducing the psychological burden in sufferers. Surprisingly, although basic forms of psychotherapy have been examined by some researchers, as yet pharmacological treatment of psychological co-morbidities in IBD with antidepressants has not been of interest to many investigators. The next two sections will briefly outline the current knowledge on psychotherapy and

antidepressants, while the final chapters of the thesis will explore in more depth the problem of using antidepressants in patients with IBD.

Psychotherapy in patients with IBD and concurrent psychological problems

The most common methods of treating anxiety and depression in the medical context are psychotherapy and pharmacotherapy with antidepressants. There are many definitions of psychotherapy but most of them refer to treating psychological problems by using insight, persuasion, suggestion, reassurance and education, in order for patients to be able to perceive their problems more realistically and cope with them more effectively. There are also many types of psychotherapy: supportive-expressive (Luborsky, 1984), cognitive-behavioural therapy (Beck, 1976), interpersonal therapy (Weissman, Markowitz, & Klerman, 2000), psychodynamic therapy (Frederickson, 1999) to name only a few. Both psychotherapy and pharmacotherapy have been established as effective in treating psychological problems in the medically ill (Derogatis & Wise, 1989; Mayou, Sharpe, & Carson, 2003; Rodin et al., 1991). Generally, a mixture of psychotherapy and pharmacological treatment is recommended for patients with more severe psychological symptoms, while psychotherapy alone is recommended for those less severely impaired or those not yet affected but at risk of becoming depressed or anxious (Mayou et al., 2003; Rodin et al., 1991). Results of multiple studies on medically ill populations have suggested that psychotherapy is helpful for many patients suffering from both chronic diseases and psychological disturbances by not only resolving psychological problems but also reducing hospitalization time (Mumford, Schlesinger, & Glass, 1982; Spiegel et al., 1999). Similarly, good quality experimental studies have suggested the efficacy of antidepressants in treating anxiety and depression in patients with medical conditions (Brown et al., 2005; Raskin et al., 2006).

Psychotherapy as a treatment for psychological problems in patients with IBD has been examined in a few studies. Maunder et al. (2001) researched supportive-expressive group therapy in a prospective uncontrolled open trial with 30 participants. The researchers found it ineffective in improving quality of life and treating anxiety/depression (Maunder & Esplen, 2001). In line with this, neither interpersonal (Jantschek et al., 1998) nor psychodynamic therapies (Keller et al., 2004; von Wietersheim et al., 2001) were found useful in treating psychological disturbances in IBD in randomised controlled multicentre trials with more than 100 participants. However, these researchers noticed a tendency towards fewer surgical operations in patients undergoing psychotherapy.

Cognitive-behavioural therapy (CBT) was examined in three trials. Schwarz and Blanchard (1991), in a randomised controlled trial with 29 participants, found CBT to be an ineffective way to treat psychological problems in a mixed IBD group of CD and UC patients. On the other hand, Mussel, Bocker et al. (2003), in a prospective but uncontrolled study with 28 IBD participants, identified CBT as a highly useful tool in a short- and long-term treatment for psychological distress in IBD. Other investigators (Szigethy et al., 2006), in a prospective non-controlled study with 11 adolescents with IBD, also found CBT to be effective as a long-term treatment for anxiety and/or depression as assessed by DSM-IV-TR criteria when additionally supported by antidepressants. However, due to issues with study design (it was an unblinded and uncontrolled study) these results should be interpreted with caution. Importantly, a recent systematic review confirmed the negative results of the randomised controlled trials, indicating that psychotherapy has not been shown to have an impact on anxiety and depression in IBD and cannot be recommended for all patients with IBD (von Wietersheim & Kessler, 2006).

In contrast to psychotherapeutic treatments, some trials have been conducted on stress management programs and they have resulted in more uniformly positive outcomes. Garcia Vega, Fernandez Rodriguez et al. (1994), in a randomised controlled trial evaluating a stress management program for CD patients, noted lower levels of tiredness, abdominal pain and constipation in patients with IBD who attended a stress management program when compared to the group treated traditionally. This result is consistent with other randomised controlled studies in this area, indicating that stress management programs may be beneficial for patients with IBD by improving their psychosocial and physical well-being measured by the Inflammatory Bowel Disease Stress Index and Crohn's Disease Activity Index (CDAI) (Milne, Joachim, & Niedhardt, 1986).

Regardless of these findings, however, psychotherapy or stress management techniques have not prevented "stress-related" relapses (Enck & Schafer, 1996; Kiss & Ferenci, 1991; Schmitt, 1985). Moreover, psychological interventions have not reduced the levels of anxiety and/or depression. Despite the inability to demonstrate that psychological interventions benefit patients with IBD, psychological problems have been shown to adversely affect physical recovery from relapses of IBD (Addolorato et al., 1997; Andrews et al., 1987; Duffy et al., 1991; Levenstein et al., 1994; Mittermaier et al., 2004). Thus, as the main goal in treatment of IBD is to maintain remission as long as possible and to resolve acute flares of disease as rapidly as possible, other treatments directed at the psychological dimension should be explored. In particular, higher quality and larger studies testing CBT could be useful as this type of therapy seems the most promising pathway for psychological treatment in patients with IBD.

Antidepressants in patients with IBD and concurrent psychological problems

To date, pharmacotherapy with antidepressants has not been systematically examined as an independent intervention in patients with IBD and one of the aims of this thesis is to explore this problem further (see Chapters 8 and 9). Walker, Gelfand et al. (1996), while comparing patients with IBD with current psychological problems to those without psychological problems, noticed that depressed patients (n=8) who were given paroxetine in an open label trial showed significant improvement regarding functional disability. The researchers had expected the rate of depression to decrease. However, patients' scores on the quality of life measure also improved in the areas of physical limitations, occupational role, emotional role, social function, pain, mental health, vitality and health perception, with higher scores associated with increased quality of life (E. A Walker, M. D Gelfand, A. N Gelfand, F. Creed, & W. J Katon, 1996). Although the importance of this result seems unquestionable, the study contained significant weaknesses which need to be addressed. These include the small sample size, open label design and the fact that investigators did not differentiate between patients with Crohn's disease and ulcerative colitis. Clearly, larger studies addressing these methodological issues are required.

Other published data on the use of antidepressants in IBD have mainly been observational case studies. Kast (1998) presented a medical history of a depressed and anxious patient with CD who was treated with phenelzine and achieved remission from IBD. In further reports, Kast and Altschuler (2001) describe two other patients who achieved long-lasting remission from CD whilst using bupropion. The investigators hypothesize that this may be a result of a decreased level of tumour necrosis factor-alpha (TNFα), which plays a vital role in the pathogenesis of CD. According to these and other investigators (Talmadge, Scott, Castelli, Newman-Tarr, & Lee, 1993), both phenelzine and bupropion regulate intracellular cyclic adenosine monophosphate (cAMP) which, in turn, is responsible for the

regulation of TNFα. When increased, cAMP has been found to decrease the level of TNFα. As phenelzine may cause a hypertensive crisis, bupropion is thought to be a safer therapeutic option. Interestingly enough, however, phenelzine and other monoamine oxidase inhibitors (MAOI) have been noted to induce remission of rheumatoid arthritis, a disease in which - similarly to CD - TNFα has a central pathogenetic role (Lieb, 1983). Kast (2003) speculated on the use of bupropion and mirtazapine in patients with CD and commented that both these antidepressants had the potential to affect inflammatory responses: bupropion by lowering TNFα and mirtazapine increasing its level. Therefore, he recommended that bupropion is advised and mirtazapine contraindicated in the treatment of depression in patients with CD.

Although Kast's explanations appear logical, their practical effectiveness needs to be experimentally confirmed in randomised controlled trials. Due to the lack of good quality data concerning the effects of antidepressants on IBD, and due to the proven interplay between psychological co-morbidities and both disease activity and quality of life (Mittermaier et al., 2004), the influence of antidepressants on the course of both Crohn's disease and ulcerative colitis warrants further research. These issues are further explored in the second part of the thesis with the systematic review of literature and an exploratory study examining gastroenterologists' attitudes towards the use of antidepressants in IBD.

The first part of this thesis is focused on the problematic relationship between psychological problems and physical outcomes/response to medical treatment (defined by remission/relapse status) in inflammatory bowel disease compared to the contemporaneous sample of IBS and HCV sufferers. Therefore, the next section will briefly discuss those disorders. In particular, it will concentrate on the psychological aspect of these conditions and the relevance of studies on IBS and HCV to studies concerning IBD.

IV. Irritable bowel syndrome, the treatment of psychological co-morbidities and its relevance to potential trials with IBD patients

Irritable bowel syndrome (IBS) is classified as a functional gastrointestinal disorder (FGID), meaning that it presents with non-structural symptoms and is identified only by symptoms ("Rome III: The Functional Gastrointestinal Disorders," 2006). From a clinician's perspective, according to a renowned survey study involving 704 members of the American Gastroenterological Association, FGIDs are defined as conditions in which no known structural abnormalities, or infectious or metabolic causes, can be found (Mitchell & Drossman, 1987). However, in the same survey, 57% of practitioners and 34% of academics claimed that FGIDs are associated with stress and 43% of practitioners and 26% of academics saw them as motility disorders. A more recent study reports that doctors perceive FGIDs as psychological disorders or merely the absence of organic disease, quite often revealing pejorative attitudes towards FGID sufferers (Drossman, 2005). However, FGID is perhaps best understood as a product of interaction between psychological factors and altered gut physiology via the brain-gut axis (Jones et al., 2006). Because of this, the biopsychosocial model has been found useful in effectively understanding FGIDs and their treatment (Drossman, 1998a, 1998b, 2006a).

Functional disorders account for up to 50% of referrals to gastroenterologists in outpatient clinics (Harvey, Salih, & Read, 1983; Mitchell & Drossman, 1987) with IBS alone accounting for 20% of gastroenterology output practice (Thompson, Heaton, Smyth, & Smyth, 2000). IBS is a chronic relapsing condition in which there is abdominal pain or discomfort associated with altered bowel habits (constipation and/or diarrhoea) in the absence of any apparent mechanical or biochemical changes in the gastrointestinal tract (Mertz, 2003). Other common symptoms include flatus and bloating. The prevalence of IBS has been estimated at 17 per 100 (Talley, Zinsmeister, Van Dyke, & Melton, 1991),

making it one of the most common disorders in gastroenterological practice (Jones et al., 2000).

In line with other FGIDs, the aetiology of IBS is controversial. Although new ideas are evident, IBS is still considered to be a disorder in which sensory (Mertz, Naliboff, Munakata, Niazi, & Mayer, 1995), motor (Camilleri & Ford, 1998) and inflammatory (Thornley et al., 2001) changes can play a role. It is conceptualised that the symptoms of IBS can be the result of altered motility impacted on by such factors as psychological difficulties, food, infections and hormones. As IBS symptoms may result from disturbed functions of intestine, brain, or in neurological links between intestine and the brain, treatment can be targeted at multiple levels of the brain-gut axis (Lesbros-Pantoflickova, Michetti, Fried, Beglinger, & Blum, 2004). Conventional pharmacological treatment includes bulking agents, antidiarrhoeals, antispasmodics, prokinetics, serotoninergic agents and antidepressants (Lesbros-Pantoflickova et al., 2004; Tack, Fried, Houghton, Spicak, & Fisher, 2006). Non-drug treatments that have been found to be effective in IBS consist of diet, psychotherapy, probiotics, acupuncture, yoga and relaxation (Boyd-Carson, 2004; Drisko, Bischoff, Hall, & McCallum, 2006; Takahashi, 2006).

Interestingly, the majority of patients with IBS who seek medical help have been found to have a life time history of some psychiatric disorder (Lydiard & Falsetti, 1999), and for between 43% and 82% of patients with IBS, anxiety and/or depression was diagnosed before the onset of gastroenterological symptoms (Fullwood & Drossman, 1995). These findings lend support to the notion that the patient's psyche plays an important role in the aetiology and course of IBS.

In the absence of structural or biochemical abnormalities that can be detected utilising routine clinical testing, IBS has been considered a psychological disorder. It is not surprising thus that psychological (psychotherapy) and psychiatric treatments (antidepressants) for IBS have been the subject of many studies and have been commonly found to be effective for symptoms of IBS (Crowell et al., 2004; Tack et al., 2006; Wilson, Maddison, Roberts, Greenfield, & Singh, 2006). However, it must be acknowledged that some researchers have criticized the quality of these studies stating that there are insufficient data to fully evaluate the efficacy of behavioural therapies as well as safety and tolerability of both tricyclics and SSRIs in patients with IBS (Jackson et al., 2000; Tack et al., 2006; Talley, Owen, Boyce, & Paterson, 1996).

Regarding trials of antidepressants, even though antidepressants have been found to be effective in reducing the symptoms of IBS, problems with design and sample size may undermine the positive results (Jackson et al., 2000). With respect to psychotherapy, which again has been found to be effective for IBS symptoms in the majority of investigations (Svedlund, 2002), the main methodological flaws of the studies are lack of blinding and problems with control groups (Talley et al., 1996). Due to these quality issues, it is difficult to judge which behavioural therapy offers the greatest benefit. In fact, in an adequately controlled trial comparing CBT, relaxation and standard medical care in IBS participants, anxiety, depression and somatic complains were significantly reduced; however, no difference was noted between the three modes (Boyce, Talley, Balaam, Koloski, & Truman, 2003). Interestingly, however, a methodologically similar trial found psychological treatment feasible and effective in two thirds of those patients with IBS who do not respond to standard medical treatment (Guthrie, Creed, Dawson, & Tomenson, 1991). In contrast to the results in IBD, both described IBS studies reported that

psychotherapy is effective not only in treating psychological disturbances but also in reducing somatic symptoms.

Another important observation has been made by researchers working on the role of hypnosis in treating IBS (Tan, Hammond, & Joseph, 2005). In a systematic review comprising 14 trials (eight without and six with a control group), Tan and colleagues (2005) observed that hypnosis improves both the cardinal symptoms of IBS and non-colonic symptoms in the majority of patients. In general, the most effective approach to treating IBS seems to be a comprehensive one including both medical treatment and psychotherapy (Scharschmidt & Feldman, 1993). Some researchers, however, claim the superiority of psychological over conventional treatments (Svedlund, 2002) stating that psychotherapy brings longer-term benefits than purely medical treatment. Typically, when psychological problems are a significant issue, a combination of psychotherapy and antidepressants has been recommended (Creed et al., 2003). Among antidepressants, tricyclics have been most commonly used with good results in IBS and have been found to be more effective than SSRIs (Jackson et al., 2000).

As previously stated, IBS commonly co-exists with IBD and both disorders additionally co-exist with psychological problems such as anxiety and depression. Some investigators have explained this co-existence by hypothesizing that chronic inflammation (IBD) may lead to persistent gut dysfunction (IBS) (Collins, Piche, & Rampal, 2001) and "psychological factors, especially anxiety and reduced vitality, are probably involved in this process" (Simren et al., 2002, p. 395). Although, traditionally, IBD was treated as an inflammatory disorder and IBS as a functional disorder, it has become increasingly difficult to separate the two conditions, as the current research provides good evidence on the existence of pathological abnormalities in the gut in patients with IBS (Gwee et al.,

1999). Because of the common co-existence of IBS with IBD, and the existence of some shared pathophysiologic mechanisms between the two conditions (i.e. altered mucosal permeability, altered interaction of luminal flora with the mucosal immune system, persistent mucosal immune activation, alterations in gut motility, and a role of severe, sustained life stressors in symptom modulation), and as therapeutic approaches demonstrated to be helpful in IBD (e.g. probiotics, antibiotics, and anti-inflammatory agents) have also been recommended as therapies for certain patients with IBS (Bradesi, McRoberts, Anton, & Mayer, 2003), future trials of particular psychological or psychiatric treatments which have been previously found effective in IBS can be justified in IBD. Moreover, the fact that doctors already treat anxiety, depression and pain in IBD using guidelines for IBS (Ginsburg & Bayless, 2005; Ringel & Drossman, 2001) adds support to this claim, especially given that these treatments have been found to improve both the psychological and somatic complaints of IBS sufferers.

This last aspect of psychological/psychiatric treatment is particularly worth exploring as reduction of symptoms could improve quality of life in patients with IBD. However, noone, as yet, has compared the prevalence of psychological problems in IBD and IBS on a contemporaneous sample of participants recruited simultaneously from the same outpatient clinic in order to observe whether the scale of psychological problems is similar in both disorders. If this is the case, the use of anti-depressive and anti-anxiety treatments (approved for the use in IBS) in patients with IBD would gain additional support. As one of the aims of this thesis is to build a foundation for future trials of antidepressants in IBD, the author wished to undertake a comparative and prospective analysis. Additionally, this comparison was enriched by the data for another patient group: chronic hepatitis C (HCV) sufferers whose psychological problems may partly result from the same causes as those found in IBD participants. The next section of this chapter, therefore, summarises the

research on the psychological aspects of HCV and demonstrates its applicability to further studies on psychological treatment of patients with IBD.

V. Hepatitis C, treatment of psychological co-morbidities and its relevance to potential trials with IBD patients

Hepatitis C (HCV) is a viral infection. It is a chronic disorder which carries a mortality risk, being a major cause of cirrhosis, end-stage liver disease and liver cancer (Liang, Rehermann, Seeff, & Hoofnagle, 2000). Typically, within two weeks of exposure to the hepatitis C virus, antibodies to the virus (HCV RNA) appear in the blood. Approximately 85% of acutely infected patients subsequently develop chronic hepatitis C. In 15% of patients, HCV RNA in serum becomes undetectable and these patients either do not develop the disease or develop it later (Feldman et al., 2006).

The current typical modes of acquisition for acute hepatitis C in Western countries are intravenous drug use and sexual intercourse (Zakim & Boyer, 2003). Drug use via injection accounts for up to 60% of cases and another 20% of cases are probably sexually acquired. Other known exposures (occupational, hemodialysis, household, perinatal) together account for about 10% of infections and in the remaining 10%, no recognized source of infection can be identified (Alter, 1999). For chronic hepatitis C, the acquisition patterns differ, with injection drug use accounting for 50% of cases, blood transfusion for 20% and sexual exposure for a small number of cases. Interestingly, up to 30% of cases report an unknown acquisition source, which can probably be partly attributed to patients' denial of high-risk behaviours (Conry-Cantilena et al., 1996). In a recent population-based survey, the prevalence of chronic HCV in Australia was estimated at about 2 per 100 (Amin et al., 2004), with the 20-24 year age group having the highest HCV prevalence of

around 5% (95% CI 3.3%-8.1%) with a male to female ratio of 1.8:1.0. The majority of patients experience no clinical symptoms (Alter & Seeff, 2000) but up to 25% of patients may develop jaundice, and 10-20% report non-specific symptoms such as fatigue, nausea and vomiting (Feldman et al., 2006).

Until this decade, the disease had a very low success rate from antiviral monotherapy with standard interferon alpha, with only about 6% to 13% of patients achieving virological clearance when on a treatment for 24 and 48 weeks, respectively (McHutchison et al., 1998). A major improvement in therapy has resulted from a combination therapy comprising interferon alpha and ribavirin, which has given a response rate of 35% during a 24-week therapy and 43% during a 48-week therapy (Poynard et al., 1998). This response rate has further increased after the recent development of pegylated forms of interferon alpha, which in combination with ribavirin produces a 56% response rate after a 48-week therapy (Fried et al., 2002). Despite this marked improvement in cure rates, current therapy is still based on interferon-alpha, which is associated with significant psychological side effects, the most common being depression.

Although the combined pegylated interferon and ribavirin treatment gives higher viral clearance rates, treatment related depression is still a significant issue in as many as 30% of patients, compared with 34% for non-pegylated interferon and ribavirin therapy (Manns et al., 2001). According to Manns and colleagues (2001), in the case of both treatment modalities, about 35% of patients suffer from irritability and 40% from insomnia. With both the disease and its therapy associated with depression, a high rate of psychological and psychiatric co-occurrence in HCV is not unexpected. In some studies, up to 90% of patients had documented psychiatric and/or substance abuse diagnoses (Nguyen et al., 2002). In particular, in research on veterans, approximately 50% of patients with HCV

have been diagnosed with depression, 40% with anxiety, 30% with post-traumatic stress disorder and 20% with psychosis (el-Serag, Kunik, Richardson, & Rabeneck, 2002; Nguyen et al., 2002). In another study with patients awaiting treatment with interferon alpha, depression was diagnosed in only 28% of patients and anxiety in 24% (Golden, O'Dwyer, & Conroy, 2005).

The discrepancies in the prevalence of anxiety and depression in patients with HCV may depend on many factors such as older age of participants or concurrent treatment with interferon alpha. Some researchers, however, have also recommended caution when interpreting the meaning of high rates of psychological and psychiatric problems as well as poorer quality of life (Spiegel et al., 2005) in patients with HCV. This is because patients' scores on psychological measures appear to vary depending on whether patients are aware or unaware (many patients may spend years with occult infection) of their HCV positivity (Crone & Gabriel, 2003; Rodger, Jolley, Thompson, Lanigan, & Crofts, 1999). This may suggest that the psychological impact of diagnosis knowledge may play an important role in these patients' psychological outcomes. Moreover, because in some studies up to 80% of patients with HCV have been classified as substance and alcohol users, addiction and other high risk behaviours are likely to be confounding factors contributing to the level of psychological problems in HCV (Crone & Gabriel, 2003; Nguyen et al., 2002). Notwithstanding the controversy about the reasons for and the exact level of psychological problems in patients with HCV, their psychological burden is clearly significant.

The psychological burden may also be multiplied by the stigma attached to HCV (Golden, Conroy, O'Dwyer, Golden, & Hardouin, 2006), as the disease is stereotypically associated with alcoholism, drug addiction and the human immunodeficiency virus (HIV). Moreover, according to some researchers, HCV itself may contribute to the psychological morbidity

through pathophysiological events resulting from infection (Koff, 1999), which may impact on cognitive functioning (Hilsabeck, Perry, & Hassanein, 2002).

In contrast to IBD, in which pharmacological treatment with antidepressants has not been specifically studied, there is some general agreement based on clinical practice on how to treat depression and other psychiatric conditions in HCV (Rifai, Indest, Loftis, & Hauser, 2006). In a recent position paper, Rifai et al. (2006) found most psychotropic medications (antidepressants, mood stabilizers, antipsychotics, and neuroleptics) to be safe to use in the management of patients with HCV and psychiatric illness, and for the management of interferon-induced neuropsychiatric adverse effects. However, although antidepressants are commonly prescribed for interferon-induced depression, to date no placebo-controlled studies have been conducted to verify their effectiveness (Loftis & Hauser, 2004). Results of several case reports and some small sample size studies reviewed by Loftis and Hauser (2004) suggest that SSRI antidepressants reduce or reverse interferon-induced depression. Moreover, antidepressants given to prevent depression before treatment with interferon alpha effectively minimised symptoms of depression during treatment and were thought to facilitate treatment completion (Kraus, Schafer, Al-Taie, & Scheurlen, 2005). Again, however, this study had a very small sample size (n=8).

In contrast to both IBD and IBS, psychotherapy has not been widely studied in HCV as yet. To the author's knowledge, only one study has examined psychotherapy in patients with HCV, however, it was not randomised and involved a small sample (n=23) (Lang, Halleguen, Vecchionacci, & Doffoel, 2003). Additionally, the study applied supportive psychotherapy together with pharmacological treatment with antidepressants. It is, therefore, hard to estimate whether the positive result was achieved due to the effectiveness of antidepressants or psychotherapy or a combination of the two.

Despite a lack of data in the area of psychotherapy, the positive results of studies into the use of antidepressants in patients with HCV may hint at potential benefits for their use in treatment of IBD. IBD and HCV are both chronic digestive diseases where chronic inflammation of an internal organ (intestine and liver, respectively) exists. The prevalence of psychological problems in both is significantly higher than in the normal population and in both, in some patients, psychological problems may be induced by treatment (with corticosteroids and interferon alpha, appropriately). Finally, both groups of patients have been found to be stigmatised. As can be expected, the proportion of patients with HCV with depression induced by treatment and of those with stigma seems higher than of patients with IBD and with depression induced by treatment or with stigma. Unfortunately, nobody has systematically studied these factors in the two conditions so assumptions can be made based only on non-contemporaneous samples. Furthermore, to the author's knowledge, comparative studies of psychological factors in IBD and HCV have not yet been conducted, although such research could be useful to evaluate both the similarities of these two conditions and the prospects for treatment of psychological problems in IBD. Consequently, the main aim of this thesis is to prospectively evaluate and compare the parameters of the psychological status and quality of life on a contemporaneous sample of participants with IBD, HCV and IBS recruited simultaneously from the same outpatient clinic. The next section will summarise the overall content of the thesis, including a specific focus on its rationale and aims.

VI. Thesis rationale, aims and structure

Chronic diseases result in increased vulnerability to psychological problems, especially anxiety and depression. Inflammatory bowel disease is a chronic illness with all its

attendant consequences. As noted earlier, whether because of its chronic nature and unpredictable course, the medication side effects or because of a particular predisposition of patients with IBD to psychological co-morbidities and the commonly co-existent IBS, many patients also suffer from psychological problems. In some investigations, psychological co-morbidities have been found to exacerbate the course of IBD and shorten its remission (Duffy et al., 1991; Levenstein et al., 2000; Mittermaier et al., 2004; North, Alpers, Helzer, Spitznagel, & Clouse, 1991; Porcelli, Leoci, & Guerra, 1996). One can argue, therefore, that screening for anxiety and depression should be a routine part of effective medical therapy, especially if treatment of psychological co-morbidities can be demonstrated to improve the course of IBD or improve a patient's quality of life. However, currently available data to justify the routine screening for psychological co-morbidities are often of poor quality and typically limited to studies conducted overseas. This thesis seeks to provide high quality local data that would contribute to creating a uniform psychological treatment approach as part of the general biopsychosocial approach to management of patients with IBD and with other chronic gastroenterological conditions in Australia. The author's belief is that research presented in this thesis has the potential to significantly contribute to the evidence base needed for establishing guidelines in this area.

This research adopted an innovative approach to studies on inflammatory bowel disease, irritable bowel syndrome and chronic hepatitis C. Although the prevalence of psychological problems and quality of life in each of these conditions has been previously examined, it has never been undertaken concurrently in a single treatment setting. Moreover, existing comparative studies of patients with IBD suffer from limitations such as ill-matched or absent controls. This work therefore examines a contemporaneous sample of patients with IBD, IBS and HCV and contributes to a better understanding of any particular character of psychological problems appearing in IBD.

Several other problems explored in this thesis have received little attention as yet. These include: the relationship between the number of functional disorders and the severity of anxiety and depression in IBD and IBS; the presence or absence of psychological problems as an independent predictor of response to therapy/physical outcomes (defined by remission/relapse status) in contemporaneous samples comprising patients with IBD, IBS and HCV; the impact of the practitioner's knowledge of the IBD patients' psychological status on the practitioner's behaviour and patients' physical outcomes/response to medical treatment; and the influence of antidepressants on the course of IBD. Therefore, the presented investigations contribute to knowledge on these topics and indicate directions for future research.

Aims

This thesis aims to:

1) Explore the prevalence of psychological problems in chronic diseases of the gastrointestinal tract, in general, and inflammatory bowel disease patients in particular.

2) Determine whether there is a relationship between the number of functional gastrointestinal disorders and the severity of psychological problems in IBD and IBS.

3) Explore whether there is any relationship between baseline psychological status and physical outcomes/response to medical treatment (defined by remission/relapse status) in patients with IBD, IBS and HCV.

4) Explore whether disclosure of the psychological status of patients with IBD to their physicians influences doctors' behaviour and affects patients' responses to treatment/their physical outcomes.

5) Investigate the currently proven role of antidepressants in inflammatory bowel disease by reviewing relevant literature.

6) Explore the gastroenterologists' views on the use of antidepressants in IBD and to determine the feasibility of and prospects for future randomised controlled trials on the use of antidepressants in IBD.

Structure

The thesis is divided into two major parts with a total of nine chapters preceded by Preamble and ending with a Conclusion. Part I – "Psychological factors and physical outcomes/response to medical treatment in IBD and other common gastrointestinal and hepatologic disorders" - comprises six chapters. Part II – "Antidepressants and the course of IBD" – consists of three chapters. In particular, the thesis begins with the broader

problem of psychological co-morbidity in chronic gastroenterological diseases. The closer to the thesis end, however, the more narrow the scope of problems becomes, focusing on specific issues such as treatment of depression and anxiety in IBD. In order to avoid repetitions and make the argument clearer, the thesis has two method chapters, each related to the thematic part of the thesis. Moreover, the method reminder tables were placed after the introduction to each study in Part I of the thesis to remind the reader about critical aspects of the methods used in a particular study.

Chapter 1 outlines the literature review, summarizing existing knowledge on the relationship of anxiety and depression with IBD. It highlights the current controversies surrounding the role and importance of psychological co-morbidity in IBD, and attempts to answer the question of whether psychological problems have an effect on the course and activity of inflammatory bowel disease. This review goes on to inform the series of four original investigations presented in subsequent chapters (Chapters 3, 4, 5 and 6).

Chapter 2 details the rationale for methodologies common to both parts I and II of this thesis. For clarity, however, it focuses mainly on the methodology used in Part I. The methodology restricted to Part II of the thesis is described later in Chapter 7. Chapter 2 defines the aims and objectives associated with all studies conducted in Part I and outlines each study approach. Here, sampling, inclusion and exclusion criteria, hypotheses, measurements, outcome measures, ethical considerations, analyses, and further information regarding the methodology applied in the three studies comprising Part I, are all discussed.

Chapter 3 reports on the cross-sectional study wherein the prevalence of anxiety and depression and quality of life measures in inflammatory bowel disease, irritable bowel syndrome and chronic hepatitis C are compared. The analyses include descriptive statistics

and group differences in patient demographics and psychological profiles along with mean comparisons in mental status and quality of life between the IBD, the IBS and the HCV group. Comparisons of the psychological status and quality of life between the studied IBD group, the data for IBD samples reported by other investigators, and data for other chronically ill samples are also provided in this chapter. Additionally, comparisons of quality of life between IBD, IBS and HCV participants and the normal population are presented as well as comparisons between the CD and UC group mean scores for the activity of the disease and the scales used in the study. The chapter also discusses these findings' implications for the first hypothesis that patients with IBD are most affected by psychological problems in comparison to patients with IBS and HCV. Finally, a qualitative analysis of patients' concerns regarding their somatic illness is presented.

Chapter 4 is an extension of Chapter 3. It describes Study 2 which focuses on the problem of co-morbid functional disorders in IBD and IBS participants and the potential relevance of these disorders to the patients' psychological status. In particular, Chapter 4 presents the prevalence of functional gastrointestinal disorders in the IBD and the IBS group, additionally providing comparisons between CD and UC subgroups. It then summarises the analysis concerning the relationship between particular functional disorders and anxiety, depression and quality of life. Furthermore, it describes the analysis of the relationship between the number of functional disorders and the severity of psychological symptoms, providing a verification of the second hypothesis. The third hypothesis is also verified in this chapter. Finally, the chapter investigates how well the new criteria for IBS compare with a clinical diagnosis of IBS.

Chapter 5 discusses the results of Study 3, an observational cohort prospective management study where patients with IBD, IBS and HCV were followed for 12 months in

order to determine whether psychological status interacts with physical outcomes/response to standard medical therapy. It is linked to Study 1 in that it compares patients' psychological status at baseline to that after a 12-month period. Moreover, it tests the hypothesis that there is a relationship between patients' mental status and their response to standard medical treatment/physical outcomes (Hypothesis 4). Additionally, it presents data on the relationship between the baseline characteristics and total number of IBD relapses.

Chapter 6 reports on Study 4 which is a sub-study within the previously described Studies 1 (Chapter 3) and 3 (Chapter 5). Study 4 is a pilot randomised controlled observational trial conducted for 12 months only in participants with IBD and co-morbid anxiety and/or depression, wherein participants' psychological status was randomly disclosed to their treating doctor. This study was performed to test the hypothesis that a treating doctor's knowledge of a patient's psychological status may improve that patient's clinical outcome. In this chapter, the experimental and the control group's baseline demographic characteristics and psychological profiles are presented and compared. A prospective analysis compares each patient's medical outcome, as assessed by positive scores for IBD activity, anxiety and depression amongst those whose psychological co-morbidity was disclosed or undisclosed to the treating doctor. A qualitative analysis of doctors' casenotes with respect to psychological interventions is also provided in this chapter.

Part II of the thesis begins with Chapter 7, which outlines the methodology used from this point onwards. In particular, it details the aims and objectives associated with Studies 5 and 6. It also discusses details of sampling, inclusion and exclusion criteria, measurements, outcome measures and further information regarding the methodology applied in the two

studies. It concludes with a discussion of the ethical considerations involved in Study 6 and a plan for analysis.

Chapter 8 presents the findings of a systematic review of literature concerning the influence of treatment with antidepressants on inflammatory bowel disease activity. The main aim of this chapter was to verify whether the literature supports the premise that pharmacotherapy with antidepressants may influence the course and activity of IBD. The results of all relevant studies are presented and discussed.

Chapter 9 continues the line of inquiry begun in Chapter 8. However, it examines this problem from a different angle in that it explores gastroenterologists' perceptions of the role of treatment with antidepressants in IBD by analysing their opinions, experiences, and attitudes towards the use of antidepressants in IBD. Participants' responses are collected, qualitatively analysed through content analysis and discussed.

The last chapter, Conclusion, reviews the most significant results associated with all six studies. The chapter also summarizes proposed future research resulting from the findings of the present studies. Moreover, recommendations for clinical and research practice resulting from findings of conducted studies are also provided here, as well as recommendations resulting from the experience of conducting psychological research within gastroenterology practice.

PART I: Psychological factors and physical outcomes/response to medical treatment in inflammatory bowel disease and other common gastrointestinal and hepatologic disorders

Chapter 1: Controversies surrounding the co-morbidity of depression and anxiety in inflammatory bowel disease patients: a literature review

This chapter serves as an introduction to a series of investigations into the role of anxiety and depression in patients suffering from inflammatory bowel disease. The chapter outlines the controversies surrounding the psychological co-morbidity in IBD and attempts to answer the question of whether psychological problems have an effect on the course and activity of inflammatory bowel disease.

1.1. Introduction

The high prevalence of psychological co-morbidities in inflammatory bowel disease has been used to support the premise that a patient's psychology may play a role in aetiology and/or in the clinical course of this disease. This hypothesis claims additional support from prospective studies in which researchers observed a relationship between depression, the course of the disease (physical outcomes) and the response to standard medical treatment (Mittermaier et al., 2004; Persoons et al., 2005), numerous studies linking stress and disease exacerbations in IBD (Anton, 1999; Drossman, 1998b; Garcia Vega & Fernandez, 1998; Levenstein et al., 1994; Milne et al., 1986; Schwartz & Schwartz, 1982) as well as from similar data linking poor outcome to psychological co-morbidities in other chronic conditions (Carney et al., 1988; Fifield, Tennen, Reisine, & McQuillan, 1998; Lustman, Griffith, Freedland, & Clouse, 1997).

Although IBD is only rarely a lethal disease, it significantly impairs health in a substantial proportion of affected patients. Furthermore, as the disease frequently affects young adults, quality of life and psychological wellbeing have the potential to be profoundly impaired over a lifetime as a consequence of systemic symptoms, surgery and medication side effects. Both CD and UC have a significant and consistent impact on patients' self-image, social relationships and sexual functioning (Moody et al., 1992; Rampton, 2000). Moreover, as the life expectancy of patients with IBD approximates that of healthy people (Andrews, Norton, Dent, & Goulston, 1995), improving these patients' quality of life and psychological wellbeing is imperative.

Although interest in the psychological aspects of IBD has increased in recent years, much of the published material is outside mainstream gastroenterology journals and thus it does not necessarily influence clinical practice. Indeed, anecdotal evidence from clinicians suggests that improvements in clinical care derived from integrating the psychological and physical aspects of IBD are often omitted from standard treatment models. Previously, gastroenterologists have been resistant to considering the possible role of psychological factors in IBD. However, as the discrete roles played by neurology versus immunology in the gut are no longer clearly demarcated, as evidenced by "inflammation" discovered in irritable bowel syndrome (Barbara et al., 2004; Gwee et al., 1999), it seems timely to re-examine the evidence for the possibility that the psyche may also affect IBD. Moreover, as psychological approaches to treatment of other gastrointestinal illnesses such as IBS and functional dyspepsia have now been demonstrated to be effective in controlled studies (Calvert, Houghton, Cooper, Morris, & Whorwell, 2002; Guthrie et al., 1991; Tan et al., 2005), it is appropriate to review the current state of knowledge regarding psychological co-morbidities in IBD.

Because there is conflicting data and divergent opinions on the psychological aspects of IBD, the author chose to review this literature with a particular emphasis on those areas where published controversies exist. As the role of stress has been previously reviewed (Maunder, 2005), and is notoriously difficult to both measure and define, this review was restricted to the more discrete, diagnosable entities of anxiety and depression. Moreover, from a therapeutic viewpoint, stress is not easily modified (though, stress appraisal or irrational cognitions can be targeted with cognitive therapy); however, accepted therapies exist for anxiety and depression. Thus, if they can be shown to have an impact on IBD, targeted therapeutic interventions may benefit patients with IBD beyond standard anti-inflammatory therapy. Therefore, the purpose of this review was to build a clearer picture of the precise nature of these areas of divergent opinions regarding IBD and anxiety/depression, and to delineate directions for future research tailored to address these unanswered questions.

1.2. Methods

Articles pertinent to the psychological aspects of IBD began to be published in the 1960s (Belov, 1963; Chatterjee & Johnson, 1969; Hrynkiewicz, Kotlarek-Haus, & Gabry's, 1967) often in languages other than English. It was not; however, till the 1980s that interest in the topic became worldwide. This review therefore focuses on articles published between 1980 and 2005 and available to researchers via the online database, PubMed. Searches were conducted in July and August 2005. Keywords used were: (Inflammatory Bowel Disease OR Crohn's Disease OR Ulcerative Colitis) AND (Psychological disorders OR depression OR anxiety). The titles and abstracts of all identified articles were examined and included for review if the report was directly related to BOTH psychological disorders AND to IBD, and included: systematic reviews; randomised controlled trials; cohort prospective studies;

case-control studies; and cross-sectional studies. Reference lists of all articles were reviewed for potential additional papers. Studies with less than 10 participants, discussion papers, case reports, letters and other publications of poor quality were excluded. The remaining articles were subsequently reviewed in terms of the quality of their study design, control group, sample size and "prospectiveness".

1.3. Results

Seventeen articles directly related to the co-morbidity of psychological problems with IBD were identified and reviewed (see Appendix 1). Eight studies were controlled (however, not always appropriately), six studies were cross-sectional, two were cohort prospective studies and one study was a systematic review. No randomised controlled trials were identified. Six studies were conducted in the United States, four in the United Kingdom, three in Italy, two in Sweden, and one each in Austria and Japan. Six were published in the 1980s, five in the 1990s and six in the 2000s. The more detailed description of the studies reviewed is presented in Appendix 1. This investigation revealed five consistent areas of controversy arising in regard to the following questions:

- Do psychological problems co-occur with IBD more often than expected by chance?

- Do psychological problems appear during relapse or during remission of the disease?

- Are particular psychological problems specific to Crohn's disease or ulcerative colitis?

- Is the frequency of psychological problems in IBD similar to or higher than in other groups of medically ill patients?

- Do psychological problems precede and/or follow onset of the disease?

1.3.1. Do psychological problems co-occur with IBD more often than expected by chance?

The fact that psychological problems occur in patients with IBD has been widely discussed in the literature (Addolorato et al., 1997; Helzer, Chammas, Norland, Stillings, & Alpers, 1984; Helzer, Stillings, Chammas, Norland, & Alpers, 1982; Mittermaier et al., 2004). Whilst there is general agreement that psychological problems are common in patients with IBD, authors disagree as to whether they co-occur more often with IBD than expected simply by chance. In two case-control studies, Helzer et al. (1982, 1984) found no evidence of an association between psychiatric illness and either UC or CD. However, they found some evidence of an excess of psychiatric disorders in CD patients compared with controls. Other studies note a strong association between both UC and CD and psychological problems (Addolorato et al., 1997; Mittermaier et al., 2004). Mittermaier et al. (2004), in a longitudinal cohort study, found depression in 28% of patients, and showed that depressed mood associated with anxiety was a risk factor for early clinical recurrence of IBD. However, this study did not use a control group to address whether psychological problems are more common in patients with IBD than expected by chance. Addolorato et al. (1997) found higher rates of both anxiety and depression in both UC and CD than in controls, however, they used healthy controls rather than controls with other chronic illnesses.

1.3.2. Do psychological problems appear during relapse or during remission of the disease?

Some researchers report that anxiety and depression appear in patients only during relapse, while during remission their mental health is similar to that found in the general population (Levenstein et al., 1994; Robertson, Ray, Diamond, & Edwards, 1989). Using a case-control design, Robertson et al. (1989) examined 80 patients with IBD during different stages of the disease and 40 diabetic controls. They found that anxiety was less common in established IBD than amongst diabetic controls, and that excess depression occurred only in patients with IBD during relapse.

However, not all authors fully agree with this second conclusion, and some argue that a significant number of patients with IBD are equally vulnerable during both relapse and remission of the disease (Simren et al., 2002; Tanaka & Kazuma, 2005). In a case-control study, Simren et al. (2002) examined quality of life and psychological wellbeing in 43 UC and 40 CD patients in remission. As a group, compared to normal Swedish controls these IBD patients' psychological wellbeing was similar to that found in the wider population. However, in the subset of patients with IBD with IBS symptoms, levels of psychological wellbeing were lower, with 33% of UC and 57% of CD patients with concurrent IBS-like symptoms demonstrating higher levels of depression and anxiety. Other researchers have confirmed this result in a cross-sectional survey with 72 ulcerative colitis outpatients (Tanaka & Kazuma, 2005).

1.3.3. Are particular psychological problems specific to Crohn's disease or ulcerative colitis?

Another point of controversy touches on the question of whether particular psychological problems are more specific to Crohn's disease or ulcerative colitis. Many researchers have described a link between psychological problems and Crohn's disease (Andrews et al., 1987; Helzer et al., 1984; Schwartz & Schwartz, 1982). Other studies show that this association is also present in patients with ulcerative colitis (Addolorato et al., 1997; Guthrie et al., 2002; Kurina, Goldacre, Yeates, & Gill, 2001; Levenstein et al., 1994; Magni et al., 1991; Robertson et al., 1989). Still other researchers have observed that the association exists for patients with Crohn's disease and not generally for ulcerative colitis (Andrews et al., 1987; Nordin, Pahlman, Larsson, Sundberg-Hjelm, & Loof, 2002; North & Alpers, 1994; Tarter, Switala, Carra, Edwards, & Van Thiel, 1987). It may also be that psychological problems interact differently with CD compared to UC (Andrews et al., 1987), with psychological problems occurring equally commonly amongst the two conditions, but impairing physical recovery only in CD. Nordin et al. (2002), in a cross-sectional investigation with 492 patients (331 UC and 161 CD), confirm a high rate of psychological co-morbidity in CD but not UC and hypothesize that this may result from more severe somatic symptoms in CD. North and Alpers (1994), in their thorough systematic review, examined 12 studies (10 controlled), each of more than 10 patients, and concluded that there appeared to be a higher lifetime burden of psychiatric disorders in CD than in UC.

On the other hand, a large nested case-control study from a database of linked hospital records in Southern England, clearly showed that patients with both Crohn's disease and ulcerative colitis were equally prone to mood disorders (Kurina et al., 2001). This finding

is supported by the results of a cross-sectional survey involving 116 consecutive patients with IBD (Guthrie et al., 2002).

1.3.4. Is the frequency of psychological problems in IBD similar to or higher than in other groups of medically ill patients?

Researchers have discussed the issue of whether psychological problems are more common in patients with IBD than in other medically ill populations. Some have noted that the rate of psychological problems in patients with IBD is similar to that found in other populations of patients with chronic physical illness (Andrews et al., 1987; Drossman et al., 1991; Helzer et al., 1982). Andrews et al. (1987) conducted a cohort prospective study with 162 consecutive patients with IBD attending a clinic for inflammatory bowel disease, and found that 34% of UC and 33% of CD patients had suffered from some psychiatric problem. This study did not include a control group, but other authors report that the prevalence of psychiatric disorders in other chronic medical disorders is approximately 30% (Cavanaugh et al., 1983; Rodin et al., 1991). Consistent with this, in a case-control study with 50 UC participants, Helzer et al. (Helzer et al., 1982) found no difference in the rate of psychological problems in IBD when compared to a control group of patients with other chronic non-gastrointestinal disorders. Finally, Drossman et al. (1991) also report similar rates in a cross-sectional random survey with 997 members of the Crohn's and Colitis Foundation of America. This observation is consistent with the generally reported rates for psychological co-morbidity in chronic medical illness (Derogatis & Wise, 1989).

In contrast, other investigators report anxiety and/or depression to be more common in patients with IBD than in other patient groups (Addolorato et al., 1997; Garcia Vega, Fernandez Rodriguez, & Sanchez Lombrana, 1994; Kurina et al., 2001; Magni et al., 1991; Nordin et al., 2002). In a case-control study with 50 UC patients, Magni et al. (1991) noted

the presence of psychological problems in 31 UC patients (62%) compared with four controls (8%), although it should be stated the controls were patients having only minor urological problems. An increased burden of psychological co-morbidity was also found in a large retrospective nested case-control study of almost 12,500 participants (Kurina et al., 2001). The control group in this study, however, were patients admitted to hospital for minor medical and surgical conditions, rather than those suffering from a chronic illness. Moreover, as this study was retrospective, a recall bias and "the effort after meaning" phenomenon (finding meaning where there is none) should be taken into consideration while evaluating its results.

1.3.5. Do psychological problems precede and/or follow onset of the disease?

A further source of controversy lies in the question of whether psychological problems appear before the onset of IBD, are in fact its sequel, or both. Of the 5 areas of controversy, the dispute concerning the time of onset of psychological problems has been the most intense and long lasting. In a retrospective nested case-control study with 12,500 participants, Kurina et al. (2001) found that anxiety and depression appeared in UC, but not CD patients, before the onset of the disease. As this was most striking in the year prior to the diagnosis of UC, they hypothesized that either anxiety and depression are causally related to UC, that patients are anxious or depressed because of early signs or symptoms of as yet undiagnosed UC or even that UC may be partly a psychoneuroimmunological disease. However, the researchers evaluated this last possibility as unlikely, as they would then expect the psychological illness to precede UC by many years. These authors found no excess psychological co-morbidity in CD prior to diagnosis, but did find excess anxiety and depression in both groups of patients with IBD in the first year after diagnosis (Kurina et al., 2001). However, Tarter et al. (1987) report a discordant finding, with an excess of fearfulness and anxiety in CD patients prior to diagnosis, but no significant excess

antecedent psychological problem in UC. Tarter et al.'s research involved a case-controlled study with 53 consecutive patients with IBD and 28 healthy controls recruited by advertisement. It is difficult to reconcile these two divergent findings, as neither study was appropriately controlled. However, the sample size of the Kurina et al.'s (2001) group was substantially larger than that of Tarter et al.'s (1987).

Other investigators have proposed that psychological problems in patients with IBD are generally a consequence of the disease activity as measured by disease activity indices (Addolorato et al., 1997; Schwartz & Schwartz, 1982), or a consequence of a recent new diagnosis, particularly of Crohn's disease (Andrews et al., 1987; Kurina et al., 2001). One study of CD even found that the presence of psychological co-morbidity makes physical recovery less likely (Andrews et al., 1987), and another that depression is a risk factor for early relapse (Mittermaier et al., 2004). Some authors have hypothesized that the association between active disease and psychological co-morbidities may result from malnutrition, disabling symptoms (Addolorato et al., 1997), frequent hospitalizations and operations, particularly the presence of an ostomy, or proctocolectomy (Schwartz & Schwartz, 1982). However, this premise is not supported by Andrews et al. (1987) who did not find any association between psychological co-morbidity and the presence or absence of a stoma.

1.4. Discussion

The initial reason for undertaking this review was to find literature that answered the important question of the effect of anxiety/depression on the IBD course and activity. Unfortunately, the subsequent literature searches revealed little on this topic, as most relevant studies were either cross-sectional or case-controlled and as such were unable to

resolve the temporal relationship between these psychological problems and the somatic condition. Therefore, the author decided to conduct such a study in an attempt to fill this gap in knowledge (see Chapters 4 and 5). However, the searches did reveal several topics surrounding the co-morbidities of anxiety/depression in IBD where divergent opinions have been frequently expressed. These controversies became the focus of this review. The main areas of controversy concerned the co-occurrence of psychological problems with IBD as compared to the general population; the co-occurrence of psychological problems with particular phase of IBD (remission versus relapse); the specificity of psychological problems for the type of IBD (CD versus UC); the rate of psychological co-morbidity compared to other disease states; and the timing of onset of psychological co-morbidity with respect to the timing of onset of IBD.

These ongoing controversies indicate that the role of psychological problems in IBD is still unclear. However, most available studies do demonstrate a high frequency of common psychological problems such as anxiety and/or depression in patients with IBD. These psychological co-morbidities appear to occur at least as frequently in IBD as in other chronic illnesses. This association indicates the potential for a patient's psychology to perhaps play a role in the aetiology and/or the course of IBD. Alternatively, IBD itself may increase the risk of patients developing psychological problems. However, because of weaknesses in study design, selection and inclusion bias, and the use of inadequately matched control groups in the research that has been undertaken in this area to date, it is impossible to draw firm conclusions on these propositions. Moreover, psychological disturbances such as anxiety and/or depression are difficult to discretely assess in patients with IBD, as no disease specific instruments to measure psychological problems have yet been validated. Many currently used instruments have items that may be influenced by active or poorly controlled disease (e.g. general well being, fatigue, sleep disturbances,

appetite and weight changes). On the other hand, IBD activity indices also contain many subjective items that may be influenced by psychological, functional or other concomitant illness of remitting/relapsing nature, rather than purely gastrointestinal inflammation. These items include but are not limited to: general well-being, fatigue, pain and extraintestinal manifestations. Therefore, until we have better instruments to quantify both the psychological and inflammatory aspects of IBD, it is likely that ongoing controversies regarding the contribution of the psyche to IBD will remain.

Furthermore, Kurina et al. (2001), as well as other investigators, suggest that patients with IBD should be thoroughly screened for psychological problems and would benefit from specific psychological treatment. Interestingly, this opinion is widespread among researchers in this field, regardless of their findings with respect to these controversies, and despite the absence of any firm evidence to support this belief. The most appropriate approach to psychological treatment, and whether it improves patients' physical or psychological wellbeing, has not been clearly demonstrated to date. In fact in published work, no somatic benefit of psychologically directed treatment has been demonstrated, with randomised controlled trials of psychotherapy (Jantschek et al., 1998; Keller et al., 2004; Schwarz & Blanchard, 1991; von Wietersheim et al., 2001) offering negative results to date. However, a recent review on the effectiveness of psychotherapy in IBD showed that although psychotherapy cannot be recommended for all patients with chronic IBD, in some cases it may positively influence patients' mental status (von Wietersheim & Kessler, 2006).

1.5. Conclusion

The above analysis of the published material on the link between anxiety, depression and IBD does not yield consistent results. Obviously, further well-designed and properly controlled and powered research and more specifically, longitudinal prospective studies are urgently needed to adequately clarify the temporal relation between these psychological co-morbidities and IBD. The following chapters in Part I experimentally examine this possibility. First of all, the psychological wellbeing of patients with IBD was compared to that of other chronically ill patients in a cross-sectional design. Secondly, the cross-sectional analysis was advanced by comparisons between IBD and IBS participants in terms of co-morbid functional gastrointestinal disorders and their impact on these patients' psychological wellbeing. Thirdly, a comparative prospective study was conducted with the same participants in order to observe the temporal relation between these psychological co-morbidities and IBD, and to evaluate the impact of the psychological co-morbidities of anxiety and depression on physical outcomes/response to standard medical care in these patients. Finally, a randomised controlled trial was performed to explore whether the doctor's knowledge of their patients' psychological status influences patients' clinical outcome. The next chapter reports on the methods used in these four studies.

Chapter 2: Research methods used in Part I of the thesis

This chapter describes the rationale for the methodologies used in Part I and Part II focusing mainly on the methodology used in Part I. The methodology applied in Part II is described in Chapter 7. For clarity, each part has its own methodology chapter. Here all the studies' rationales, goals and objectives conducted in Part I are described. Ethical considerations, details of sampling, inclusion and exclusion criteria, hypotheses, measurements, outcome measures and further information regarding the methodology applied in the three studies comprising Part I are also discussed.

2.1. Methodology rationale

As the aims of this thesis were both to generalize the findings to the population and develop a comprehensive in-depth analysis, a mixture of both quantitative and qualitative methods was used. This methodological approach originates in studies conducted in the mid-20th century (Campbell & Fiske, 1959), in which investigators quantitatively and qualitatively surveyed psychological traits. For the last thirty years researchers have observed that social research is generally best addressed through an amalgam of methods, as triangulating data may neutralize or cancel the biases of one type of method. Mixed methods have therefore understandably become popular in social sciences (Creswell, 2003; Jick, 1979) and are based on collecting both qualitative and quantitative data through sequential, concurrent, and transformative procedures or variations of these approaches (Creswell, 2003). However, the research presented in this thesis did not apply these standard strategies in a commonly used manner, but rather focused on their variations. In line with this, studies were divided into two thematical parts with different methodologies.

The first part of the thesis employed concurrent quantitative designs supported by small semi-qualitative investigations (Creswell, 2003). The literature review (see Chapter 1) revealed a gap in knowledge and these studies attempted to fill this gap, especially in relation to interactions between patients' psychological status and their physical outcomes/response to standard medical treatment. The second part of this thesis used a variation of the sequential explanatory strategy. This strategy comprises two phases: initial quantitative data collection and analysis and subsequent qualitative data collection and analysis (Creswell, 2003). The purpose of this strategy was to utilize qualitative results to asist in interpreting the quantitative data. In this particular case, the systematic review, which was initially designed to be quantitative became qualitative due to the lack of reliable statistical data. Therefore, as a result, the thesis was divided into two parts: predominantly quantitative (Part I) and predominantly qualitative (Part II). The following section details aims, objectives and hypotheses tested in Part I.

2.2. Aims, objectives and hypotheses

Part I of this thesis consists of four studies aiming to understand the relationship between psychological problems and disease activity in patients with chronic conditions of the gastrointestinal tract in general, and inflammatory bowel disease in particular.

Study 1 (Chapter 3) involved a cross-sectional study, a design enabling a comparison of the prevalence of psychological problems and the level of quality of life in patients with IBD, IBS and HCV before the prospective study began. The aim of this study was:

- To observe and compare the psychological co-morbidity in patients with IBD, IBS and HCV in relation to the activity of their disease.

The objectives were:

- To determine and then compare the prevalence of psychological problems and the level of quality of life in each group of patients;

- To determine the activity of the disease in each group of patients;

- To determine whether patients with IBD have the highest rate of psychological problems amongst these three groups;

The hypothesis tested in this study was:

- Patients with IBD are most affected by psychological problems in comparison to patients with IBS and HCV (Hypothesis 1);

Study 2 (Chapter 4) involved a cross-sectional investigation into the prevalence of functional gastrointestinal disorders in IBD and IBS patient groups and the relationship between the number of these disorders and severity of psychological problems. The aim of this study was:

- To observe the influence of functional gastrointestinal disorders on the psychological status of patients with IBD and IBS.

The objectives were:

- To determine the prevalence of functional gastrointestinal disorders in IBD and IBS patients;

- To verify whether IBD and IBS patients with a greater number of functional gastrointestinal disorders have higher levels of anxiety and depression and poorer quality of life;

- To verify whether patients with IBD with co-morbid IBS have a higher rate of psychological problems and lower level of quality of life than patients with IBD without IBS;

- To validate the new Rome III criteria by testing the diagnosis of IBS by the Rome III against the "gold standard" of an existing clinical diagnosis of IBS by an experienced gastroenterologist.

Hypotheses tested in this study were:

- Patients with IBD and patients with IBS with a greater number of functional gastrointestinal disorders have higher levels of depression and anxiety and poorer quality of life than those with fewer functional disorders (Hypothesis 2);
- Patients with IBD with co-morbid IBS have higher rate of psychological problems and poorer quality of life than patients with IBD without co-morbid IBS (Hypothesis 3).

Study 3 (Chapter 5) involved an observational cohort prospective management study. It enabled the evaluation of the temporal relationship between psychological co-morbidities and the likelihood of a successful response to treatment/better physical outcomes (remission of symptoms) in patients with IBD, IBS and HCV. The aim of this study was:

- To observe and compare prospectively the course of IBD, IBS and HCV in relation to psychological co-morbidity.

The objective was:

- To determine whether patients with higher rates of anxiety and/or depression and poorer quality of life at baseline had worse outcomes after 12 months.

The hypothesis tested in this study was:

- Patients with psychological co-morbidities are less likely to have a satisfactory response to standard treatment/better physical outcomes at 12 months (Hypothesis 4).

Study 4 (Chapter 6) involved a pilot randomised controlled trial examining whether disclosure of IBD patients' psychological status to their treating doctors alters doctors' behaviour and/or influences patients' responses to the clinical treatment/their physical outcomes. It also enabled an estimate of sample sizes for future studies in this area to be made based on local patient characteristics.

The aim of this study was:

- To discover whether disclosure of the psychological status of patients with IBD to their physicians alters doctors' behaviour and/or influences patients' responses to treatment/their physical outcomes.

The objectives were:

- To determine whether physicians' knowledge of the patients' psychological status improves patients' clinical outcomes;

- To determine whether improving physicians' knowledge alters physicians' behaviour.

The hypothesis tested in this study was:

- Physicians' knowledge of patients' psychological status alters physicians' behaviour and/or improves patients' clinical outcome (Hypothesis 5).

2.3. Participants

Four hundred and thirty-seven patients were invited to participate in these studies by their gastroenterologists between November 2005 and June 2006 (see Figure 1). Of these, 238 had been previously diagnosed with inflammatory bowel disease, 94 with chronic hepatitis C, and 105 with irritable bowel syndrome. Patients were recruited through the Outpatient Clinic at the Royal Adelaide Hospital's Department of Gastroenterology and Hepatology.

One hundred and thirty-nine patients accepted the invitation to participate in the studies (31.8% of all patients invited). Of these, 64 patients had been previously diagnosed with inflammatory bowel disease: 34 with ulcerative colitis and 31 with Crohn's disease. Forty-one patients had been previously diagnosed with chronic hepatitis C and 34 – with irritable bowel syndrome. Twenty-six percent of all invited patients with IBD, 43.6% of all invited patients with HCV, and 32.4% of all invited patients with IBS accepted the invitation to participate in the studies. The reasons behind the low response rate will be described in more detail in discussion sections in Chapter 3 and 5.
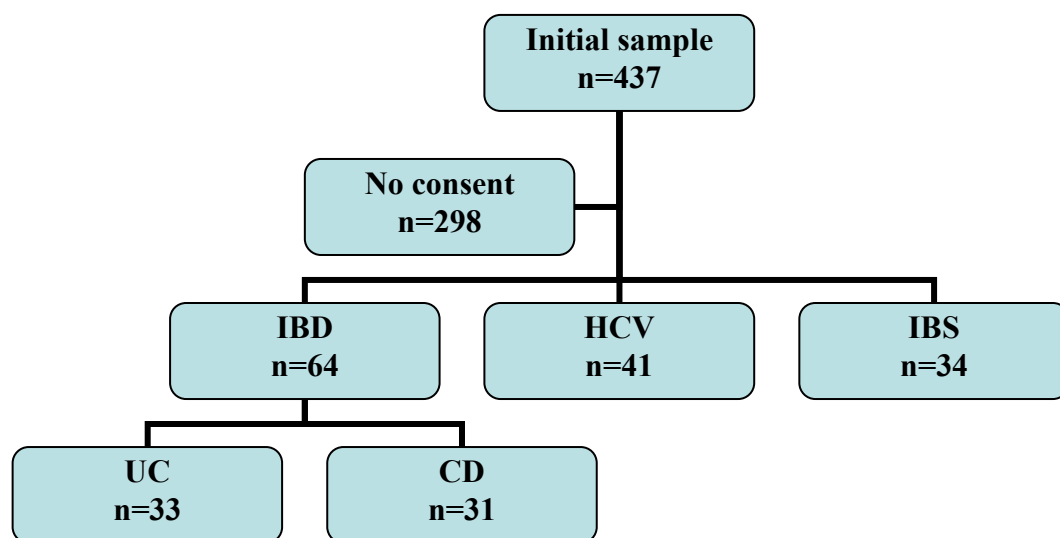
Figure 1: Recruitment procedure

All four studies were based on the same participants. Studies 1 and 3 employed IBD, IBS and HCV participants. Study 2 employed IBD and IBS participants. Study 4 focused on selected IBD participants; 64 patients with IBD were initially included in Study 4 (see Figure 2). After completing additional selection criteria (see section 2.4.2.), 25 patients remained in the study.
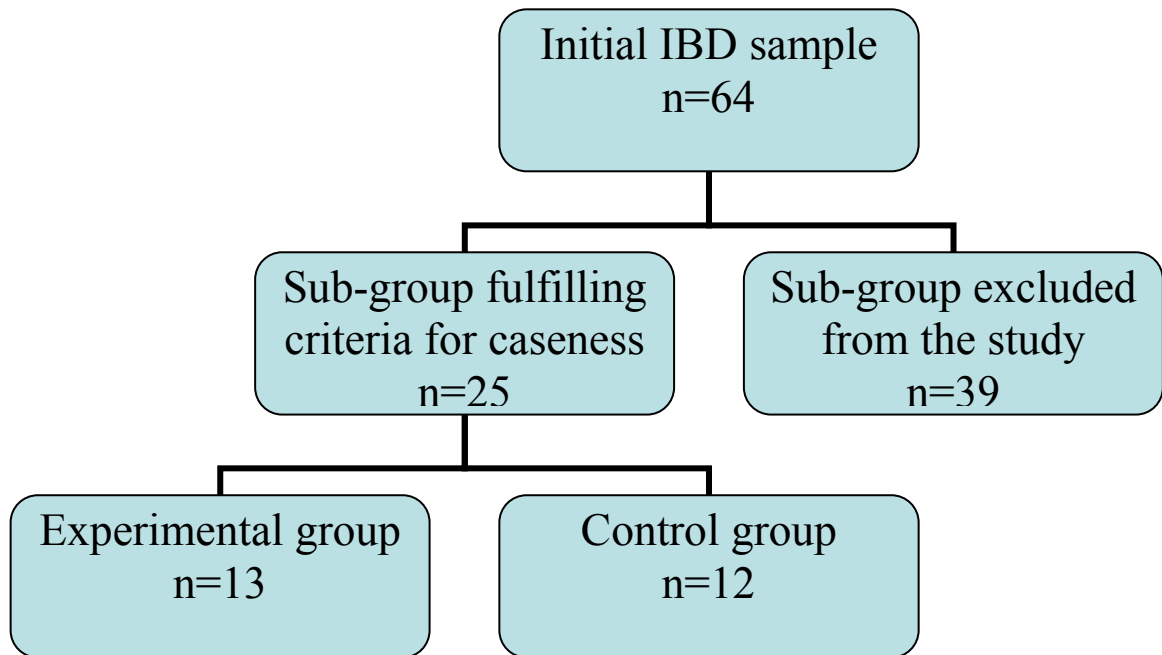
Figure 2: The RCT recruitment procedure

2.4. Inclusion, exclusion and withdrawal criteria

Due to the fact that the studies were supposed to be conducted in a limited time (a year out of the three years of the doctoral candidature), groups were not as homogenous as they could be. Inclusion criteria in studies with the broader time frame could also include similar time since diagnosis in all patient groups as well as similar disease activity.

2.4.1. Studies 1, 2 and 3

Patients included in the studies must have satisfied any one of criteria 1-3 AND both 4 and 5:

(1)   Patients with IBD (Crohn's disease or ulcerative colitis) diagnosed by standard clinical, endoscopic, histologic and/or radiologic criteria;

(2)   Patients with IBS diagnosed by accepted clinical, endoscopic, histologic and/or radiologic criteria by a gastroenterologist;

(3) Patients diagnosed serologically with chronic hepatitis C;

(4) Patients with sufficient knowledge of English to understand and answer questionnaires;

(5) Patients who signed written informed consent.

Patients excluded from the study satisfied any one of the following:

(1) Patients with insufficient knowledge of English or with cognitive impairment, as the study required filling in and understanding questionnaires written in English;

(2) Patients who did not give informed consent;

(3) Hepatitis C patients with cirrhosis (other than Child's A) or cancer of the liver, as this may confound psychological factors due to disease severity/known effect on mortality.

2.4.2. Study 4

Patients included in Study 4 must have satisfied the below inclusion criteria for Studies 1, 2 and 3. Additionally, they must have satisfied either of 1-2:

1. Patients with IBD fulfilling the Hospital Anxiety and Depression Scale Anxiety criterion for caseness (score > 7);

2. Patients with IBD fulfilling the Hospital Anxiety and Depression Scale Depression criterion for caseness (score > 7).

Patients excluded from the study must have satisfied both of 1-2:

1. Patients with IBD not fulfilling the HADS Anxiety criterion for caseness (score < 7);

2. Patients with IBD not fulfilling the HADS Depression criterion for caseness (score < 7).

Patients were able to withdraw from the study at any time. They were asked by the author about their reasons for withdrawal for statistical purposes; however, they were not obliged to provide this. Withdrawal from the study did not affect ongoing standard medical treatment.

2.5. Sample

The sample calculation is provided mainly for Studies 3 and 4 as these involved interventions. Moreover, samples for Studies 1 and 2 were derived from the same sample as Study 3. Thus, they all relate to the same groups of patients.

2.5.1. Studies 1, 2 and 3

Initially, the expected sample size for the IBD group was between 50 and 125 participants. For the IBS and HCV patients it was estimated to be between 50 and 75 patients in each group. The author's intention was to recruit between 2-5 IBD, 2-3 IBS and 2-3 HCV patients per week. The estimated total sample (for IBD, IBS and HCV) was estimated to be between 150 and 275 patients. This was based on the number of patients treated at the clinic, provided by the Head of Department of Gastroenterology and on numbers of patients with psychological co-morbidities presented in other studies. However, due to the low quality of data in this area (see Chapter 1) the power calculation presented below should be treated as an indication only.

The power calculation was produced to yield differences of more than 15% for the primary outcome variables with an alpha-level of 0.05 and a beta-level of 0.86 (see Table 1 below). An intended sample size of at least 150 patients (50 in each patient group) was estimated as

being acceptable for this trial. Due to the low response rate to the invitation to this study, the recruitment period was extended to two additional months, to recruit more participants.

Table 1: Effect size, power and sample size

Effect size	Power	Sample size
0.15	86	50

2.5.2. Study 4

During relapses, 80% of patients with IBD suffer from anxiety and 60% from depression (Addolorato et al., 1997). During remission, approximately 30% of patients with IBD suffer from psychological problems (Mittermaier et al., 2004). Patients visiting the RAH were thought to be mainly in relapse. The assumption was made that at least about 60% would have psychological problems. As previously stated, the planned sample of patients with IBD was between 50 and 125. The sample of patients with psychological problems was therefore expected to be between 30 and 65 patients. Half of these cases were to be randomly disclosed to the physician.

After having analysed the data in Study 1, the prevalence of anxiety in the studied group was estimated at 37% and depression at 11%. This demonstrates that the numbers taken from other studies for the sample size calculation were not relevant to this SA population. Additionally, a majority of the group was in remission from disease (64% participants with inactive disease). Therefore, not surprisingly, the final sample was smaller than predicted and consisted of only 25 participants of who 13 were randomly selected to the experimental group and 12 to the control group. The power calculation was not conducted

in this instance because the study was a pilot and its results will be used to calculate sample sizes for future larger trials.

2.6. Design

2.6.1. Studies 1, 2 and 3

The design of studies is included in Figure 3. Studies 1 and 2 are cross-sectional designs, which made it possible to conduct a comparison of the prevalence of psychological problems and the level of quality of life in IBD, IBS and HCV patients at one point in time (at baseline of the prospective study). It also enabled an analysis of the role of functional gastrointestinal disorders in the IBD and IBS groups. Study 3 involved an observational cohort prospective management study. This design permitted testing the hypothesis that psychological co-morbidities affect physical outcomes/response to medical treatment (defined by remission/relapse status).
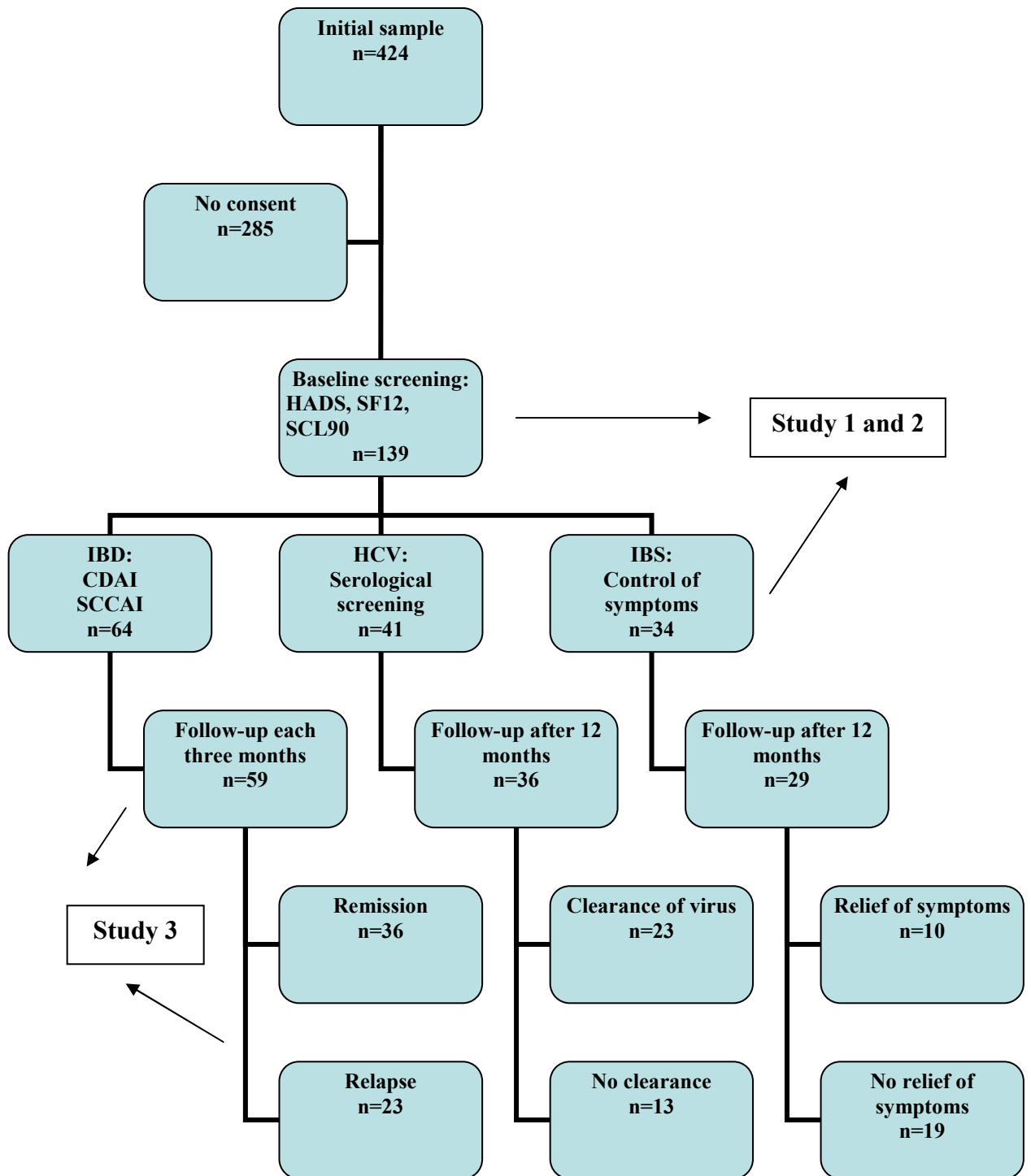
Figure 3: The design of Studies 1, 2 and 3

2.6.2. Study 4

Study 4 was conducted as a randomised controlled trial (RCT) design. The trial aimed at examining whether disclosure of IBD patients' psychological status to their physician alters doctors' behaviour and influences patients' responses to the clinical treatment/their physical outcomes. Participants with diagnosed psychological problems detected by the screening instrument (HADS) were randomly allocated into one of two groups. The psychological status of patients assigned to the experimental group was disclosed to the treating physicians via a letter. The psychological status of patients assigned to the control group was not disclosed to the treating physician. As psychological co-morbidities in patients with IBD are frequently unrecognised in standard care settings (Mittermaier et al., 2004), and often not specifically treated, this methodology was intended to reveal whether a physician's knowledge of the patient's mental health status influenced their actions and/or the patients' response to clinical treatment/their physical outcomes. It could also provide information about what sample size might be adequate in future randomised controlled trials of psychological interventions in this area.

Random permuted blocks were used to create a randomisation matrix before the beginning of the trial (Pocock, 1991). "A" was regarded as a disclosure of the score to the treating physician, while "B" was considered a non-disclosure of the score to the treating physician. The matrix was organised in the following way: digits 1-4 AABB, digits 5-8 ABAB, digits 9-12 ABBA, digits 13-16 BBAA, digits 18-20 BABA, digits 21-24 BAAB, digits 25-28 AABB, digits 29-32 ABAB, digits 33-36 ABBA, digits 37-40 BBAA, digits 41-44 BABA, digits 45-48 BAAB, digits 49-52 AABB, digits 53-56 ABAB, digits 57-60 ABBA, and digits 61-64 BBAA.

No stratification was conducted and the ratio between the groups was 1:1.

2.7. Procedure

2.7.1. Studies 1, 2 and 3

In general, the clinic consultants individually invited where possible consecutive eligible patients to participate and provided them with written information regarding the study (see Appendix 2). Before each clinic, the author met with the consultants and discussed which patients will be invited. This allowed the author to collect the numbers and basic demographics of potential participants. Interested patients visited the author after their appointments with the doctors. Doctors brought participants to the author's office at the hospital and introduced them to the author. In some cases, when the author was not at the hospital, doctors individually invited patients to the study and after obtaining their consent, gave patients' contact details to the author. The author described the study to patients and provided patients with a consent form (see Appendix 3), questionnaires and a reply paid envelope. Patients were given the choice of completing the questionnaires at hospital or at home. The majority of participants preferred to complete the questionnaires at home. Participants provided the author with their contact details in case they forgot about completing the questionnaires. After completing the questionnaires, participants sent them back to the author. When this had not occurred after a month, the author contacted participants by telephone to remind them about the study. If the telephone number was not provided, a reminder letter was sent. This procedure was repeated up to three times. The time to complete questionnaires was approximately 40 minutes. The author piloted this on herself and a number of PhD students. The pilot took on average 20-30 minutes; however, due to the fact that PhD students were familiar with some of the questionnaires, the author estimated the time should be around 40 minutes in a lay person. Those participants who received an additional questionnaire (BDQ), on one occasion had to spend additional 10 minutes completing this questionnaire.

After a baseline assessment (Study 1) was completed, the prospective studies (Studies 3 and 4) began. Participants with IBD were contacted at three month intervals for 12 months as they were the main focus of this thesis. Participants with IBS and HCV (control groups) were contacted after twelve months. Additionally, patients with IBD and IBS were also contacted on one occasion in the middle of the trial to complete the newer (Rome III) version of diagnostic criteria for functional disorders (Study 2). During the trial, the author systematically scored the questionnaires sent back by participants and entered data to the database (Microsoft Office Access 2003).

2.7.2. Study 4

Participants with IBD who fulfilled the inclusion criteria for Studies 1, 2 and 3 were automatically ascribed to this study. After the baseline analyses of participants' psychological profiles, those who fulfilled the HADS Anxiety or Depression criteria for caseness (score > 7) were included into this trial. During the study, all participants received the usual medical care. In addition, they filled in questionnaires measuring their disease activity, quality of life and psychological status every three months for 12 months, similar to other patients with IBD participating in Study 3.

Participants were randomly allocated to either an experimental or a control group. The experimental group's psychological evaluation was disclosed to the treating doctor. The control group's data were not disclosed to the treating doctor. However, any patient diagnosed with severe psychological problem (i.e. psychosis or depression) was reported to his/her doctor irrespective of the process of randomisation. The severity was based on the HADS score and later confirmed by the SCL90 score according to usual cut-off values. A letter to the treating doctor did not suggest any particular treatment approach to be undertaken, leaving the decision on this matter at doctors' discretion (see Appendix 4).

After one year, the author reviewed participants' case-notes searching for any evidence of doctors' behavior relevant to psychological problems and treatment of patients in both groups. At first, the author searched for referrals to mental health specialists, correspondence with such specialists or comments/advice to patients to see such specialists. Secondly, the author searched for doctors' attempts to conduct counseling themselves. This might have included talking about their patients' psychological problems or, in the experimental group, revealing to a patient the content of the author's letter to them and informing a patient of his/her score on the HADS and its implications. Thirdly, the author sought information on prescribing of anti-depressive or anti-anxiety medication, its name and the results of such treatment. If any of the above three steps was recorded, this was coded as 'action'. If, however, the author was not able to identify any of the three, the result was coded as 'no action'.

2.8. Measurements in Studies 1, 2, 3 and 4

2.8.1. Evaluation of general health and disease activity

As all participants must have been previously diagnosed by a gastroenterologist with IBD, HCV, or IBS, respectively, the author did not confirm the diagnosis. The general health survey designed by the author was, however, given to participants. This survey included three versions and asked about basic demographic characteristics, medical history and patients' concerns regarding their disease (see Appendices 5, 6, and 7). It was given to all the participants on one occasion (at baseline during Study 1).

The disease activity in IBD participants was assessed using the Crohn's Disease Activity Index (CDAI) (Best, Becktel, Singleton, & Kern, 1976) or the Simple Clinical Colitis

Activity Index (SCCAI) (Walmsley, Ayres, Pounder, & Allan, 1998) (see Appendices 8 and 9 as appropriate). The CDAI includes the following items: number of liquid or very soft stools, abdominal pain ratings, general well-being, symptoms related to CD, use of opioids, abdominal mass, haematocrit, and body mass index (BMI). The SCCAI includes the following items: general well-being, bowel frequency, urgency of defecation, blood in stool, and extraintestinal manifestations. A CDAI score ≤ 150 was considered remission from CD and a SCCAI score of ≤ 2 was considered remission from UC (Best et al., 1976; Walmsley et al., 1998).

The disease activity in patients with IBS was measured by two questions added to the general health survey: "Have you got satisfactory control of your IBS symptoms over the last 3 months?" and "Are you now feeling better or worse when compared to your last visit in the clinic?". Answering "yes" and "better" to both these questions was considered remission in IBS (as part of the general health survey Appendix 6).

The disease activity in HCV (or, more precisely, ongoing viral replication) was measured by an rt-pcr HCVRNA. An rt-pcr HCVRNA "Not detected" was considered remission of HCV.

2.8.2. Evaluation of psychological well-being

Screening for anxiety and depression was undertaken with the Hospital Anxiety and Depression Scale (HADS) (see Appendix 10). This validated self-assessment mood scale was developed for medical outpatients rather than the normal population and is therefore suited to this population (Zigmond & Snaith, 1983). The physical symptoms of mood disorders which are likely to be present in the medically ill, such as insomnia, are excluded from the scale as confounding factors (Snaith & Zigmond, 1986). The HADS contains 14

questions graded on a 4-point Likert scale (0-3), with subscales of anxiety (seven items) and depression (seven items), with a sum score ranging from 0 to 21. A cut-off value for clinical caseness is 7. Scores between 8 and 10 are interpreted as possible cases, and ≥ 11 as certain cases. The HADS has been validated against the Diagnostic and Statistical Manual of Mental Disorders-III (DSM-III) and demonstrated a sensitivity of 76% and specificity of 79% for the diagnosis of anxiety or depression in patients with IBD (Andrews et al., 1987). It has also been previously used in Australia (Pallant & Bailey, 2005; Pascoe, Edelman, & Kidman, 2000), however, not with an IBD sample.

Participants' broad psychological profile was assessed with the SCL-90-R Symptom Checklist-90-R (SCL-90). This scale is a 90-item self-report instrument. Each item is rated on a five-point scale of distress (0-4) ranging from "Not at all" to "Extremely". The SCL-90 contains 9 subscales: Somatization, Obsessive-Compulsive, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism. It also comprises three global indices: Global Severity Index (GSI), Positive Symptom Distress Index, and Positive Symptom Total (Derogartis, 1994).

There are no specified cut-off values for this scale; however, caseness has been calculated as a GSI score $\geq$ a T score of 63 or when any two primary dimension scores are $\geq$ a T score of 63. The internal consistency for this scale is between 0.77 and 0.90 (Derogatis, Rickels, & Rock, 1976; Horowitz, Rosenberg, Baer, Ureno, & Villasenor, 1988). One-week test-retest reliability ranges from 0.78 to 0.90 (Derogatis et al., 1976). The strong factor structure of this scale, in addition, supports the validity of the construct measured by the SCL-90. The results of this scale are reported as T scores (with normative mean score = 50, and standard deviation = 10). The SCL-90 is especially useful in prospective studies as it has been found to adequately measure changes in the psychological status of various

outpatient groups (Derogartis, 1994). The SCL-90 has been previously used in studies of IBD populations (Drossman et al., 1991; Magni et al., 1991). It has also been applied to Australian samples of chronically ill subjects (McGuire & Shores, 2001; Wallis, Lord, Barnsley, & Bogduk, 1996).

2.8.3. Evaluation of health related quality of life

Measuring quality of life was done with the Short Form 12 Health Survey (SF-12). This abbreviated scale was derived from 12 questions of the Medical Outcomes study Short Form 36 health status questionnaire (SF-36), a commonly used scale that measures different aspects of quality of life (Jenkinson, Coulter, & Wright, 1993; Ware & Sherbourne, 1992). The SF-12 contains two subscales: the Mental Component Summary (MCS) and the Physical Component Summary (PCS) (Ware, Kosinski, & Keller, 1996). Scores for each subscale range between 0 and 100, with increasing values indicating better health. The test-retest reliability for the PCS-12 scale is between 0.86 and 0.89, and for the MCS-12 scale between 0.76 and 0.77 (Ware, 1998). A multiple-staged validation procedure has demonstrated that the PCS-12 scale and the MCS-12 scale are likely to reach the same statistical conclusion as PCS-36 and MCS-36 (Ware, 1998). Correlations between the SF-12 and the SF-36 versions of PCS and MCS have been found to be very high and ranged between 0.951 and 0.969 (Ware, 1998). To the best of the author's knowledge the SF-12 has not been previously used in studies on the IBD sample; yet, many IBD studies have employed the SF-36 to measure quality of life (Larsson et al., 2003; Nordin et al., 2002; Pace et al., 2003). The SF-12 has also been validated in South Australia (Avery, Dal Grande, & Taylor, 2004).

2.8.4. Evaluation of functional disorders

Functional disorders in participants with IBD and IBS were initially planned to be assessed with the Rome II criteria and the use of the Bowel Disease Questionnaire (Talley, Phillips, Melton, Wiltgen, & Zinsmeister, 1989). However, the Rome II criteria were supersceded by the publication in April 2006 of the Rome III criteria (Drossman, 2006c; Rome III: The Functional Gastrointestinal Disorders," 2006). Consequently, the author decided to use the newer version of the BDQ (see Appendix 11). Professor Nicholas Talley, who devised the BDQ, permitted the author to use a draft version of this questionnaire. The author adjusted the questionnaire to Australian conditions, as the newer version of the BDQ (BDQ-6) was originally designed for the American population. In the case of patients with IBD, the author later modified the instruction informing participants that while answering questions they should describe how they feel during remission of their disease and not during relapse. This was done in order to avoid confounding factors such overlap of inflammatory GI symptoms.

The complete BDQ was 18 pages long and contained 8 demographic questions, 127 main items pertinent to gastrointestinal problems, and 16 additional general health questions. The functional disorders identified by the questionnaire included: functional oesophageal disorders (functional heartburn; functional chest pain of presumed oesophageal origin; functional dysphagia; and globus); functional gastroduodental disorders (functional dyspepsia including postprandial distress syndrome and epigastric pain syndrome; belching disorders including aerophagia and unspecified excessive belching; nausea and vomiting disorders including chronic idiopathic nausea, functional vomiting and cyclic vomiting syndrome; and rumination syndrome in adults), functional bowel disorders (irritable bowel syndrome; functional bloating; functional constipation; functional diarrhoea; and unspecified functional bowel disorder); functional abdominal pain syndrome; functional

gallbladder and Sphincter of Oddi disorders (functional gallbladder disorder and functional biliary SO disorder); and functional anorectal disorders (functional anorectal pain including chronic proctalgia and proctalgia fugax; and functional defecation disorders). Rome III criteria and, consequently, the BDQ-6 have introduced some changes in the classification and diagnosis of certain functional disorders. These changes include: change in the time frame for diagnosis of all functional disorders; shifts in classification categories for rumination syndrome and functional abdominal pain syndrome; and criteria changes in functional dyspepsia, functional gallbladder and Sphincter of Oddi disorders and in subtyping of IBS. These changes were introduced to make the diagnosis of functional disorders more precise and to facilitate research and clinical practice (Drossman, 2006b).

2.9. Outcome measures and response

2.9.1. Study 1

Primary outcome measures in Study 1 were:

- The prevalence of psychological problems in each group of patients at study enrolment;
- The level of quality of life in each group of patients at study enrolment;
- The activity of the disease in each group of patients at study enrolment.

2.9.2. Study 2

Primary outcome measures in Study 2 were:

- The prevalence of functional gastrointestinal disorders in patients with IBD and IBS;
- The prevalence of IBS in the IBD group;

- The prevalence of psychological problems in patients with IBD with co-morbid IBS;

- The proportion of patients with IBD and IBS with both functional gastrointestinal disorders and psychological problems;

- The proportion of patients diagnosed with IBS both clinically and by the Rome III criteria.

These data were assessed within three months of enrolment.

2.9.3. Study 3

Primary outcome measures in Study 3 were:

- The proportion of patients with IBD in clinical remission of IBD after a year of standard therapy (different for particular condition, see Preamble for examples of typical medication used in each disease);

- The proportion of patients with IBS with sufficient relief of symptoms after a year of standard therapy;

- The proportion of patients with HCV with clearance of the virus after a year of standard therapy.

In CD, a CDAI score of < 150 points or a drop of at least 70 points was scored as response to treatment (remission/better physical outcomes). In UC, a SCCAI score of ≤ 2 points or a drop of at least 3 points for 3 weeks was regarded as a response. In IBS, answering "yes" and "better" to the following questions: "Have you got satisfactory control of your IBS symptoms over the last 3 months?" and "Are you now feeling better or worse when compared to our first meeting?" was scored as a satisfactory response. In HCV, anti-HCV antibody (quantitative result) score of < 600 and rt-pcr HCVRNA (qualitative result) of "Not detected" were considered a response.

Secondary outcome measures were:

- The proportion of patients in all disease groups with an improved psychological status;

- The proportion of patients in all disease groups with improved quality of life.

2.9.4. Study 4

The primary outcome measures in Study 4 were:

- Doctors' behaviour assessed by the documentation in patients' case-notes referring to psychological issues;

- The proportion of participants in the experimental group in clinical remission of IBD after a year of standard therapy.

Any recommendation for psychological treatments or a discussion of psychological factors, where none existed before the disclosure, was considered as a response. In particular, a referral to a mental health professional (e.g. psychologist, counsellor, psychiatrist); recommendation for a patient to see a mental health professional; individual counselling by the treating doctor (including a disclosure to the patient the content of the letter from the author to the treating doctor); and therapy with antidepressants prescribed by the treating doctor were considered a response.

In CD, a CDAI score of < 150 points or a drop of at least 70 points was scored as a response to treatment (remission/better physical outcomes). In UC, a SCCAI score of ≤ 2 points or a drop of at least 3 points for 3 weeks was regarded as a response.

Secondary outcome measures were:

- The proportion of patients in each group with an improved psychological status;

- The proportion of patients in each group with improved quality of life.

2.10. Ethical considerations

2.10.1. Ethics Committee approval

Ethical approval for conducting studies was obtained from the Royal Adelaide Hospital Research Ethics Committee. A notification was sent to the University of Adelaide Human Ethics Committee.

2.10.2. Informed consent

In each study, informed written consent was obtained prior to commencement. The author ensured that the participants were given full verbal and written information about the nature, purpose, possible risks and benefits of the trial. No patient received less than standard tertiary referral hospital care for his/her condition. All treatment decisions were at the discretion of the usual treating physician, and were not altered by the trial – except that in some patients additional information regarding his/her mental health status was available. Currently, this is not proven to influence clinical outcomes.

2.10.3. Potential risk for participants

In Studies 1, 2 and 3 the risk for participants was thought to be minimal. Participants received standard medical treatment. The results of studies were analysed so that no individual patients were identified. However, the study involved a small time burden for participants. They had to spend about 40 minutes filling in questionnaires (in Study 3 this might have happened up to five times per year). In Study 3, in order to reach the least biased results, participants had a choice to do their follow-up tests in the hospital or at

home. If they chose to do them at home, reply paid envelopes they received from the researcher were sent to the secure mailbox in the Discipline of General Practice. Participants had been informed that the person who scored the questionnaires was not involved in their usual treatment.

The goal of Study 4 was to investigate whether the standard medical care of patients with IBD can be improved by routine psychological screening of patients with IBD. This is not current standard clinical practice, despite the known high rate of psychological co-morbidities. As all patients received the usual standard of care (i.e. no-one received less than usual care), the Research Ethics Committee and the author saw no ethical issue in only disclosing the results of some of the psychological co-morbidities discovered in patients' screening tests. In this fashion, even random disclosure of patients' mood disturbances to their physicians was thought to improve standard care. However, as this is not proven to be the case, there was no ethical issue in withholding treatment suggested from these screening tests. Additionally, physicians may have independently diagnosed and treated any psychological problem in patients with IBD if the physician had perceived this to be necessary (without regard to the study screening instruments – to which the treating physicians were blinded). Additionally, the protocol specified that any patient diagnosed with severe psychological problems (i.e. depression, psychosis), would be reported to his/her treating doctor.

2.10.4. Confidentiality and anonymity

All information obtained in the studies was treated as confidential, and all answers given in questionnaires were anonymous. Reporting of results consisted only of aggregated data. Follow-up results were also sent to the secure mailbox in the Discipline of General Practice.

2.10.5. Data storage

According to the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines, all computer-processed data were identified by patient number only, thereby ensuring that the patient's identity was not disclosed ("ICH Topic E6 (R1) Guideline for Good Clinical Practice," 2002). The only place where the patient's name appeared was on the consent form which was kept in a secure locked storage room in the Discipline of General Practice.

2.10.6. Reporting of results

The results were reported as de-identified data. No confidential data were revealed. The results were analysed and submitted for publication in peer reviewed journals.

2.11. Statistical analyses

All statistical analyses were undertaken using the Statistical Package for the Social Sciences (SPSS for Windows, Release 13.0, Chicago 2004).

2.11.1. Study 1 (A cross-sectional study comparing the prevalence of psychological problems and the level of quality of life in patients with IBD, IBS and HCV)

Descriptive statistics on basic demographic data for the three disease groups (age, sex, education, activity of disease, years since diagnosis, years with symptoms) and on the three main scales used in the study (the HADS, the SF-12, and the SCL90) were provided. The prevalence of depression and anxiety in the three disease groups was also described. With

the parametric data, the differences between the groups were assessed with a one way analysis of variance (ANOVA) with disease (HCV, IBD or IBS) as the only factor. In order to observe the direction of the differences, post hoc tests (Tukey's Honestly Significant Difference (HSD)) were conducted in cases when a significant overall F test was found ($p<0.05$). A significant difference meant that there were at least 2 groups that were different on the dependent variables. The Chi-Square test was used to analyse categorical data. Hypothesis 1 was verified at this stage and the process of its verification and the results obtained were described.

A five-step hierarchical regression of baseline group differences in terms of demographic characteristics and mean scores for the three main scales was subsequently conducted. At first, the mean effects of disease, sex, age, education, activity and years since diagnosis were entered. In the second step, the disease interactions with sex and age were added. In the third step, the disease interactions with years since diagnosis were entered. The fourth step involved adding disease interactions with disease activity, and in the final step, the disease and level of education interactions were entered. At each step the "r^2" and the "r^2" change were reported. A change in the "r^2" was tested statistically.

Comparisons of means for each subscale used in the study for the IBD group with the data from other studies on IBD samples, other chronic disease groups and from the normal population (when appropriate) were then performed with the independent samples t-tests. For the HADS, the means for the Anxiety subscale and the Depression subscale in the IBD group were compared to the HADS scales means in similar British (Guthrie et al., 2002) and Swedish (Simren et al., 2002) samples. The means were then compared with the German sample of coronary heart disease patients (Barth & Martin, 2005), the British sample of breast cancer sufferers (Rodgers, Martin, Morse, Kendell, & Verrill, 2005), and

another British sample of chronic obstructive pulmonary disease patients (Withers, Rudkin, & White, 1999). For the SF-12, the means for the Mental component and the Physical component were compared to the appropriate SF-36 subscales in the similar Swedish (Nordin et al., 2002) and British (McColl, Han, Barton, & Welfare, 2004) samples of patients with IBD. The author decided to use the data from the SF-36 studies due to the lack of data from SF-12 studies on the population of interest. Then, the means were compared to the SF-12 means in other South Australian (SA) chronic disease groups (people with diabetis, asthma and arthritis) and to the normal SA population (Avery et al., 2004). The SF-12 is the only scale among those used in this study to have population norms. In this case, also the IBS and the HCV groups' means were compared to the population norms. For the SCL90, due to the lack of data, the IBD group means for the GSI subscale only were compared to the GSI means for the American sample (Drossman et al., 1991). All the SCL90 subscales means for the IBD group were then compared to other samples, specifically the Australian sample of chronic pain patients (McGuire & Shores, 2001) and the Canadian sample of patients with whiplash injuries and musculoskeletal pain (Peebles, McWilliams, & MacLennan, 2001).

Furthermore, comparisons between UC and CD patients in terms of their differences in demographics and on the HADS, the SF-12 and the SCL90 subscales were conducted with the independent samples t-test. Differences in sex, education and the activity of symptoms were assessed with the Chi-Square test as data were non-parametric. In order to obtain the exact probability and as the expected values were in some cases below 10, Fisher's Exact Test was conducted.

Finally, a semi-quantitative content analysis was conducted in order to compare the differences in IBD, IBS and HCV patients' concerns regarding their disorders. Patients'

responses were divided into mutually exclusive categories where possible, and subsequently coded. Participants' responses were then summarised.

2.11.2. Study 2 (A cross-sectional investigation into the prevalence of functional gastrointestinal disorders in IBD and IBS patients and exploring the relationship between the number of these disorders and the severity of psychological problems)

The prevalence of functional disorders was determined using the scoring guideline for BDQ-6 developed by the author according to the Rome III criteria ("Rome III: The Functional Gastrointestinal Disorders," 2006). In order to examine how those participants who met criteria for IBS with the Rome III criteria differed from those who did not meet the criteria (thus, disagreeing with the doctors' diagnosis), frequencies for the IBS diagnosis and all the other outcomes from the BDQ were obtained. To compare the prevalence of FGID between the CD and the UC subgroup the Fisher's Exact Test (2-sided) was applied. The association between functional disorders and anxiety, depression and quality of life analysis was performed using multiple linear regression for patients with IBS and using independent samples t-tests in the case of IBD participants. The relationship between the number of functional disorders (one, two or >2) and the rate of anxiety, depression and quality of life were calculated with ANOVA. ANOVA comparisons were also conducted to compare the psychological status and quality of life between patients with IBD with concurrent IBS and those without concurrent IBS. As psychological problems and IBS are more prevalent among females, the comparisons controlled for sex.

2.11.3. Study 3 (A cohort prospective management study exploring the temporal relationship between psychological co-morbidities and the likelihood of a successful response to standard medical treatment/better physical outcomes in patients with IBD, IBS and HCV)

A logistic regression with a binomial dependent variable was conducted to observe a relationship between baseline characteristics (Point 0) and patients' medical outcomes (response to standard medical treatment) after 12 months (Point 4). The results were adjusted for sex, years since diagnosis and age. In order to obtain more parsimonious results, after building a general model for all the psychological variables versus relapse, data were explored as part of a model with significant and demographic variables only.

A Poisson regression analysis was conducted to observe a relationship between baseline characteristics and a total number of relapses in the IBD group. Demographic comparisons and comparisons between CD and UC participants were included into the analysis. The Hypothesis 4 was tested and described

2.11.4. Study 4 (A pilot randomised controlled trial examining whether disclosure of IBD patients' psychological status to their treating doctors alters doctors' behaviour and/or influences patients' responses to the clinical treatment/their physical outcomes)

Differences between the groups for continuous variables were assesed using independent samples t-test. Differences in categorical variables were assessed with the Chi-Square test or the Fisher's Exact Test when the expected values were below 10. Moreover, the two-way repeated measure ANOVA comparing clinical and psychological changes over time between the experimental and the control group was performed. The results were adjusted

for multiple comparisons with the Holm's correction. The effect size and power estimates were provided. A total number of relapses was calculated with the use of Gamma statistics. The Chi-square test and the Fisher's Exact Test (in the case where cells had expected count less than 5) were used to detect group differences in the relapse/remission status at each stage of the trial. Finally, the data from the case-notes were subjected to a semi-qualitative analysis. The doctors' interventions were described and Hypothesis 5 was tested.

The next chapter reports on the results of Study 1, a cross-sectional investigation into the differences in the psychological status of patients with IBD, IBS and HCV. The following chapters explore the relationship between the psychological problems and physical outcomes/response to standard medical treatment in these three disease groups.

Chapter 3: Prevalence of psychological problems and the levels of quality of life in patients with inflammatory bowel disease, irritable bowel syndrome and hepatitis C: A cross-sectional investigation (Study 1)

This chapter reports on the cross-sectional study which aimed to compare the prevalence of anxiety and depression and quality of life in patients with inflammatory bowel disease, irritable bowel syndrome and chronic hepatitis C. The group differences between participants with IBD, IBS and HCV in relation to demographic characteristics and the scales are described as well as comparisons between the CD and UC group mean scores for the activity of the disease and the scales used in the study. Moreover, the chapter provides mean comparisons of mental status and quality of life between the current IBD group and previously published data on IBD groups studied by other investigators as well as between the studied IBD group and chronically ill samples. Furthermore, quality of life between IBD, IBS and HCV participants and the normal population is compared here. This chapter also reports on the implications of those findings for the first hypothesis (Patients with IBD are most affected by psychological problems in comparison to patients with IBS and HCV).

3.1. Introduction

As outlined in the Preamble, irritable bowel syndrome and chronic hepatitis C are common chronic disorders of the gastrointestinal tract. Like IBD, both conditions have been associated with psychological problems such as anxiety and depression (Crone & Gabriel, 2003; Fullwood & Drossman, 1995) and decreased quality of life (Dean et al., 2005; Spiegel et al., 2005). Despite studies referring to the co-occurrence of IBD and IBS (Barratt et al., 2005; Simren et al., 2002) as well as IBD and HCV (Holtmann, Galle, & Neurath, 2003), little research comparing quality of life and the prevalence of psychological problems between these three diseases has been identified.

Interestingly, common treatments for two of these conditions are linked to mood disorders. This is particularly so for interferon-alpha treatment in patients with hepatitis C and corticosteroids in IBD. Thus, these patients' anxiety and depression may in part have iatrogenic origins. Somewhat puzzlingly, IBS, which causes the least objectively quantifiable disturbance to gastrointestinal functions, has been noted to have the largest prevalence of anxiety and depression among these three conditions. This result, however, was reported in non-comparative studies (Crone & Gabriel, 2003; Walker et al., 1990). As there are no current local data available for these groups of patients, such studies are needed.

The prevalence of psychological problems among patients with IBD, IBS and hepatitis C in a contemporaneous (recruited simultaneously from the same outpatient clinic) sample is therefore worth exploring. This type of study is particularly needed as the psychological evaluation of patients suffering from chronic gastrointestinal disorders is not currently part of usual care in Australia and the results could be used to change the policy and practice and subsequently improve the standard medical care. As the majority of controlled studies

in this area suffer from methodological flaws, such as comparisons with inadequately matched controls (as discussed in Chapter 1), it is important to avoid this limitation and present the real differences in the psychological status of these three groups of patients. This may result, in future, in more efficient, evidence-based treatment protocols and allocation of resources.

One may anticipate that in a study with a contemporaneous sample of participants, patients with the largest physical morbidity should have the highest prevalence of anxiety and depression and the poorest levels of quality of life. Thus, IBD participants appear to be most vulnerable to psychological problems and, as previously stated, the levels of psychological problems in this group have been found to be substantial (Addolorato et al., 1997; Mittermaier et al., 2004). If, however, this is not the case, and one of the other groups (IBS or HCV) is more affected by psychological problems, this might mean that the disturbance in psychological wellbeing results from factors other than disease activity. In order to improve patients' psychosocial status, these factors should be explored and interventions designed to help sufferers. This study aimed to begin this process. It focused on observing and comparing the psychological co-morbidity in patients with IBD, IBS and HCV in relation to the activity of their disease. It also aimed at avoiding the common methodological flaw of choosing inadequate comparators. Thus, the following hypothesis is investigated in this study:

- Patients with IBD are most affected by psychological problems as compared to patients with IBS and HCV.

This study is also an introduction to the next studies. The psychological data on rates of anxiety, depression and quality of life in patients with IBD and IBS were used in the subsequent analysis of the relationship between the number of functional disorders and the severity of psychological symptoms (Chapter 4). The chapter's findings were also utilised

as a baseline data that were subsequently compared with the data collected after twelve months of observations in the cohort prospective management study (see Chapter 5). Additionally, the baseline findings became a part of the randomised controlled trial with IBD participants only and were used as a comparator for a prospective analysis within this investigation (see Chapter 6).

A summary of methods used in this study is presented in Figure 4 below (for detailed description of methods see Chapter 2).

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Study 1
A summary of methods

Aim:
To observe and compare the psychological co-morbidity in patients with IBD, IBS and HCV in relation to the activity of their disease

Hypotheses tested:
Patients with IBD are most affected by psychological problems as compared to patients with IBS and HCV (Hypothesis 1)

Estimated sample size:
The sample was derived from Study 3. See Methods for detail.

Design:
A cross-sectional survey was conducted with IBD, IBS and HCV patients recruited from the Royal Adelaide Hospital. Patients were given a battery of psychological and disease activity measures on one occasion.

Outcome measures:
- The prevalence of psychological problems in each group of patients at study enrolment;
- The level of quality of life in each group of patients at study enrolment;
- The activity of the disease in each group of patients at study enrolment.

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Figure 4: A summary of methods used in Study 1

3.2. Results

Overall, 139 patients participated in the study. Of these, 64 suffered from IBD (33 from UC and 31 from CD), 41 from HCV, and 34 from IBS. As regards treatments that may influence psychological well being; six IBS patients were on antidepressants. Ten HCV patients were receiving combination therapy with interferon & ribavirin and seven were taking antidepressants. In the IBD group, one CD patient and eight UC patients were on antidepressants while three CD patients and four UC were on oral prednisolone.

3.2.1. Descriptive statistics of the three studied disease groups

Sixty-one percent of participants were female (see Table 2). The proportion of female to male participants in the IBS group was significantly higher than in the IBD or the HCV group ($\chi^2(2)=6$, p=0.050) (see Figure 5 and Table 2). Participants did not significantly differ in their level of education ($\chi^2(6) = 5.48$, p=0.483) (see Table 2).

Table 2: Sex and education in HCV, IBD and IBS participants

Disease		HCV (n = 41)	IBD (n = 64)	IBS (n = 34)	Total (n = 139)
			N (%)		
Sex	Male	21 (51)	25 (39)	8 (23)	54 (39)
	Female	20 (49)*	39 (61)*	26 (77)*	85 (61)
Education	Primary	3 (7)	3 (5)	3 (9)	9 (7)
	Secondary	22 (54)	29 (45)	13 (38)	64 (46)
	Trade/TAFE	1 (2)	8 (12)	5 (15)	14 (10)
	Tertiary	11 (27)	18 (28)	12 (35)	41 (29)
	Not specified	4 (10)	6 (10)	1 (3)	11 (8)

* p≤0.050
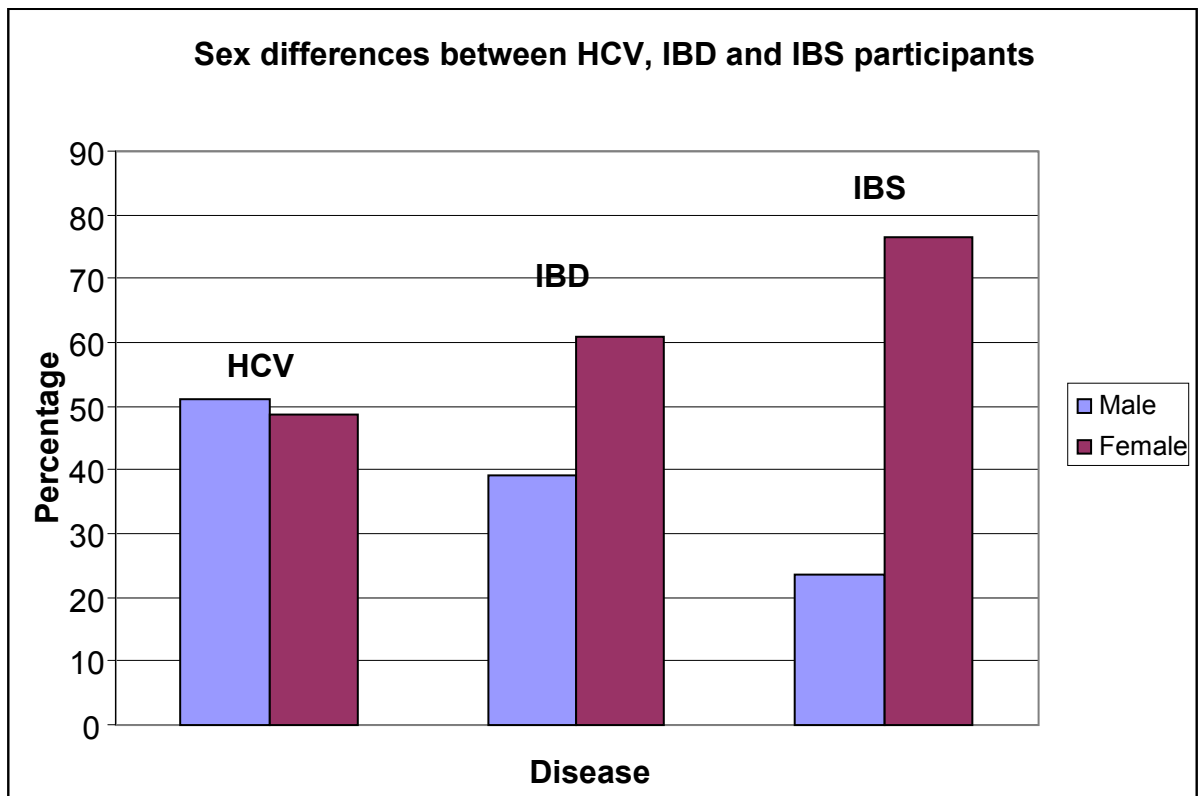
Figure 5: Sex differences between the HCV, the IBD and the IBS group

The HCV group was significantly younger than the IBS group and had significantly shorter period since the diagnosis than the IBD group (p≤0.05) (see Table 3), however, the number of years with symptoms was similar in all the three groups (p>0.05). Interestingly, the spread around means in the HCV group is different than in other groups, indicating greater homogeneity within this group.

Table 3: Age, years since diagnosis, years with symptoms in HCV, IBD and IBS

participants

	HCV Mean (SD)	IBD Mean (SD)	IBS Mean (SD)	F	p
Age	45.51 (10.88)*	51.06 (15.68)	54.11 (13.61)*	3.793	0.023
Years since diagnosis	7.92 (4.92)*	14.60 (10.60)*	10.35 (9.95)	6.808	0.001
Years with symptoms	16.09 (9.89)	16.01 (11.81)	16.33 (13.72)	0.008	0.992

Groups did not significantly differ in their disease activity (see Table 4).

Table 4: Disease activity in HCV, IBD and IBS

Disease	HCV (n = 41)	IBD (n = 64)	IBS (n = 34)	Total (n = 139)
	N (%)			
Active disease	23 (56)[1]	23 (36)	18 (53)	64 (46)
Not active disease	18 (44)	41 (64)	14 (41)	73 (52)
Not specified	0 (0)	0 (0)	2 (6)	2 (2)

[1] Active viral replication was used as a measure of disease activity in HCV

<u>Differences in psychological profiles and quality of life between HCV, IBD and IBS participants</u>

Groups did not significantly differ in anxiety or depression as measured by the HADS nor in either physical or Mental components of quality of life (p>0.05) (see Table 5). Neither did groups significantly differ on the following subscales of the SCL90: Interpersonal-Sensitivity subscale, Depression subscale, Hostility subscale, Psychoticism subscale and PSDI subscale (p>0.05).

The HCV group differed from the IBD group on six of 12 subscales. In particular, for the SCL90 Somatization, Obsessive-Compulsive, Anxiety, Paranoid Ideation, GSI and PST analysis, the HCV group had a higher score than the IBD group (p≤0.05). Moreover, the HCV group differed from the IBS group on one of 12 subscales. In particular, for the SCL90 Phobic Anxiety analysis, the HCV group scored higher on the SCL90 Phobic Anxiety than the IBS group (p=0.048). The HCV group had the highest mean scores on all these subscales of the SCL90 indicating higher psychological morbidity in this group compared to the IBS and IBD groups.

Table 5: One-way ANOVA for group differences on the HADS, the SF-12 and the

SCL90 in HCV, IBD and IBS participants

	HCV Mean (SD)	IBD Mean (SD)	IBS Mean (SD)	F	p
HADS Anxiety	6.97 (4.83)	6.57 (3.44)	7.97 (2.92)	1.498	0.227
HADS Depression	5.36 (4.96)	4.07 (2.86)	4.29 (3.70)	1.513	0.224
SF12 Mental	44.59 (13.41)	49.10 (10.76)	46.36 (10.09)	2.024	0.136
SF12 Physical	43.41 (11.66)	45.93 (10.85)	43.11 (11.30)	0.974	0.380
Somatisation	61.17 (12.90)*	55.35 (10.18)*	59.85 (8.23)	4.277	0.016
Obsessive-Compulsive	61.43 (11.59)*	56.48 (8.17)*	59.05 (9.77)	3.331	0.039
Interpersonal Sensitivity	60.43 (11.96)	55.43 (11.03)	57.52 (11.48)	2.397	0.095
Depression	62.26 (12.50)	58.04 (9.94)	59.99 (10.16)	1.909	0.152
Anxiety	57.63 (13.61)*	51.79 (9.74)*	56.82 (8.77)	4.462	0.013
Hostility	57.43 (11.98)	52.96 (9.86)	55.85 (11.00)	2.281	0.106
Phobic Anxiety	54.95 (11.60)*	51.54 (8.28)	49.79 (7.96)*	3.073	0.050
Paranoid Ideation	56.58 (11.99)*	50.73 (10.18)*	51.88 (11.86)	3.568	0.031
Psychoticism	58.24 (10.58)	54.46 (8.97)	56.23 (10.18)	1.878	0.157
GSI	62.00 (12.22)*	55.95 (9.66)*	59.94 (9.75)	4.450	0.013
PST	60.92 (11.34)*	55.93 (9.51)*	58.85 (9.33)	3.201	0.044
PSDI	57.97 (9.78)	54.29 (9.80)	56.61 (8.36)	1.997	0.140

* differences significant at the level ≤ 0.05

Prevalence of anxiety and depression

A total of 58 of 139 participants overall (42%) fulfilled the anxiety criterion for caseness (> 7) and 26 participants (19%) fulfilled the depression criterion for caseness (> 7) (see Table 6). There was no significant difference between the groups in the prevalence of anxiety (χ^2 (2)=0.948, p=0.623). However, there was a statistically significant difference in the prevalence of depression between two of the groups. The HCV group had significantly

higher prevalence of depression than the IBD group (χ^2 (1)=8.41, p=0.004). The difference in the prevalence of depression between the HCV and the IBS group was barely significant (χ^2 (1)=3.71, p=0.054).

Table 6: Percentage of anxious and depressed patients in three disease groups based on the HADS criteria for caseness (score > 7)

Disease	HCV (n = 41)	IBD (n = 64)	IBS (n = 34)	Total (n = 139)
	N (%)			
Anxiety	18 (44)	24 (37)	16 (47)	58 (42)
Depression	14 (34)*	7 (11)*	5 (15)	26 (19)

* χ^2 (1)=8.41, p=0.004

Hypothesis 1 testing summary

The first hypothesis (that patients with IBD are more affected by psychological problems than IBS and HCV patients) was first tested during the Chi-Square test comparisons of the prevalence of anxiety and depression in the HCV, IBD and IBS group and it was found to be false. The differences in the prevalence of anxiety were not statistically significant (p>0.05). However, a significant difference between the HCV and IBD group was found during comparisons of prevalence of depression. It is clear from the descriptive statistics that the HCV group had a higher mean HADS Depression score than the other two groups. However, a one-way ANOVA did not confirm that the groups significantly differed on the mean scores of either of the HADS subscales. Nevertheless, the descriptive statistics indicated the direction of this relationship. Further ANOVA comparisons of quality of life did not demonstrate any significant difference in either mental or physical quality of life among the groups. Of the SCL90 subscales comparisons, the Phobic Anxiety subscale showed a significant difference between the IBS and the HCV group, with the HCV group found to be more severely affected. Moreover, there was no statistically significant difference between the IBS and IBD group in any measures. Therefore, the first hypothesis

was found not to be true. The IBD participants were not more affected by psychological problems than two remaining groups. The group that had the most severe psychomorbidity was the HCV group. This difference was especially significant between the HCV and the IBD group. On 6 out of 12 of the SCL90 subscales, the patients with HCV had significantly higher mean scores which means that they were further from the normal population mean than the IBD group (p<0.05).

3.2.2. Demographic characteristics and mean scores for the HADS, the SF-12 and the SCL90 in IBD (CD and UC), IBS and HCV

Dependant variables showing a significant difference included the HADS Depression, the SF-12 Physical component, the SCL90 Anxiety subscale, the SCL90 Hostility subscale, the SCL90 Paranoid Ideation subscale, and the SCL90 PST subscale. However, only the SF-12 Physical component and the SCL90 PST variables explained the results. Regarding the HADS Depression, SCL90 Anxiety subscale, SCL90 Hostility subscale, and SCL90 Paranoid Ideation subscale, while the models as a whole predicted a significant amount of variance, none clearly account for the change. Because of this, data are presented for the SF-12 Physical component and SCL90 PST variables only. In this part of the analysis the data for CD and UC patients were analysed separately creating four groups: CD=31; UC=33; HCV=41; and IBS=34 participants. The detailed description of the analysis is presented in Chapter 2 (see section 2.11.1).

<u>The SF-12 Physical component</u>

In the third step of the analysis, when the interaction between disease and years since diagnosis was added, the increase in R^2 of 0.061 was statistically significant (p = 0.041) (Table 7).

Table 7: The SF-12 Physical component, disease type, sex, education, and disease activity interactions in the four disease groups (HCV, IBS, CD and UC)

Model (Step)	R^2	F(df)	p	R^2 change	F(df) change	p
1	0.139	1.829(10,113)	0.063	-	-	-
2	0.202	1.696(16,107)	0.058	0.063	1.409(6,107)	0.217
3	0.263	1.953(19,104)	0.017	0.061	2.852(3,104)	0.041*
4	0.322	2.181(22,101)	0.005	0.059	2.933(3,101)	0.037*
5	0.422	2.168(31, 92)	0.002	0.100	1.770(9, 92)	0.083

This result means that older participants tended to have poorer physical quality of life than younger people. Those with HCV had poorer physical quality of life than those with UC; and those participants who had had the disease for a longer time had better physical quality of life than those who had had it for a shorter time (Table 8 below).

Table 8: SF-12 Physical component and disease interactions with years since diagnosis in the four disease groups (HCV, IBS, CD and UC) (Model 3)

	Coefficient	Std. Err.	t	P>|t|	95% Conf. Interval	
Males vs. females	-2.770156	4.068881	-0.68	0.498	-10.8389	5.298589
Age	-.3506307	.1408346	-2.49	0.014*	-.6299111	-.0713503
Education:Secondary	4.072024	3.994581	1.02	0.310	-3.84938	11.99343
Education:TAFE	-.5183879	4.988016	-0.10	0.917	-10.40981	9.373036
Education:Tertiary	4.514155	4.10916	1.10	0.274	-3.634463	12.66277
Relapse vs. remission	-5.303345	2.101963	-2.52	0.013*	-9.471617	-1.135072
Years since diagnosis	.3616114	.1477084	2.45	0.016*	.0687	.6545228
CD vs. UC	-20.61881	9.83039	-2.10	0.038*	-40.11284	-1.124778
IBS vs. UC	.0351372	11.05389	0.00	0.997	-21.88514	21.95541
Males_HCV	.2955642	5.389978	0.05	0.956	-10.39296	10.98409
Males_IBD	9.050627	5.960262	1.52	0.132	-2.768796	20.87005
Males_IBS	2.50113	6.409736	0.39	0.697	-10.20962	15.21188
HCV vs. UC	-7.552776	11.14656	-0.68	0.500	-29.65683	14.55127
Age_HCV	.26653	.2122823	1.26	0.212	-.1544338	.6874939
Age_IBD	.4213335	.1991202	2.12	0.037*	.0264707	.8161964
Age_IBS	.0594838	.2121937	0.28	0.780	-.3613043	.4802719
Years_HCV	-.979311	.3851142	-2.54	0.012*	-1.743007	-.2156151
Years_IBD	-.4212984	.2565461	-1.64	0.104	-.9300389	.0874422
Years_IBS	-.4607991	.2676663	-1.72	0.088	-.9915915	.0699932

* p ≤0.05

R-Square Diff. Model 3 - Model 2 = 0.061, F(3,104) = 2.852, p = 0.041

Moreover, participants with CD tended to have poorer physical quality of life than UC participants, but their physical quality of life improved with age. Finally, HCV participants with longer disease had poorer physical quality of life. In the fourth step, when the interaction between disease type and disease activity was added, the increase in R^2 was also significant (F = 2.933, p = 0.037). This result confirms that older participants tended to have poorer physical quality of life than those who were younger. Those participants who had the disease for a longer time had better physical quality of life than those who had it for a shorter time; and HCV participants with longer enduring disease had poorer physical quality of life than than those with disease who had it for a shorter time (Table 9).

Table 9: SF-12 Physical component, disease type and disease activity interactions in the four disease groups (HCV, IBS, CD and UC) (Model 4)

	Coefficient	Std. Err.	t	P>| t |	95% Conf. Interval	
HCV vs. UC	-9.364626	11.0691	-0.85	0.400	-31.32274	
CD vs. UC	-18.85304	10.13827	-1.86	0.066	-38.96464	1.258567
IBS vs. UC	-1.428544	10.88158	-0.13	0.896	-23.01467	20.15758
Males vs. females	-2.858897	3.966543	-0.72	0.473	-10.72745	5.009658
Age	-.3564671	.1372059	-2.60	0.011*	-.6286468	-.0842874
Education:Secondary	2.417134	3.944764	0.61	0.541	-5.408216	10.24248
Education:TAFE	-1.414912	5.005464	-0.28	0.778	-11.3444	8.514582
Education:Tertiary	3.173192	4.105383	0.77	0.441	-4.970784	11.31717
Relapse vs. remission	-6.211684	3.932526	-1.58	0.117	-14.01276	1.589389
Years since diagnosis	.3660421	.1437834	2.55	0.012*	.0808145	.6512697
Males_HCV	-.6670915	5.27148	-0.13	0.900	-11.12429	9.790107
Males_IBD	10.19	5.849045	1.74	0.085	-1.412934	21.79293
Males_IBS	3.369518	6.273816	0.54	0.592	-9.076044	15.81508
Age_HCV	.1725214	.2094176	0.82	0.412	-.2429067	.5879495
Age_IBD	.3695736	.1993408	1.85	0.067	-.0258649	.7650121
Age_IBS	.1108649	.209519	0.53	0.598	-.3047645	.5264943
Years_HCV	-.7586262	.3829581	-1.98	0.050*	-1.518312	.0010596
Years_IBD	-.3580745	.2536741	-1.41	0.161	-.8612956	.1451467
Years_IBS	-.433143	.2609648	-1.66	0.100	-.9508269	.084541
Activity_HCV	9.366357	5.396839	1.74	0.086	-1.33952	20.07223
Activity_IBD	-7.408751	7.250477	-1.02	0.309	-21.79175	6.974246
Activity_IBS	-3.77987	5.470085	-0.69	0.491	-14.63105	7.071307

* p ≤0.05

R-Square Diff. Model 4 - Model 3 = 0.059, F(3,101) = 2.933, p = 0.037

The SCL90 PST (Positive Symptom Total) subscale

In the third step of the SCL90 PST subscale analysis, the interaction between disease and years since diagnosis was added (Table 10).

Table 10: The SCL90 PST subscale, disease type, sex, education, and disease activity interactions in the four disease groups (HCV, IBS, CD and UC)

Model (Step)	R^2	F(df)	p	R^2change	F(df) change	p
1	0.120	1.543 (10,113)	0.133	-	-	-
2	0.149	1.167 (16,107)	0.306	0.028	0.595(6,107)	0.734
3	0.217	1.513 (19,104)	0.096	0.068	3.007(3,104)	0.034*
4	0.234	1.401(22,101)	0.132	0.017	0.762(3,101)	0.518
5	0.289	1.208(31, 92)	0.242	0.055	0.798(9, 92)	0.619

The increase in R^2 of 0.068 resulted in a significant change (p = 0.034). In particular, this means that HCV participants with longer disease duration had a higher PST score than those with shorter disease duration, which illustrates their higher morbidity with respect to physical quality of life (see Table 11).

Table 11: The SCL90 PST subscale and disease interactions with years since diagnosis in the four disease groups (HCV, IBS, CD and UC) (Model 3)

	Coefficient	Std. Err.	t	P>| t		95% Conf. Interval	
Males vs. females	5.647532	3.813175	1.48	0.142	-1.914138	13.2092
Age	-.1477508	.131984	-1.12	0.266	-.40948	.1139784
Education:Secondary	-3.855633	3.743544	-1.03	0.305	-11.27922	3.567956
Education:TAFE	-.4565887	4.674548	-0.10	0.922	-9.726393	8.813215
Education:Tertiary	-5.321069	3.850922	-1.38	0.170	-12.95759	2.315455
Relapse vs. remission	.3777063	1.969867	0.19	0.848	-3.528614	4.284026
Years since diagnosis	-.08985	.1384258	-0.65	0.518	-.3643536	.1846536
HCV vs. UC	-6.831692	10.44606	-0.65	0.515	-27.54663	13.88324
CD vs. UC	1.606717	9.212606	0.17	0.862	-16.66223	19.87566
IBS vs. UC	-8.428232	10.35921	-0.81	0.418	-28.97094	12.11448
Males_HCV	-2.781806	5.051249	-0.55	0.583	-12.79862	7.23501
Males_IBD	-4.766861	5.585693	-0.85	0.395	-15.8435	6.309779
Males_IBS	1.581374	6.006921	0.26	0.793	-10.33058	13.49332
Age_HCV	.1020861	.1989416	0.51	0.609	-.2924226	.4965948
Age_IBD	.0855391	.1866066	0.46	0.648	-.2845089	.455587
Age_IBS	.1250685	.1988585	0.63	0.531	-.2692754	.5194124
Years_HCV	.7839428	.360912	2.17	0.032*	.0682408	1.499645
Years_IBD	-.2484949	.2404236	-1.03	0.304	-.725264	.2282742
Years_IBS	.3449052	.250845	1.37	0.172	-.1525299	.8423402

* p ≤0.05, R-Square Diff. Model 3 - Model 2 = 0.068, F(3,104) = 3.007, p = 0.034

3.2.3. Mean comparisons for the HADS, the SF-12 and the SCL90 between the studied groups and other samples

The comparisons were conducted between IBD group and IBD samples researched by other investigators, other chronic disease groups and the normal population. Normal population comparisons of the SF-12 mean scores were provided also for the HCV and the IBS group.

<u>The HADS mean comparisons between the IBD group and other IBD samples</u>

For comparisons of means of the studied IBD sample and a similar sample of British patients with IBD, there was no statistical difference between the groups in mean anxiety (the mean of 6.57 vs. 7.1, p=0.424) (Table 12). However, groups differed in mean depression (p=0.046). The studied IBD group was less depressed than the British sample (4.07 vs. 5.3).

Table 12: Mean comparisons in the HADS Anxiety and Depression subscales between the studied IBD group (n=64) and a similar sample of British patients with IBD (n=116) (Guthrie et al., 2002)

HADS scales	t	df	p
Anxiety (CD/UC)	-0.08	178	0.424
Depression (CD/UC)	-2.17	178	0.046*

Compared to a similar Swedish sample (Table 13), there was no significant difference between the groups in both anxiety (the mean of 6.57 vs. 5.6) and depression (the mean of 4.07 vs. 3.5) subscales (p>0.05). Moreover, there were no statistically significant differences when the anxiety means for the CD group (the mean of 6.58 vs. 6.3) and the UC group (the mean of 6.57 vs. 5.2) were compared separately with the Swedish sample

(p>0.05). No difference emerged in comparisons of depression mean scores in the CD group (the mean of 4.12 vs. 4.2) and the UC group (the mean of 4.03 vs. 3.3).

Table 13: Mean comparisons in the HADS Anxiety and Depression subscales between the studied IBD group (n=64: CD=31, UC=33) and the similar sample of Swedish patients with IBD (n=492: CD=161, UC=331) (Nordin et al., 2002)

NOTE: This table is included on page 101 in the print copy of the thesis held in the University of Adelaide Library.

The HADS mean comparisons between the IBD group and other samples of the chronically ill

Regarding comparisons with a German sample of coronary heart disease patients (Table 14), no statistically significant differences between the groups in mean anxiety (the mean of 6.57 vs. 6.14, p=0.415) were identified. However, the groups significantly differed in mean depression (p=0.009). The studied IBD group was less depressed than the coronary heart disease patients (4.07 vs. 5.41).

Table 14: Mean comparisons in the HADS Anxiety and Depression subscales between the IBD group (n=64) and the sample of German coronary heart disease patients (n=1320) (Barth & Martin, 2005)

NOTE: This table is included on page 101 in the print copy of the thesis held in the University of Adelaide Library.

For comparisons between the studied IBD group and a British sample of breast cancer sufferers (Table 15), no significant difference between the groups in means for both the

anxiety and depression subscales (6.57 vs. 7.43, p=0.161 and 4.07 vs. 3.25, p=0.074, respectively) was observed.

Table 15: Mean comparisons in the HADS Anxiety and Depression subscales between the IBD group (n=64) and the sample of British breast cancer patients (n=110) (Rodgers et al., 2005)

NOTE: This table is included on page 102 in the print copy of the thesis held in the University of Adelaide Library.

The third comparison, between the IBD group and a British sample of chronic obstructive pulmonary disease patients showed no difference in mean anxiety (the mean of 6.57 vs. 7.1, p=0.419), but a statistically significant difference in the mean for the depression subscale (p=0.001) (Table 16). The studied IBD group was less depressed than patients with chronic obstructive pulmonary disease (4.07 vs. 5.8).

Table 16: Mean comparisons in the HADS Anxiety and Depression subscales between the IBD group (n=64) and the sample of British chronic obstructive pulmonary disease patients (n=95) (Withers et al., 1999)

NOTE: This table is included on page 102 in the print copy of the thesis held in the University of Adelaide Library.

<u>The SF-12 and the SF-36 (Physical and Mental subscales) mean comparisons between the IBD group and other IBD samples</u>

Due to the lack of studies with the SF-12 scale in other IBD samples, the author compared the means with the appropriate scales of the SF-36. For comparisons in the SF-12 Physical and Mental components between the IBD sample and a British IBD sample (Table 17), a significant difference in the Physical component between the groups (p=0.032) was noted.

The studied IBD group had better physical quality of life than their British counterparts (45.93 vs. 41.3). There was, however, no difference between the groups in the Mental component (the mean of 49.10 vs. 46.4, p=0.159).

Table 17: Mean comparisons in the SF-12 Physical and Mental components and the SF-36 (Physical and Mental subscales) between the IBD group (n=64) and British patients with IBD (n=111) (McColl et al., 2004)

SF-12 components	t	df	p
Physical component (CD/UC)	2.16	173	0.032*
Mental component (CD/UC)	1.41	173	0.159

For comparison with a Swedish sample of patients with IBD (Table 18), a statistically significant difference in the Physical component between the studied UC participants (p=0.039) and Swedish UC sufferers was observed. The studied UC patients had poorer physical quality of life than their Swedish counterparts (46.48 vs. 50.00). However, the CD group did not differ in the Physical component (45.34 vs. 46.7, p=0.527), nor did it differ in the Mental component (the mean of 47.35 vs. 43, p=0.070) from the Swedish patients. There was also no difference in the Mental component between the Swedish and the studied UC participants (50.75 vs. 46.7, p=0.058).

Table 18: Mean comparisons in the SF-12 Physical and Mental components and the SF-36 (Physical and Mental subscales) between the IBD group (n=64) and Swedish patients with IBD (n=492) (Nordin et al., 2002)

NOTE: This table is included on page 103 in the print copy of the thesis held in the University of Adelaide Library.

The SF-12 mean comparisons between the IBD group and other South Australian samples of the chronically ill

For comparisons of SF-12 Physical and Mental components between the IBD sample and other South Australian samples of the chronically ill, a statistically significant difference between the studied IBD group and South Australian diabetic patients in the Physical component (the mean of 45.93 vs. 40.5) and Mental component (the mean of 49.10 vs. 52.4) was found. The studied IBD group had better physical quality of life (p=0.002), but poorer mental quality of life than diabetic patients (p=0.03) (Table 19).

Table 19: Mean comparisons in the SF-12 Physical and Mental components between the IBD group (n=64) and South Australian diabetic patients (n=157) (Avery et al., 2004)

NOTE: This table is included on page 104 in the print copy of the thesis held in the University of Adelaide Library.

For comparison with South Australian patients who have asthma, no significant difference in either Physical or Mental component was noted (the mean of 45.93 vs. 47.2, p=0.391 and the mean of 49.10 vs. 51.1, p=0.134, respectively) (Table 20).

Table 20: Mean comparisons in the SF-12 Physical and Mental components between the IBD group (n=64) and South Australian asthmatic patients (n=324) (Avery et al., 2004)

NOTE: This table is included on page 104 in the print copy of the thesis held in the University of Adelaide Library.

However, a statistically significant difference in both components existed between the IBD group and South Australian patients with arthritis (Table 21). The IBD group had better

physical quality of life (the mean of 45.93 vs. 40.9, p=0.001) and poorer mental quality of life (the mean of 49.10 vs. 52.7, p=0.004) than patients with arthritis.

Table 21: Mean comparisons in the SF-12 Physical and Mental components between the IBD group (n=64) and South Australian arthritic patients (n=522) (Avery et al., 2004)

NOTE: This table is included on page 105 in the print copy of the thesis held in the University of Adelaide Library.

<u>The SF-12 mean comparisons between the IBD group, the HCV group and the IBS group and the normal population</u>

As the rate of psychological problems in the three groups was not very high, the author decided to conduct comparisons with the normal population in terms of quality of life in order to observe whether and how much the groups differ from the healthy population.

For comparisons of SF-12 Physical and Mental components between the IBD group, the HCV group, and the IBS group and the normal South Australian population, significant differences in both components of quality of life were detected (Table 22). The IBD group, HCV group and IBS group had poorer physical quality of life (means of 45.93, 43.41, and 43.11, respectively vs. 48.73) and poorer mental quality of life (means of 49.10, 44.59, and 46.36, respectively vs. 52.3) than the normal South Australian population. There was a statistically significant difference in the Physical component means between the IBD group, HCV group, IBS group and normal population (p=0.032, p=0.003, p=0.004, respectively). There was also a significant difference in the mental quality of life between the IBD group and the normal population (p=0.009), and a highly statistically significant difference between the HCV and IBS group and the normal population (p=0.000 and p=0.000, respectively).

Table 22: Mean comparisons in the SF-12 Physical and Mental component

between the IBD (n=64), the IBS (n=34) and the HCV (n=41) groups and the

normal South Australian population (n=971) (Avery et al., 2004)

NOTE: This table is included on page 106 in the print copy of the thesis held in the University of Adelaide Library.

The SCL90 GSI (General Severity Index) subscale mean comparisons between the

IBD group and the American sample of IBD sufferers

Due to a lack of data from studies using the SCL90 in IBD samples, the GSI subscale mean only was compared. For comparisons in the SCL90 GSI subscale between the IBD sample and an American sample of IBD sufferers (Table 23), no significant difference between the groups in the GSI subscale (means of 55.95 and 55.09, respectively, p=0.554) was observed. Comparisons with the UC subgroup (the mean of 55.21 vs. 53.71) and the CD subgroup (the mean of 56.80 vs. 55.69) were also not statistically significant (p=0.455 and p=0.599, respectively).

Table 23: Mean comparisons in the SCL90 GSI subscale between the IBD group

(n=64) and an American sample of IBD sufferers (n=997) (Drossman et al., 1991)

SCL90 GSI subscale	t	df	p
GSI (CD/UC)	0.59	1059	0.554
GSI (UC)	-0.74	352	0.455
GSI (CD)	-0.52	699	0.599

The SCL90 main subscales and the GSI subscale mean comparisons between the IBD group and other samples of the chronically ill

A number of significant differences were observed for comparisons of the SCL90 main subscales and the GSI subscale between the IBD sample and other groups of chronically ill (Table 24). There was a highly statistically significant difference between the IBD group and an Australian sample of patients with chronic pain (all p=0.000). The IBD group scored lower on the Somatization subscale (the mean of 55.35 vs. 71.8), Obsessive-Compulsive subscale (the mean of 56.48 vs. 67.9), Interpersonal Sensitivity subscale (the mean of 55.43 vs. 67.1), Depression subscale (the mean of 58.04 vs.69.3), Anxiety subscale (the mean of 51.79 vs. 69.1), Hostility subscale (the mean of 52.96 vs. 65.6), Phobic Anxiety subscale (the mean of 51.54 vs. 65), Paranoid Ideation subscale (the mean of 50.73 vs. 64.3), Psychoticism subscale (the mean of 54.46 vs. 66.3), and GSI subscale (55.95 vs. 71.4). This finding means that the studied group of patients with IBD had lower psychological morbidity than this comparator group with scores closer to normal population means.

Table 24: Mean comparisons in the SCL90 main subscales and the GSI subscale between the IBD group (n=64) and the Australian sample of patients with chronic pain (n=50) (McGuire & Shores, 2001)

SCL90 subscales	t	df	p
Somatization	-9.36	112	0.000**
Obsessive-Compulsive	-6.29	112	0.000**
Interpersonal Sensitivity	-5.49	112	0.000**
Depression	-5.82	112	0.000**
Anxiety	-8.84	112	0.000**
Hostility	-6.36	112	0.000**
Phobic Anxiety	-7.30	112	0.000**
Paranoid Ideation	-6.32	112	0.000**
Psychoticism	-6.29	112	0.000**
GSI	-8.12	112	0.000**

In comparisons with patients having whiplash injuries (Table 25), a highly statistically significant difference between the groups in the mean Somatization (the mean of 55.35 vs. 68.6, p=0.000) was observed. The IBD group scored closer to the population mean than the whiplash patients. There was also a statistically significant difference between the groups in the Anxiety subscale (the mean of 51.79 vs. 56.6, p=0.006), Hostility subscale (the mean of 52.96 vs. 57.6, p=0.005), Paranoid Ideation subscale (the mean of 50.73 vs. 54.6, p=0.023), Psychoticism subscale (the mean of 54.46 vs. 59.2, p=0.006) and GSI subscale (the mean of 55.95 vs. 61.3, p=0.001) showing that the studied IBD group had a lower psychological morbidity than the whiplash patients. There was no significant difference between the groups in the Obsessive-Compulsive subscale (the mean of 56.48 vs. 59.8, p=0.083), Interpersonal Sensitivity subscale (the mean of 55.43 vs. 57.6, p=0.235), Depression subscale (the mean of 58.04 vs. 59.7, p=0.321), and Phobic Anxiety subscale (the mean of 51.54 vs. 53.3, p=0.223).

Table 25: Mean comparisons in the SCL90 main subscales and the GSI subscale between the IBD group (n=64) and a Canadian sample of patients with whiplash injuries (n=67) (Peebles et al., 2001)

SCL90 subscales	t	df	p
Somatization	-8.89	220	0.000**
Obsessive-Compulsive	-1.74	220	0.083
Interpersonal Sensitivity	-1.19	220	0.235
Depression	-0.99	220	0.321
Anxiety	-2.75	220	0.006*
Hostility	-2.82	220	0.005*
Phobic Anxiety	-1.22	220	0.223
Paranoid Ideation	-2.29	220	0.023*
Psychoticism	-2.79	220	0.006*
GSI	-3.39	220	0.001*

The third comparison conducted was between the IBD group and muscoloskeletal pain patients (Table 26). There was a highly statistically significant difference between the

groups in mean Somatization (the mean of 55.35 vs. 67, p=0.000). There was also a significant difference between the groups in the Anxiety subscale (the mean of 51.79 vs. 56.3, p=0.015), Psychoticism subscale (the mean of 54.46 vs. 58.6, p=0.007), and GSI subscale (the mean of 55.95 vs. 60.8, p=0.001). There was no differences between the groups in the Obsessive-Compulsive subscale (the mean of 56.48 vs. 56.8, p=0.837), Interpersonal Sensitivity subscale (the mean of 55.43 vs. 57.6, p=0.181), Depression subscale (the mean of 58.04 vs. 57.4, p=0.671), Hostility subscale (the mean of 52.96 vs. 55.1, p=0.177), Phobic Anxiety subscale (the mean of 51.54 vs. 53, p=0.316), and Paranoid Ideation subscale (the mean of 50.73 vs. 53.9, p=0.070).

Table 26: Mean comparisons in the SCL90 main subscales and the GSI subscale between the IBD group (n=64) and the Canadian sample of patients with musculoskeletal pain (n=91) (Peebles et al., 2001)

SCL90 subscales	t	df	p
Somatization	-8.59	220	0.000**
Obsessive-Compulsive	-0.20	220	0.837
Interpersonal Sensitivity	-1.34	220	0.181
Depression	0.42	220	0.671
Anxiety	-2.45	220	0.015*
Hostility	-1.35	220	0.177
Phobic Anxiety	-1.00	220	0.316
Paranoid Ideation	-1.82	220	0.070
Psychoticism	-2.72	220	0.007*
GSI	-3.26	220	0.001*

3.2.4. Comparisons of demographic characteristics, the HADS, the SF-12 and the SCL90 mean scores between UC and CD patients

For the CD and UC comparisons, disease activity, sex and education variables were not normally distributed, whilst the distribution of other variables was normal.

Mean differences in sex, education, age, years since diagnosis, and years with symptoms

The distribution of sex was almost identical in both groups ((χ^2 (1) = 0.003, p=0.955 and

Fisher's Exact Test p=1.00) (Table 27).

Table 27: Distribution of the sex variable in the CD and the UC group

		CD	UC	Total
Sex	Male	12	13	25
	Female	19	20	39
Total		31	33	64

Groups did not differ on the education variable, either (χ^2 (3) = 0.818, p=0.845). Similarly,

the independent sample t-test comparisons showed that the CD and the UC group did not

significantly differ in terms of age, years since diagnosis nor in years with symptoms

(p>0.05) (Table 28).

Table 28: The independent sample t-test comparisons of age, years since diagnosis

and years with symptoms in the CD and the UC group

	CD Mean (SD)	UC Mean (SD)	t	p
Age	48.10 (16.22)	53.85 (14.87)	-1.48	0.144
Years since diagnosis	15.73 (11.05)	13.55 (10.22)	0.80	0.422
Years with symptoms	18.15 (12.17)	14.08 (11.32)	1.328	0.189

Mean differences on the HADS, the SF-12, the SCL90 subscales and the activity of the

disease between the CD and the UC group

CD participants did not significantly differ from the UC participants on any of the scales

(all p>0.05) (Table 29).

Table 29: Mean comparisons of the HADS, the SF-12 and the SCL90 subscales

between CD and UC participants

	CD Mean (SD)	UC Mean (SD)	t	p
HADS Anxiety	6.58 (3.53)	6.57(3.40)	0.01	0.995
HADS Depression	4.12 (2.81)	4.03 (2.95)	0.14	0.891
SF-12 Mental	47.34 (12.13)	50.74 (9.17)	-1.27	0.208
SF-12 Physical	45.34 (11.70)	46.48 (10.15)	-0.42	0.678
Somatization	55.29 (11.17)	55.424 (9.34)	-0.05	0.958
Obsessive- Compulsive	57.16 (7.99)	57.16 (8.41)	0.64	0.525
Interpersonal Sensitivity	55.35 (11.34)	55.51 (10.90)	-0.06	0.954
Depression	58.87 (10.38)	57.27 (9.61)	0.64	0.524
Anxiety	52 (9.81)	51.60 (9.74)	0.16	0.873
Hostility	54 (11.40)	52 (8.23)	0.81	0.422
Phobic Anxiety	51.58 (7.66)	51.51 (8.95)	0.03	0.975
Paranoid Ideation	50.90 (10.65)	50.57 (9.89)	0.13	0.899
Psychoticism	53.77 (8.93)	55.12 (9.10)	-0.60	0.552
GSI	56.16 (10.09)	55.75 (9.39)	0.17	0.868
PST	56.06 (9.71)	55.81 (9.46)	0.10	0.918
PSDI	55.74 (10.24)	52.93 (9.33)	1.15	0.256

There was a marked difference in disease activity between the UC and CD participants (see Table 30). Fifty-eight percent of UC patients had active disease compared to only 13% in the CD group. This difference was statistically significant (χ^2 (1) = 11.71, p=0.0006). In order to obtain the exact probability and as the expected values were below 10, Fisher's Exact Test was conducted and it confirmed that the two groups significantly differed in the activity of symptoms (two-sided probability = 0.007).

Table 30: Disease activity in UC and CD

Disease	UC (n = 33)	CD (n = 31)
	N (%)	
Active disease	19 (58)*	4 (13)
Not active disease	14 (42)	27 (87)*

* p≤0.050

The relative risk of activity for CD and UC participants is presented in Table 31.

Table 31: Estimates of the relative risk for the disease activity in CD and UC participants

	Value	95% Confidence Limits	
CD	0.320	0.142	0.722
UC	2.262	1.414	3.620

3.2.5. Semi-quantitative content analysis of patients' concerns regarding their condition

A semi-quantitative content analysis was conducted to compare the differences in IBD, IBS and HCV patients' concerns regarding their disorders. The question about patients' concerns regarding their disease was asked as part of the general health questionnaire (Appendix 5-7). Patients' responses were divided into mutually exclusive categories where possible, and subsequently coded. Participants' responses were then summarized. As can be seen, the total number of responses does not equal the number of participants, as some participants gave more than one response.

The majority of patients with HCV (21 responses – 47%) reported general malaise (e.g. poor quality of life) as their largest disease-related concern, followed by fear of dying as a result of liver cancer (10 responses – 22%) (Table 32).

Table 32: Disease-related concerns in participants with HCV

Concerns HCV	No of people (%)
General malaise (includes: liver damage, lack of energy, malnutrition, poor quality of life, dependence on others and inability to work)	21 (47)
Dying (includes: shortened life span and cancer)	10 (22)
Infecting others	5 (11)
Treatment (includes: side effects and lack of good treatment)	5 (11)
Other (includes: uncertainty whether the virus returns and public ignorance)	4 (9)
Total	45 (100)

Similarly, the majority of participants with IBD (28 responses – 31%) reported possible complications (e.g. cancer) as their major concern (see Table 33). This was followed by frequent visits to toilets (24 responses – 27%) and general malaise (21 responses 23%).

Table 33: Disease-related concerns in participants with IBD

Concerns IBD	No of people (%)
Complications (includes: cancer, colon bag, surgeries, dying, bowel obstruction, infertility)	28 (31)
Frequent visits to toilets (includes: no control over bowel symptoms, not finding toilet on time, making mess of yourself)	24 (27)
General malaise (includes: low quality of life, inability to plan, losing weight, diet)	21 (23)
Medication side effects (includes: long term effects, impact on immune system, weight gain)	8 (9)
Dependence (includes: inability to work, study, be a provider, care for children)	5 (6)
Other (includes: embarrassment, genetic risk to kids, no cure)	4 (4)
Total	90 (100)

Participants with IBS reported bowel problems (19 responses – 49%) and unpredictability of the disease (10 responses – 26%) as their major concerns (see Table 34).

Table 34: Disease-related concerns in participants with IBS

Concerns IBS	No of people (%)
Bowel problems (includes pain, discomfort, cramps, constipation, diarrhoea, bloating, incontinence, passing winds, flatulence)	19 (49)
Unpredictability (includes: lack of control over symptoms, cancelling engagements, inability to travel, social life disturbance)	10 (26)
General malaise (includes: inability to have a normal life, weariness, sleep problems, diet)	7 (18)
Other (includes: embarrassment, bad odour, worry it is something more)	3 (7)
Total	39 (100)

3.2.6. Summary of the most significant results

IBD, IBS and HCV groups did not significantly differ in anxiety and depression when measured by the HADS nor in either component of quality of life ($p>0.05$). The HCV group, however, differed from the IBD group on six of 12 subscales of the SCL90 and differed from the IBS group on one of 12 subscales. The HCV group had the highest mean scores on each of these subscales indicating higher psychological morbidity compared to the IBS and IBD groups. This disproved the hypothesis that participants with IBD are most affected by psychological problems. This result gains additional support from the fact that the HCV group had significantly higher prevalence of depression than the IBD group ($p=0.004$).

A total of 58 participants overall (42%) fulfilled the anxiety criterion for caseness and 26 participants (19%) fulfilled the depression criterion for caseness, which makes anxiety the more significant problem in this sample. All three groups had significantly lower quality of life than the normal population ($p<0.05$). However, in comparison with the contemporaneous sample of IBS and HCV patients, as well as with IBD samples reported

by other investigators and with other disease groups, the studied IBD group seemed to have generally good psychological wellbeing and relatively high quality of life.

3.3. Discussion

There is little research comparing psychosocial co-morbidity in a contemporaneous sample of patients with inflammatory bowel disease, irritable bowel syndrome and chronic hepatitis C. Interestingly, while previous investigations reported a high prevalence of psychological problems in IBS (Cole, Rothman, Cabral, Zhang, & Farraye, 2006; Ladep, Obindo, Audu, Okeke, & Malu, 2006) and only a moderate level of these problems in HCV (Golden, Conroy, & O'Dwyer A, 2006; Kraus, Schafer, Csef, Scheurlen, & Faller, 2000), this study indicates that HCV and IBD patients significantly differ in their prevalence of depression, with patients with HCV being more depressed.

Notably, the prevalence of depression in the three groups was only moderate rather than high, with 34% of HCV, 15% of IBS and 11% of IBD patients being depressed. In fact, patients were more anxious than depressed. Both, HCV and IBS patients had a prevalence of anxiety of about 45% and the IBD group stood at 37%. This relatively low level of depression is surprising in light of the fact that participants were recruited at a tertiary clinic that tends to attract those with more severe disease. However, compared to the general South Australian population, all three groups had significantly poorer physical and mental quality of life. Moreover, the differences in the severity of psychological symptoms measured by SCL-90, confirmed that the HCV patients' scores were significantly further from the general population mean than either the IBD or IBS patients' scores.

Groups did not statistically differ on the screening measure for anxiety and depression (HADS) or in overall quality of life (SF-12). However, they did differ on 7 out of 12

SCL90 subscales. In particular, patients with HCV were considerably more affected by psychological problems than patients with IBD on 6 subscales (Somatisation, Obsessive-Compulsive, Anxiety, Paranoid Ideation, GSI and PST) and also more affected than patients with IBS on the Phobic Anxiety subscale ($p \leq 0.05$). Multiple regression showed that demographic characteristics such as age, education, and disease activity did not explain this difference. However, time since diagnosis might have explained this result on the SCL90 PST (Positive Symptom Total) subscale, as HCV participants with longer disease duration had higher PST score than those with shorter disease duration. Moreover, the HCV group seemed more homogenous than the remaining groups as indicated by the narrower spread around the mean in the time since diagnosis variable. The fact that patients with IBD were the group least affected by psychological problems compared to IBS and HCV participants indicated that general physical morbidity was not directly associated with psychological morbidity in these patients.

These findings suggest that patients with HCV experience more psychological problems than IBS and IBD participants. However, even in patients with HCV, the overall prevalence of depression was comparable to the reported average (30%) for other chronic diseases (Cavanaugh et al., 1983). Furthermore, in IBS and IBD it was significantly lower than usually reported in other chronic conditions and lower than reported in other independent studies on HCV, IBD and IBS (Andrews et al., 1987; Cole et al., 2006; Kraus et al., 2000; Mittermaier et al., 2004). The prevalence of anxiety in all three groups (42%), on the other hand, was elevated compared to a usually reported 20% prevalence in chronic diseases (Rodin et al., 1991). In comparison with other studies on prevalence of anxiety in HCV, IBD and IBS, the prevalence found in this study seems elevated with respect to HCV and IBD participants (Kraus et al., 2000; Simren et al., 2002). However, it is consistent with existing data for IBS (Creed et al., 2005).

The relatively low level of depression (19%) in this setting may be a sign that depression is now better known, understood and more easily detected in this particular hospital or in South Australia. This assumption may, in part, be supported by the results of the interview study (Chapter 9) in which South Australian gastroenterologists (including some of those responsible for care of patients in this study) revealed their interest in their patients' psyches. It may also result from recent Australian media campaigns aiming to target depression and a subsequent general recognition of the problem of depression in Australian society generally. In fact, according to the findings of a recent Australian population survey, 67% of people compared to only 39% in 1995 are now able to recognise the signs of depression (Jorm, Christensen, & Griffiths, 2006).

The low depression level in this sample might also be evidence of an adequate level of care provided by the hospital, whereby effective management of somatic disease has led to the minimalisation of depressive symptoms. However, this does not appear to be likely as a substantial number of patients (46%) had active disease at the time of this investigation. Nevertheless, if this was the case, other studies comparing standard care in terms of practitioners' interests in mental health in gastroenterological outpatient clinics in other Australian and international hospitals would be useful. Other reasons behind these low rates may include potential for under reporting, social desiribility bias, cultural differences between this study participants and participants from overseas studies as well as the low response to the study. The latter may implicate that patients with more severe disease and thus possibly greater depression might not have participated in the study. For these reasons, the results should be interpreted with caution.

By contrast, the high level of anxiety among participants warrants further attention. These patients reported anxiety levels similar to those encountered only in patients with

arrhythmia and respiratory disease, in which anxiety is proposed to be causally related to the somatic symptoms of the condition (Derogatis & Wise, 1989). The fact that 56% of IBS participants and 36% of IBD participants had active disease during the study may contribute to this finding, as frequent visits to toilets and, as a consequence, a disruption to normal functioning, may lead to anxiety. In fact, the content analysis of participants' concerns revealed that both these groups reported lack of control over their symptoms as a major issue. Interestingly, however, participants with IBD were mostly worried about possible complications such as cancer or needing a stoma, whereas participants with IBS were more concerned about current symptoms (e.g. pain, discomfort, bloating). Worrying about the future is a basis for most anxiety problems (Stein, 2002), as people cannot predict and control future events. The fact that patients with IBD reported possible complications as their most significant concern may explain the high level of anxiety in this group.

The reason for the high rates of anxiety in the HCV group is even less clear and may be related to the following factors: disease stigma, frequent coexistent drug and alcohol addiction, and co-occurrence of HCV with other diseases such as AIDS (Golden, Conroy, O'Dwyer et al., 2006). Interestingly, content analysis of patients' concerns revealed that these patients' greatest concerns included poor current quality of life and future fear of dying from cancer. Similarly to the IBD group, anticipation of negative future events may contribute to high levels of anxiety in patients with HCV. Moreover, hepatitis C is the only infectious disease among the three studied groups and this may influence the higher prevalence of psychological problems, as some patients may feel directly responsible for catching the virus or fear infecting others (as indicated by the content analysis results). Studies exploring the problem of guilt in patients with HCV may shed some insight on this premise.

Intriguingly, the psychological well-being of HCV patients is also known to be dependent on diagnosis knowledge, as patients' scores on psychological measures appear to vary depending on whether patients are aware or unaware (many patients may spend years with occult infection) of their HCV positivity (Rodger et al., 1999). Another factor contributing to this finding may be the psychological side effects of treatment, with Interferon–Ribavirin in particular (De Bie, Robaeys, & Buntinx, 2005; Lang et al., 2003). Another hypothesis is that the HCV virus may have a direct effect on brain functions (Forton et al., 2001) and infect the central nervous system, causing neurological damage. It has been found that this neurological damage may manifest itself through cognitive impairment in the domains of attention, concentration and information processing speed (Forton et al., 2005; Forton et al., 2002). One cannot be sure whether this may also lead to anxiety and depression, however, this possibility cannot be ignored. Moreover, other variables that were not examined in the present study may also explain these results. These may include, but are not limited to, individual differences in personality and in appraisal of stressful situations as well as copying styles. Unquestionably, future studies should focus on interventions targeting anxiety, which seems to be an under-recognised problem in patients with gastrointestinal and hepatologic disorders. Patients with HCV should be routinely monitored and psychologically treated for their anxiety and depression. Qualitative studies exploring HCV patients' perspectives on these co-morbidities could prove useful.

Interestingly, further comparisons of the psychological status between the IBD group and other samples of patients with IBD indicated that the studied IBD group was less depressed and had better physical quality of life than a British sample of 116 outpatients with IBD (75 with CD and 37 with UC) who visited a clinic with a special interest in IBD (Guthrie et al., 2002). The group was similar to the present study with respect to the disease activity,

as 45% of patients had active disease, however, the participants in the present study were older (mean of 51 years compared with 43 years for the study by Guthrie). Moreover, the present study had a nearly identical distribution of CD and UC cases whereas the British study was CD predominant.

When comparisons were extended to other groups of chronically ill, the studied IBD group was observed to be more depressed than a German sample of coronary heart disease inpatients (Barth & Martin, 2005) and less depressed than a British sample of chronic obstructive pulmonary disease patients (Withers et al., 1999). The German sample was, however, male predominant (80% male participants compared with 60% in the present study) and much larger (n=1320) than the present study. Moreover, it included only inpatients. British pulmonary disease patients, on the other hand, were much older (the mean of 66 years), however, they had similar time since diagnosis (12 years versus 14 years in the present study) to the present study participants. Moreover, the IBD group had better physical quality of life, but poorer mental quality of life than South Australian diabetic patients and South Australian patients with arthritis (Avery et al., 2004). Furthermore, the studied group of patients with IBD had lower psychological morbidity and their SCL90 scores were closer to the normal population means than an Australian sample of patients with chronic pain (McGuire & Shores, 2001), however, this sample was smaller (50 participants), younger (the mean of 38 years) and suffered from more severe symptoms than the present study sample. The present study sample also scored closer to the population mean than the Canadian patients with whiplash injuries (Peebles et al., 2001) and had a lower psychological morbidity than Canadian muscoloskeletal pain patients (Peebles et al., 2001), which could probably be explained by the nature of these disorders.

Overall, the studied IBD group was psychologically healthier compared to other groups of patients with IBD and other chronically ill patients and had better physical quality of life. Their mental quality of life was, however, poorer than in other groups of South Australian chronically ill people. Therefore, in comparison with the contemporaneous sample of IBS and HCV patients, as well as with other IBD samples and other disease groups, the studied IBD group seemed to have good psychological wellbeing and relatively good quality of life. The reasons behind this finding may be again adequate care and, when compared to international samples (British, American, and Canadian), some differences in access to medical services. This appears to be especially likely as only comparisons with other South Australian samples showed lower levels in mental quality of life for the studied IBD group. Therefore, when we compare different disease groups who have similar access to medical facilities, we can assume these differences result from factors associated with the disease itself, not the conditions in which it is being treated. Furthermore, comparisons with German participants, where the access to medical services is generally better than in Australia (van Doorslaer, Masseria, & Koolman January 2006), showed higher levels of depression in the studied group indicating that better access to doctors might contribute to the better psychological outcomes.

Moreover, studied UC and CD participants did not differ in their anxiety, depression and quality of life. However, multiple regression indicated a tendency of participants with CD to have poorer physical quality of life than UC participants. Somewhat puzzlingly, the groups did not differ psychologically even though, or maybe due to the fact that 58% of UC patients had active disease compared to only 13% in the CD group. This finding contradicts results of other studies showing that CD patients are generally more affected by psychological problems than UC (Tarter et al., 1987). One can, however, try to explain this finding by differences in the severity of symptoms. Thus, if UC sufferers in remission are

less prone to be anxious and/or depressed than CD patients, in the situation when they are in relapse their prevalence of psychological problems may equal that of CD participants in remission.

Finally, the greatest limitation of this study was the fact that despite the collective effort of many consultants, only 32% of all invited patients agreed to participate in the study. This may implicate that patients with more severe disease were too sick to participate (creating a potential bias) or that many patients in remission or having their illness for a long time felt no urgency to help with research as they have come to accept the disease. The latter could be improved in the future research by inviting only newly diagnosed patients to the study. Moreover, this low response rate may be associated with the potential time burden of completing questionnaires, which were estimated to take an average of 40 minutes. In addition, due to the concerns of the hospital ethics committee, the author could not approach patients before their visit with the treating clinician (that is, while they were waiting for the visit). Furthermore, the doctors were responsible for inviting patients to the study and the limited time they had for examining a patient and explaining the details of the study could result in a low response rate. In order to take part in the study, participants were also obliged to stay at the clinic longer than they had expected and some of them chose not to do this. Additionally, again due to ethical issues, potential participants were only allowed to be approached once. Furthermore, the author was not an employee of the hospital and was not known to participants. This may have prevented patients from taking part in the study. Thus, future trials should modify recruitment strategies and, if possible, invite patients to the study while they are waiting for their visit. When practically possible, hospital staff (e.g. nurses, doctors) should be directly involved in recruitment and distributing questionnaires.

Some results discussed above will now be used in Chapter 4 to analyse the character of the relationship between the number of co-morbid functional disorders and the severity of psychological problems in participants with IBD and IBS.

Chapter 4: Functional gastrointestinal disorders and psychological co-morbidity in patients with IBD and IBS (Study 2)

This chapter describes Study 2 and focuses on the problem of co-morbid functional disorders in IBD and IBS participants and the relevance of the complexity of these disorders to the psychological status of patients. In particular, the chapter presents the prevalence of functional gastrointestinal disorders in the IBD and IBS groups, and also provides comparisons between the CD and UC subgroups. It then summarises analysis of the relationship between particular functional disorders and anxiety, depression and quality of life. Furthermore, it analyses the relationship between the number of functional disorders and severity of psychological symptoms, examining the second hypothesis (IBD and IBS patients with a greater number of functional gastrointestinal disorders have higher levels of anxiety and depression and poorer quality of life than those with fewer functional disorders). The third hypothesis (IBD patients with co-morbid IBS have a higher rate of psychological problems and poorer quality of life than IBD patients without functional disorders) is also examined here. Finally, the chapter presents an investigation of how well the new Rome III criteria for IBS detect this disorder in clinically diagnosed patients.

4.1. Introduction

As stated in the Preamble, functional gastrointestinal disorders are a group of conditions in which no known structural abnormalities or infectious or metabolic causes can be found (Mitchell & Drossman, 1987). The first attempt to develop criteria for diagnosing

functional gastrointestinal disorders, and IBS in particular, was undertaken by Manning and colleagues in the late 1970s (Manning, Thompson, Heaton, & Morris, 1978). In 1991, an international team of experts initiated a process to develop criteria for all functional gastrointestinal disorders resulting in the Rome I criteria (Thompson, 1993). Further attempts to improve the applicability of the Rome I criteria led to the development of the Rome II criteria in 2000 (Drossman, Corazziari, Talley, Thompson, & Whitehead, 2000), and more recently, in 2006, to refinements published as the Rome III (Drossman, 2006c; Thompson, 2006). Although the initial thrust of these diagnostic criteria was to facilitate research in the field, with investigators at different sites able to compare "apples with apples", the advent of targeted therapeutic options for certain patient groups (Talley, 2001) has made it more important from a clinical perspective for gastroenterologists to accurately apply the criteria in their daily clinical practice.

It is well recognised that on direct questioning, patients who fulfil the criteria for diagnosis of one functional gastrointestinal disorder will frequently also meet diagnostic criteria for other functional gastrointestinal disorders (Drossman et al., 1993). Some studies have estimated that up to 61.7% of patients have ≥ 1 functional gastrointestinal disorder (Thompson, Irvine, Pare, Ferrazzi, & Rance, 2002) and 75% have ≥ 2 functional gastrointestinal disorders (Papatheodoridis & Karamanolis, 2005). However, it is not yet known whether the number of functional gastrointestinal disorders correlates with the burden of psychological co-morbidity. In fact, previous research has revealed that up to 93% of patients consulting a specialist with IBS have a lifetime history of some psychiatric disorder (Walker et al., 1990), and in the majority of these patients (43% - 82%), anxiety and/or depression was diagnosed before the onset of gastroenterological symptoms (Fullwood & Drossman, 1995). Because of this strong link between IBS and psychological co-morbidity, it seems likely that those participants with a greater burden of functional

gastrointestinal disorders (as assessed by number of functional diagnoses) should also have a greater burden of psychological problems (anxiety/depression). Similarly, as IBD commonly co-exists with functional gastrointestinal disorders and with psychological problems, it is probable that there will also be a relationship between the number of co-morbid functional gastrointestinal disorders and psychological morbidity in this group.

To the author's knowledge, a study on the relationship between the number of functional gastrointestinal disorders (as assessed by the Rome III criteria) and psychological co-morbidity in patients with IBD and patients clinically diagnosed with IBS has not yet been undertaken. Nor have studies been performed with these new criteria to discover whether patients with IBD, with or without concurrent IBS, differ on psychological variables. Moreover, whereas the Rome I and II criteria have been widely employed both in research and clinical practice for 16 years (Shinozaki et al., 2006; Talley, Boyce, & Jones, 1997; Whitehead et al., 2003), the new Rome III criteria have been little used and have not been used clinically nor validated in an Australian sample.

The main aim of this study was, therefore, to observe the influence of functional gastrointestinal disorders on the psychological status of patients with either IBD or IBS, or both. The objectives were to determine the prevalence of functional gastrointestinal disorders in the IBD and IBS patients; to ascertain whether IBD and IBS patients with a greater number of functional gastrointestinal disorders have higher levels of anxiety and depression and poorer quality of life; to verify whether patients with IBD with concurrent IBS have a higher rate of psychological problems and poorer quality of life than patients with IBD without IBS; and to validate the new Rome III criteria by testing the diagnosis of IBS by the Rome III criteria against the "gold standard" of an existing clinical diagnosis of IBS by an experienced gastroenterologist. The following hypotheses are investigated in

this study: 1) IBD and IBS patients with a greater number of functional gastrointestinal disorders have higher levels of anxiety and depression and poorer quality of life than those with a smaller number of functional disorders (Hypothesis 2); 2) IBD patients with co-morbid IBS have higher rate of psychological problems and poorer quality of life than IBD patients without IBS (Hypothesis 3). A summary of methods used in this study is presented in Figure 6 (for detailed description of methods see Chapter 2).

Study 2
Summary of methods

Aim:
To observe the influence of functional gastrointestinal disorders on the psychological status of patients with IBD and IBS.

Hypotheses tested:
- IBD and IBS patients with a greater number of functional gastrointestinal disorders have higher levels of depression and anxiety and poorer quality of life than those with fewer functional disorders (Hypothesis 2);
- IBD patients with co-morbid IBS have higher rate of psychological problems and poorer quality of life than patients with IBD without co-morbid IBS (Hypothesis 3).

Estimated sample size:
The sample was derived from Study 3. See Methods for detail.

Design:
A cross-sectional survey was conducted on IBD and IBS patients recruited from the Royal Adelaide Hospital. Patients were given a battery of psychological, disease activity and functional disorders measures on one occasion.

Outcome measures:
- The prevalence of functional gastrointestinal disorders in patients with IBD and IBS;
- The proportion of patients with IBD and IBS with both functional gastrointestinal disorders and psychological problems;
- The prevalence of IBS in the IBD group;
- The prevalence of psychological problems in IBD patients with co-morbid IBS;
- The proportion of patients diagnosed with IBS both clinically and by the Rome III criteria.

Figure 6: A summary of methods used in Study 2

4.2. Results

Ninety-eight patients who had agreed to participate in Study 1 were approached to complete the Rome III criteria questionnaire, the Bowel Disease Questionnaire (the BDQ) (see Appendix 11). Sixty-four participants were previously clinically diagnosed with IBD, either CD or UC, and 34 were clinically diagnosed with IBS. Five patients (three with IBD and two with IBS) withdrew from the study and did not return the questionnaires. Of these, three patients with IBD were not contactable, one IBS patient's diagnosis was changed to Coeliac disease and one IBS patient did not wish to be further involved in the study. Overall, 93 of 98 patients (95%) who agreed to participate (61 with IBD and 32 with IBS) were enrolled in this cross-sectional study. Among the 61 IBD participants, 32 patients (52%) had UC and 29 patients (48%) had CD.

4.2.1. The prevalence of functional gastrointestinal disorders

Functional gastrointestinal disorders were more prevalent in the IBS than in the IBD group, however, the difference was not statistically significant (Fisher's Exact Test p=0.256). Overall, 49 (80%) patients with IBD and 31 (97%) clinically diagnosed IBS participants met the Rome III criteria for functional bowel disorders (Table 35). This difference was statistically significant (Fisher's Exact Test p=0.031) meaning that functional bowel disorders are more prevalent in patients with IBS than patients with IBD. In particular, 19 (31%, CI: 20-42) IBD participants and 16 (50%, CI: 33-67) IBS participants matched the specific criteria for irritable bowel syndrome. Overall, 10 (16%) patients with IBD and seven (22%) IBS participants met criteria for functional constipation. Interestingly, while 11 (18%) IBD participants met criteria for unspecified functional bowel disorder, no IBS participant met these criteria (p<0.05). Six (10%) IBD participants and seven (22%) IBS participants met criteria for functional bloating.

Other functional gastrointestinal disorders were also highly prevalent in these groups. Criteria for functional gastroduodenal disorders were met in 19 (31%) IBD participants and 17 (53%) IBS participants. More IBS participants than IBD participants had aerophagia (p<0.05). Eighteen (29%) IBD participants and 12 (37%) IBS participants met criteria for functional oesophageal disorders. Functional anorectal disorders were also found to commonly coexist in this sample, with 11 (18%) IBD participants and 18 (56%) IBS participants meeting the Rome III criteria for these disorders (p<0.05). No participant met criteria for functional gallbladder or Sphincter of Oddi disorders. As can be seen in Table 35, the total percentages add to >100%, as 72% of patients with IBS and 52% of patients with IBD had more than one disorder.

Table 35: Prevalence of functional gastrointestinal disorders using Rome III criteria in the IBS (n=32) and the IBD (n=61) participants (percentages add to >100% due to overlap)

Disorder	IBD N (%)	IBS N (%)	p value
A. Functional oesophageal disorders			
A1. Functional heartburn	7 (11)	5 (16)	0.746
A2. Functional chest pain	1 (2)	0 (0)	1
A3. Functional dysphagia	6 (10)	3 (9)	1
A4. Globus	4 (6)	4 (12)	0.440
B. Functional gastroduodenal disorders			
B1. Functional dyspepsia	14 (23)	13 (41)	0.094
B1a. Postprandial distress syndrome	1 (2)	0 (0)	1
B1b. Epigastric pain syndrome	0 (0)	0 (0)	
B2. Belching disorders			
B2a. Aerophagia	1 (2)	4 (12)	0.046
B2b. Unspecified excessive belching	0 (0)	0 (0)	
B3. Nausea and vomiting disorders			
B3a. Chronic idiopathic nausea	0 (0)	0 (0)	
B3b. Functional vomiting	1 (2)	0 (0)	1
B3c. Cyclic vomiting syndrome	2 (3)	0 (0)	0.544
B4. Rumination syndrome in adults	0 (0)	0 (0)	
C. Functional bowel disorders			
C1. Irritable bowel syndrome	*19 (31)*	*16 (50)*	0.075
C2. Functional bloating	6 (10)	7 (22)	0.127
C3. Functional constipation	10 (16)	7 (22)	0.516
C4. Functional diarrhoea	3 (5)	1 (3)	1
C5. Unspecified functional bowel disorder	11 (18)	0 (0)	0.007
D. Functional abdominal pain syndrome	1 (2)	1 (3)	1
E. Functional gallbladder and Sphincter of Oddi disorders			
E1. Functional gallbladder disorder	0 (0)	0 (0)	
E2. Functional biliary SO disorder	0 (0)	0 (0)	
F. Functional anorectal disorders			
F1. Functional fecal incontinence	-*	-*	-*
F2. Functional anorectal pain			
F2a. Chronic proctalgia	3 (5)	4 (12)	0.228
F2b. Proctalgia fugax	0 (0)	0 (0)	
F3. Functional defecation disorders	8 (13)	14 (44)	0.001

*F1 not possible to detect with a survey only

CD and UC participants did not significantly differ in the prevalence of any of functional gastrointestinal disorders (p>0.05) (see Table 36).

Table 36: Differences in prevalence of functional gastrointestinal disorders between CD and UC participants

Functional disorders	CD	UC	p
	N(%)		
Functional heartburn	3(10)	4(13)	0.707
Functional chest pain	1(3)	0(0)	1.000
Functional dysphagia	2(7)	4(13)	0.425
Globus	3(10)	1(3)	0.612
Functional dyspepsia	7(22)	7(23)	1.000
Postprandial distress syndrome	1(3)	0(0)	1.000
Aerophagia	0(0)	1(3)	0.492
Functional vomiting	1(3)	0(0)	1.000
Cyclic vomiting syndrome	2(7)	9(0)	0.492
Irritable bowel syndrome	10(32)	9(30)	1.000
Functional constipation	6(19)	4(13)	0.731
Functional diarrhoea	1(3)	2(7)	0.612
Functional bloating	2(7)	4(13)	0.425
Unspecified functional bowel disorder	7(22)	5(17)	1.000
Functional abdominal pain syndrome	1(3)	0(0)	1.000
Chronic proctalgia	0(0)	3(10)	0.113
Functional defecation disorders	6(19)	2(7)	0.255

4.2.2. The relationship between anxiety, depression, quality of life and functional disorders in the IBD and the IBS groups

Overall, 24 (39%) IBD and 16 (50%) IBS patients met the HADS criteria for anxiety. Seven (11%) patients with IBD and four (12%) patients with IBS met the HADS criteria for depression. The groups did not differ either in the prevalence of anxiety (χ^2 (1)=0.927, p=0.324) or depression (Fisher's Exact Test p=1.00). The groups did, however, differ in the mean score for anxiety (p=0.040), with greater anxiety in patients with IBS. There was no difference between groups on the mean score for depression or either Physical or Mental component scores for quality of life (see Table 37).

Table 37: Mean comparisons on the HADS and the SF-12 between the IBD and the

IBS group

	IBD n=61	IBS n=32
	Mean (SD)	
HADS Anxiety	6.57 (3.52)	8.09 (2.96)*
HADS Depression	4.18 (2.89)	4.06 (3.36)
SF-12 Mental component	48.87 (10.93)	46.06 (10.25)
SF-12 Physical component	45.70 (11.06)	42.95 (11.63)

* $t(91)$=-2.08 p=0.040

The independent samples t-test revealed that IBD participants with concurrent IBS had poorer physical quality of life than those without IBS (p=0.028) (see Table 38). Those IBD participants with concurrent functional dyspepsia had higher scores for anxiety than those without (p=0.047). Patients with IBD and functional defecation disorders had higher levels of anxiety (p=0.015) and depression (p=0.020) than those without these disorders. Those patients with IBD with postprandial distress syndrome had higher levels of depression (p=0.016) and poorer mental quality of life (p=0.033) than those without this syndrome. However, this group consisted of only one participant. Similarly the one IBD participant with co-existent functional vomiting, two patients with IBD with cyclic vomiting syndrome and one IBD patient with functional abdominal pain syndrome had significantly poorer physical quality of life than participants without these disorders (p=0.022, p=0.005 and p=0.022, respectively).

Table 38: Interactions between anxiety, depression, physical and mental quality of life and functional disorders in patients with IBD with and without particular functional gastrointestinal disorder (as diagnosed by the BDQ)

Functional disorders	Anxiety	Depression	Physical QOL	Mental QOL
			t	
Functional heartburn	-0.564	-1.217	0.724	-0.636
Functional chest pain	-1.271	0.408	0.203	0.877
Functional dysphagia	1.279	0.752	-0.535	-0.101
Globus	-0.540	0.662	-0.608	0.743
Functional dyspepsia	-2.033*	-0.890	1.069	1.670
Postprandial distress syndrome	-1.271	-2.474*	2.180	1.089*
Aerophagia	-0.979	1.110	-0.001	-1.169
Functional vomiting	0.163	-0.283	-0.309*	2.347
Cyclic vomiting syndrome	0.638	0.335	-1.038*	2.943
Irritable bowel syndrome	-0.553	-1.010	1.195*	2.696
Functional constipation	-1.392	-1.483	1.730	0.520
Functional diarrhoea	1.478	-0.296	-1.625	0.485
Functional bloating	-1.512	-0.379	0.325	0.094
Unspecified functional bowel disorder	-0.440	1.389	-0.771	-0.729
Functional abdominal pain syndrome	0.163	-0.283	-0.309*	2.347
Chronic proctalgia	-0.715	-2.438	1.367	1.699
Functional defecation disorders	-2.514*	-2.388*	2.786	0.682

*p≤0.05 (refers to differences between patients with IBD with and without concurrent particular functional gastrointestinal disorder)

Multiple linear regression analysis revealed that, similarly to the IBD group, clinically diagnosed patients with IBS meeting the BDQ criteria for functional dyspepsia had a higher mean score for anxiety than those without functional dyspepsia (p≤0.05) (see Table 39). Those participants from the clinically diagnosed IBS group who met the Rome III criteria for globus and IBS were found to have better physical quality of life compared with those patients without globus or IBS. However, when the analysis was repeated for globus and IBS only, the association for globus was weaker than for IBS (see Table 40). This may be due to the fact that only four participants had globus whilst 16 had IBS in the clinically diagnosed patients with IBS. No other functional disorder was associated with increased levels of anxiety, depression or impaired quality of life in the IBS group.

Table 39: Interactions between anxiety, depression, physical and mental quality of life and functional disorders in clinically diagnosed IBS with and without particular functional gastrointestinal disorder (as diagnosed by the BDQ)

Functional disorders	Anxiety	Depression	Physical QOL	Mental QOL
		B (SE)		
Functional heartburn	1.25 (1.48)	2.45 (1.62)	-9.56 (5.37)	-7.05 (5.03)
Functional dysphagia	-1.53 (1.85)	-2.08 (2.03)	-2.72 (6.71)	1.49 (6.28)
Globus	-1.26 (1.63)	-1.70 (1.78)	12.53 (5.89)*	6.89 (5.51)
Functional dyspepsia	2.35 (0.98)*	-0.13 (1.22)	0.26 (4.14)	-4.11 (3.67)
Aerophagia	-1.04 (1.49)	1.07 (1.85)	-7.96 (6.25)	1.75 (5.54)
Irritable bowel syndrome	0.59 (1.27)	-0.44 (1.44)	9.44 (4.64)*	-2.53 (4.44)
Functional constipation	-1.39 (1.35)	-1.51 (1.54)	-3.33 (4.96)	2.21 (4.75)
Functional bloating	-1.28 (1.85)	-0.17 (2.10)	-1.46 (6.80)	-2.60 (6.50)
Chronic proctalgia	0.40 (1.62)	-0.58 (1.84)	4.95 (6.37)	-1.70 (5.66)
Functional defecation disorders	0.83 (1.08)	-0.85 (1.23)	-0.45 (4.24)	-0.14 (3.77)

*$p<0.05$ (refers to differences between clinically diagnosed patients with IBS with and without concurrent particular functional gastrointestinal disorder)

Table 40: The additional analysis of the relationship between physical quality of life and functional disorders in clinically diagnosed IBS with and without particular functional gastrointestinal disorder (as diagnosed by the BDQ)

	B (SE)	P
Globus	11.80 (5.94)	0.056
Irritable bowel syndrome	9.24 (3.82)	0.022*

* $p<0.05$

4.2.3. Number of functional disorders, anxiety/depression and quality of life

In the IBD group, 47% of participants had one functional disorder whereas in the IBS group, 44% had more than two functional disorders (see Table 41). Overall, 52% of IBD participants and 72% of IBS participants had more than one functional gastrointestinal disorder. This difference was statistically significant ($\chi^2(1)=8.02$, p=0.005).

Table 41: The number of participants with no disorder, one, two and >2 disorders in

IBS

	IBD Frequency (%)	IBS Frequency (%)
No disorders	7 (11)	1 (3)
One disorder	29 (47)	8 (25)
Two disorders	15 (25)	9 (28)
More than two disorders	10 (27)	14 (44)
Total	61 (100)	32 (100)

ANOVA comparisons showed no relationship between the number of functional disorders (one, two or >2), anxiety, depression, and quality of life (p>0.05) in the IBS group. However, such a relationship existed in the IBD group in the Physical component of quality of life (see Table 42).

Table 42: ANOVA comparisons of the relationship between the number of functional

disorders (one, two or >2) and anxiety, depression, or quality of life in the IBD group

	F (df)	P
HADS Anxiety	1.22 (60)	0.309
HADS Depression	0.608 (60)	0.613
SF-12 Mental	0.746 (60)	0.529
SF-12 Physical	3.024 (60)	0.037*

In particular, Tukey's HSD post hoc test showed that those IBD participants with no functional disorders had significantly better physical quality of life than those with more than two functional disorders (p=0.025) (Table 43).

Table 43: Tukey's HSD post hoc comparisons of means in the HADS and the SF-12 between IBD participants with no FGID, one, two and >two FGID

	No disorders n=7 Mean (SD)	1 disorder n=29 Mean (SD)	2 disorders n=15 Mean (SD)	> 2 disorders n=10 Mean (SD)
HADS Anxiety	5.00(3.36)	6.55(3.56)	6.27(3.69)	8.20(3.12)
HADS Depression	3.71(2.28)	3.97(2.69)	4.07(3.19)	5.30(3.49)
SF-12 Mental	48.28(11.51)	50.46(9.13)	49(12.81)	44.45(12.81)
SF-12 Physical	55.94(4.03)[1]	44.71(9.60)	46.13(11.96)	40.77(13.52)[1]

[1] p=0.025

Hypothesis 2 testing

These results show that Hypothesis 2 (IBD and IBS patients with greater number of functional gastrointestinal disorders have higher levels of depression and anxiety and poorer quality of life than those with fewer functional disorders) was found to hold true for the IBD but not the IBS group in terms of the physical quality of life measure. Those IBD participants with fewer functional disorders had better physical quality of life than IBD participants with more functional disorders. There was, however, no relationship between the number of functional disorders and mental quality of life, anxiety or depression in either group of patients.

4.2.4. Comparisons of the psychological status and quality of life between IBD patients with and without concurrent IBS

Nineteen of 61 IBD participants (30%) were diagnosed with concurrent IBS. Thirteen of these 19 patients were female and six were male. The scores from the HADS, the SF-12 and the SCL90 subscales in IBD participants with and without IBS are presented in Table

44. There was no difference between the groups on any subscale except for SF-12 Physical component, where those with concurrent IBS were shown to be more impaired.

Table 44: Means and standard errors for the HADS, the SF-12 and the SCL90 subscales in patients with IBD without concurrent IBS and with concurrent IBS

	IBD without IBS (n=42) Mean (SE)	IBD with IBS (n=19) Mean (SE)
HADS Anxiety	6.34 (0.558)	6.83 (0.837)
HADS Depression	3.99 (0.453)	4.86 (0.680)
SF-12 Mental component	50.95 (1.718)	46.51 (2.577)
SF-12 Physical component	48.04 (1.658)*	40.10 (2.487)*
SCL90 Somatisation	55.29 (1.581)	57.25 (2.372)
SCL90 Obsessive-Compulsive	56.62 (1.300)	57.17 (1.950)
SCL90 Interpersonal Sensitivity	54.70 (1.736)	57.63 (2.605)
SCL90 Depression	57.69 (1.555)	60.99 (2.332)
SCL90 Anxiety	51.73 (1.561)	51.99 (2.341)
SCL90 Hostility	52.81 (1.547)	53.35 (2.321)
SCL90 Phobic Anxiety	51.32 (1.268)	50.93 (1.902)
SCL90 Paranoid Ideation	51.43 (1.623)	48.92 (2.434)
SCL90 Psychoticism	54.36 (1.381)	55.62 (2.072)
SCL90 GSI	55.29 (1.528)	58.38 (2.293)
SCL90 PST	55.63 (1.502)	58.02 (2.253)
SCL90 PSDI	53.68 (1.558)	55.40 (2.337)

*p=0.009

Participants with concurrent IBS did not significantly differ in their psychological outcomes from participants without concurrent IBS on the majority of subscales (see Table 45). The groups significantly differed in their physical quality of life (p=0.009). Participants with concurrent IBS had considerably poorer physical quality of life than those without concurrent IBS. As psychological problems and IBS are more prevalent in females, the comparisons controlled for sex. However, the sex variable did not explain this result. The second significant difference was noted on the SCL90 Psychoticism subscale where a difference between sexes was observed (p=0.045). Male participants had higher

mean scores on this subscale but participants with and without concurrent IBS did not significantly differ on this subscale.

Table 45: Mean comparisons of the HADS, the SF-12 and the SCL90 subscales between IBD participants with and without concurrent IBS

	Effects	F (df)	p
HADS Anxiety	Sex	0.405 (1)	0.527
	IBS	0.244 (1)	0.623
HADS Depression	Sex	0.802 (1)	0.374
	IBS	1.168 (1)	0.284
SF-12 Mental Component	Sex	0.055 (1)	0.816
	IBS	1.349 (1)	0.250
SF-12 Physical Component	Sex	0.148 (1)	0.701
	IBS	7.286 (1)	0.009*
SCL90 Somatisation	Sex	1.109 (1)	0.297
	IBS	0.490 (1)	0.487
SCL90 Obsessive-Compulsive	Sex	2.542 (1)	0.116
	IBS	0.058 (1)	0.811
SCL90 Interpersonal Sensitivity	Sex	1.144 (1)	0.289
	IBS	0.903 (1)	0.346
SCL90 Depression	Sex	3.320 (1)	0.074
	IBS	1.426 (1)	0.237
SCL90 Anxiety	Sex	0.413 (1)	0.523
	IBS	0.009 (1)	0.924
SCL90 Hostility	Sex	0.160 (1)	0.691
	IBS	0.038 (1)	0.846
SCL90 Phobic Anxiety	Sex	0.584 (1)	0.448
	IBS	0.030 (1)	0.863
SCL90 Paranoid Ideation	Sex	0.326 (1)	0.570
	IBS	0.762 (1)	0.386
SCL90 Psychoticism	Sex	4.190 (1)	0.045*
	IBS	0.264 (1)	0.610
SCL90 GSI	Sex	1.868 (1)	0.177
	IBS	1.306 (1)	0.258
SCL90 PST	Sex	3.034 (1)	0.087
	IBS	0.805 (1)	0.373
SCL90 PSDI	Sex	0.018 (1)	0.895
	IBS	0.391 (1)	0.534

*p≤0.05

Hypothesis 3 testing

The third hypothesis (IBD patients with co-morbid IBS have a higher rate of psychological problems and poorer quality of life than IBD patients without co-morbid IBS) was therefore found to only partly hold true. IBD participants with concurrent IBS did not have significantly higher levels of psychological problems than IBD participants without concurrent IBS (p>0.05). This result is supported by the fact that the groups did not differ in their mental quality of life (p=0.250). However, the physical quality of life of participants with concurrent IBS was rated as considerably poorer than physical quality of life of participants without concurrent IBS (p=0.009). This may reflect the fact that IBD participants with concurrent IBS experience more physical symptoms of their disease and thus their physical functioning is more impaired compared with IBD participants without concurrent IBS.

4.2.5. Diagnosis of IBS by the Rome III criteria versus the gold standard

As only 16 participants (50%) met the Rome III criteria for IBS, the author wanted to verify whether the BDQ adequately measures what it purports to measure and whether doctors who diagnosed participants with IBS might have confused this functional disorder with others. Nearly half of those who did not meet criteria for IBS (7 participants/22%) met the criteria for functional bloating (p=0.007). Thus, clinicians might have diagnosed IBS in patients who should have been diagnosed with functional bloating. The Fisher's Exact Test (2-sided) showed that 11 participants (34%) who met criteria for IBS also tended to meet criteria for functional dyspepsia (p=0.032).

4.2.6. Summary of most significant findings

The results indicate partial support for Hypothesis 2. There was no relationship between the number of functional disorders and anxiety and depression in either group of patients. However, there was a statistically significant relationship between the number of functional disorders and the levels of quality of life in the IBD participants. Those IBD participants with fewer functional disorders had better mental and physical quality of life than participants with more functional disorders. This relationship did not exist for participants with IBS.

The third hypothesis was also found to partly hold. IBD participants with concurrent IBS did not have significantly higher levels of psychological problems than participants without concurrent IBS nor did they differ in their mental quality of life. However, physical quality of life of IBD participants with concurrent IBS was considerably poorer than physical quality of life of participants without concurrent IBS.

4.3. Discussion

The Rome III criteria have only recently been published and as a result only a few studies have been published thus far (Klupinska et al., 2006; Sperber, Shvartzman, Friger, & Fich, 2007). This research is the first attempt to examine whether those participants meeting diagnostic criteria for a greater number of functional gastrointestinal disorders based on the Rome III criteria have more psychological co-morbidities (anxiety/depression) than those with fewer functional gastrointestinal disorders. It is also the first study comparing IBD and IBS participants in terms of prevalence of functional gastrointestinal disorders and the relationship between them and psychological morbidity based on these new Rome III criteria. This study also examined the differences in psychological status between patients

with IBD with and without concurrent IBS. Finally, it was the first study aiming to validate the new Rome III criteria against expert clinician judgement in Australia.

The most important positive finding of this study was that the number of functional gastrointestinal disorders correlated with patients' physical quality of life in the IBD group. Those participants with fewer functional disorders had better physical quality of life than participants with a greater number of these disorders. There was no relationship between the number of functional disorders and mental quality of life, anxiety or depression in either group of patients. In contrast, the striking negative finding of this study was that the number of functional gastrointestinal disorders did not predict the rate or severity of psychological co-morbidities or patients' quality of life in IBS. This may mean that as functional gastrointestinal disorders commonly co-occur, patients with IBS do not perceive multiple symptoms as a sign of many disorders, but rather as several manifestations of a single disorder with which they have been diagnosed by their doctors. However, it is not clear why this was the case that IBD patients were burdened by their additional symptoms, whilst IBS patients were not. It may perhaps lend support to the opinion that, in contrast to IBS, psychological problems in IBD patients are more a reaction to the disease itself than a cause of it. Moreover, a not dissimilar finding has been demonstrated in other studies in patients with hepatitis C, with those aware of their diagnosis having poorer quality of life than those ignorant of their infection (Rodger et al., 1999). It would be interesting to examine whether disclosing the additional diagnoses to patients led to a measurable change in psychological co-morbidities or quality of life.

It is also possible that the negative association between burden of functional gastrointestinal disorders and burden of psychological co-morbidities may be due to the small sample size: if the magnitude of this effect was small, it would require a much larger

study to be demonstrable. This seems particularly likely as the relationship existed in the IBD group which was twice as large as the IBS group. However, it should also be noted that the patients in this sample had already been referred to a metropolitan teaching hospital. Psychological co-morbidities may be greater in this group (50% of IBS participants were clinically anxious), and thus the negative finding may not be applicable to unreferred patients with IBS. Another possible explanation of this finding may be that, on average, participants had had their symptoms for 17 years and had lived with their diagnosis for 10 years. Thus, they could be in the Integration phase of coping with their disease (see the Preamble for more details concerning this theory). According to Fennell (2001, 2003), an individual who manages to reach this phase no longer treats the disease as an ultimate tragedy and is able to perceive it as an only one of many facets of life. This observation is supported by the mean scores for anxiety (only slightly elevated) and depression (within the normal range) in this sample. As IBS participants did not significantly differ from participants with IBD in terms of the length of their disease (see Chapter 3), the small sample size possibly explains the negative association between burden of functional gastrointestinal disorders and burden of psychological co-morbidities in the IBS group.

Another somewhat surprising result was that clinically diagnosed patients with IBS who met the Rome III criteria for globus and IBS had better physical quality of life than those without these disorders. For globus, this finding, although intriguing, is not robust, as the sample size of only four participants is insufficient to claim an accurate correlation. For IBS, the result is more difficult to dismiss, however, it may also be due to chance. In general, both physical and mental quality of life was poorer in this sample of IBS participants than in healthy South Australians (see Chapter 3). Thus, the fact that globus and IBS predicted better quality of life does not necessarily alter the picture of people

suffering from functional gastrointestinal disorders as those with significantly impaired quality of life.

Consistent with other studies (Haug, Svebak, Wilhelmsen, Berstad, & Ursin, 1994; Talley, Fung, Gilligan, McNeil, & Piper, 1986) and with the findings for the IBD group, functional dyspepsia (FD) in the IBS group was found to be associated with higher levels of anxiety. These participants form an interesting sub-group of patients with clinical IBS as those participants with FD also tended to meet the Rome III criteria for IBS. However, the IBS group as a whole was not found to have higher levels of anxiety than other functional gastrointestinal disorders. It would be interesting to test this observation further in a larger group to determine whether this combined FD and IBS group does, in fact, experience more problems with psychological co-morbidities and poorer quality of life compared to FD without IBS and/or IBS without FD.

Furthermore, when testing Hypothesis 3 (IBD patients with co-morbid IBS have higher rate of psychological problems and poorer quality of life than IBD patients without functional disorders), IBD participants with concurrent IBS were not found to differ from IBD participants without concurrent IBS in terms of their psychological co-morbidities. Therefore, the high level of anxiety in the IBD group does not appear to be explained by concurrent IBS. This result contradicts the results of previous studies on this topic where concurrent IBS was reported to contribute to higher levels of anxiety and depression (Simren et al., 2002). However, consistent with other studies (Minderhoud et al., 2004), concurrent IBS was found to predict poorer physical quality of life in IBD sufferers. The relationship slightly changed after adjusting for sex (p=0.028 versus p=0.009).

Another interesting positive finding of this study was that only 50% of patients diagnosed with IBS by gastroenterologists met the new Rome III criteria for this diagnosis. It should be noted, however, that over 90% of clinically diagnosed patients with IBS did meet the Rome III criteria for at least one functional bowel disorder. Many of the clinically judged patients with IBS who did not meet questionnaire criteria for IBS did however meet the "lesser" criteria for functional bloating (6/32; 19%) and functional constipation (7/32; 22%). These two disorders require fewer criteria for diagnosis than IBS and include some criteria which are included in the IBS criteria ("Rome III: The Functional Gastrointestinal Disorders," 2006). This fact, combined with the familiarity and publicity associated with a diagnosis of IBS, may have led to a relative over-diagnosis of IBS by clinicians and an under-diagnosis of both functional bloating and functional constipation.

Anecdotally, clinicians appear to regard bloating as a cardinal symptom of IBS. However, in this study, none of the participants who met the Rome III criteria for IBS reported symptoms of bloating whilst nearly half of those not meeting the Rome III criteria for IBS did meet criteria for functional bloating. It is important to note that, according to the Rome III criteria, functional bloating cannot be diagnosed in those having sufficient symptoms to also meet criteria for IBS. Furthermore, in contrast to the IBD group, many IBS participants met the Rome III criteria for more than two functional disorders. As the diagnosis of a particular functional disorder may not always be straightforward within the real world constraints of a routine clinical appointment, mislabelling some of these patients with IBS may have also contributed to these findings. The discordance between clinician and questionnaire diagnosis may also be explained in part by the small sample size. However, the participants comprised a typical sample of patients referred to the outpatient service at this hospital over an eight month period and there is no reason to presume that

they differ substantially from other patients clinically diagnosed with IBS in the Adelaide region.

Another issue to be considered pertains to the accuracy of the clinical versus the questionnaire or criteria based approach to diagnosis. It might be suggested that the new criteria are not as sensitive in detecting IBS as the previous ones, particularly the Rome I criteria. This suggestion is supported by the results of another study (Chey et al., 2002). Chey et al. (2002) observed that the Rome II criteria detected IBS with a sensitivity of only 47% compared to 83% sensitivity for the Rome I when compared to clinician judgement. However, in the current study, the new Rome III criteria have been demonstrated to have excellent sensitivity in detecting any functional bowel disorder, although there is poor agreement between clinicians and the new criteria as to the specific subtype of functional bowel disorder (i.e. IBS, functional bloating and functional constipation). Whether this "inaccuracy" is important in routine clinical practice is uncertain. Nonetheless, it needs to be acknowledged in any interpretation of criteria-based clinical trial data in the clinical setting. With continuing advances in the understanding of the pathophysiology underlying functional gastrointestinal disorders, accurately classifying these subtypes of functional bowel disorders may be more important as new more specifically targeted therapies become available.

Several other intriguing observations have been made in this study. As noted earlier, a discrepancy between clinician and research-based (BDQ) diagnoses was demonstrated. The importance of this at present is uncertain but is likely to affect the efficiency of future translations of research advances into clinical care. Larger studies to better define where clinicians and criteria fail to concur would be helpful in this regard. A population-based series, to re-examine the potential link between the number of functional gastrointestinal

disorders and psychological co-morbidities in IBS would also be valuable. As clinicians become more comfortable and familiar with the Rome III criteria, studies comparing the sensitivity of the Rome I, II and III criteria in detecting IBS and other FGID compared to standard clinicians' diagnosis can only add to the discussion on the evolution of the Rome process, and ensure that researchers and clinicians are speaking the same language.

Some results discussed above will now be used in Chapter 5 to analyse the temporal relationship between the psychological status and physical outcomes/response to standard medical treatment. Based on the cohort prospective study design, the next chapter will report on the differences between IBD, IBS and HCV patients' psychological profiles and the activity of their disease.

Chapter 5: Psychological status and the course of the disease in patients with inflammatory bowel disease, irritable bowel syndrome and hepatitis C: An observational cohort prospective management study (Study 3)

Chapter 5 reports on the results obtained in Study 3, an observational cohort prospective management study. It presents the prospective data on the relationship between psychological status and medical outcomes/response to standard medical treatment (defined by the remission/relapse status) in three groups of patients. It relates to the findings of Study 1 and compares patients' psychological and demographic variables at baseline and after a 12-month period. Moreover, it presents analysis on the relationship between the baseline characteristics and a total number of relapses in patients with IBD. Finally, it discusses the results providing implications for practice arising from results.

5.1. Introduction

Diseases of the digestive tract frequently coexist with psychological problems and especially with anxiety as evidenced by the findings of study 1 (Chapter 3). However, a temporal relationship between psychological problems and response to medical treatment/physical outcomes (defined by remission/relapse status) in patients with gastroenterological disorders has not been widely researched. Regarding studies on the impact of depression on response to medical treatment in IBD available via PubMed, only one study has been found and it was limited to treatment with infliximab (Persoons et al., 2005). The results of this prospective research clearly show that depression is a risk factor for failure to achieve remission of Crohn's disease. Other investigations reported the

negative influence of depression on compliance to treatment with mesalazine (Shale & Riley, 2003). In IBS, to the author's knowledge such studies have not been conducted. In HCV, studies on treatment with interferon have demonstrated that depression was responsible for termination of treatment (Yu et al., 2006) and interestingly, that depression appearing as a consequence of this treatment is a predictor of better response to treatment if patients remain on treatment but also receive antidepressants (Loftis et al., 2004). To date, no prospective study has focused on the relationship between patients' psychological status and their physical outcomes/response to standard medical treatment in these three diseases.

With respect to the relationship between psychological status and physical outcomes, prospective studies on hepatitis C and inflammatory bowel disease patients are a rarity. In fact, when one searches PubMed for prospective studies on depression in HCV, among the 49 results found, the only papers relate to interferon therapy and its side effects. In the case of IBD, among 18 identified studies, the majority relate to stress and psychotherapy, with only three prospective investigations into the relationship between depression/anxiety and physical outcomes (Andrews et al., 1987; Mittermaier et al., 2004; North et al., 1991). The two largest of these three studies have recognized a link between psychological problems and poorer medical outcomes (Andrews et al., 1987; Mittermaier et al., 2004). One study with a small sample (n=32) but with the longest trial period did not show a positive relationship with this regard (North et al., 1991).

In regard to IBS, there has been little prospective research conducted on the relationship between psychological status at baseline and physical outcomes after a period of observation. A prospective study with 400 participants surprisingly found that anxiety, depression and stress are all predictors of better health outcomes in patients with IBS after

12 months of observations (Mearin et al., 2006). Another 5-year follow-up study with 43 participants indicated that anxiety but not depression may have a negative impact on the course of IBS (Fowlie, Eastwood, & Ford, 1992). In contrast, a systematic review including 14 observational longitudinal studies has not fully endorsed these findings showing that both anxiety (two studies including the one by Fowlie et al. 1992) and depression (one study) at baseline predicted worse physical outcomes after a period of observation (El-Serag, Pilgrim, & Schoenfeld, 2004). These conflicting results make it impossible to evaluate whether psychological status affects medical outcomes in patients with IBS.

Moreover, as stated in Chapter 3, the majority of controlled studies in this area suffer from methodological flaws such as comparisons with inadequately matched controls. In fact, among the three available studies on the relationship between depression and somatic outcomes in IBD, none is controlled (Andrews et al., 1987; Mittermaier et al., 2004; North et al., 1991). The following study aims to avoid this limitation. It prospectively evaluates the psychological profiles of inflammatory bowel disease patients compared to 1) a contemporaneous sample of controls with another chronic disease of the gastrointestinal tract in which psychological factors are implied in causation (IBS); and 2) a contemporaneous sample of controls with a hepatologic disorder in which psychological problems usually result from treatment side effects and co-morbid alcohol and drug addictions (HCV).

The innovative aspects of this study are therefore the studied group, its prospective design, comparisons with well-matched controls and, most importantly, its focus on the relationship between anxiety, depression and physical outcomes/response to standard medical treatment. Furthermore, as the temporal differences in psychological profiles, the

quality of life and disease activity between patients with inflammatory bowel disease, irritable bowel syndrome and hepatitis C have not been previously examined, discovering their character and directions might contribute to understanding the nature of problems affecting these patients and, consequently, to improved medical care. The following hypothesis is investigated in this study:

- Patients with psychological co-morbidities are less likely to have a satisfactory response to standard treatment/better physical outcomes (remission) at 12 months.

A summary of methods used in this study is presented in Figure 7 (for a detailed description of methods see Chapter 2).

Study 3
A summary of methods

Aim:
To observe and compare prospectively the course of IBD, IBS and HCV in relation to psychological co-morbidity at baseline

Hypothesis tested:
Patients with psychological co-morbidities are less likely to have a satisfactory response to standard treatment/better physical outcomes (remission of symptoms) at 12 months (Hypothesis 4).

Estimated sample size:
Powering the study to detect differences of more than 15% for the primary outcome variables with an alpha-level of 0.05 and a beta-level of 0.86 a sample size of at least 150 patients (50 in each patient group) was estimated to be acceptable for this study.

Design:
A cohort prospective management study was conducted for a period of 12 months on a sample of patients recruited from the Royal Adelaide Hospital. A battery of psychological and disease activity measures was distributed three-monthly.

Outcome measures:
- The proportion of patients with IBD in clinical remission of IBD after a year of standard therapy (different in each disease group, see Preamble for details);
- The proportion of patients with IBS with sufficient relief of symptoms after a year of standard therapy;
- The proportion of patients with HCV with clearance of Hepatitis C after a year of standard therapy.
- The proportion of patients in all disease groups with an improved psychological status;
- The proportion of patients in all disease groups with improved quality of life.

Figure 7: A summary of methods used in Study 3

5.2. Results

Overall, 139 patients were enrolled in this cohort prospective management study. During the 12 months of this study, 13 (9.3%) participants withdrew. These included seven patients with IBD, five patients with HCV and one patient with IBS. Five participants were

not contactable, and three were too sick to be able to participate (cancer, Alzheimer's disease, serious relapse of IBD). Another three participants did not send back the questionnaires despite reminders. One IBS patient's diagnosis changed into Coeliac disease and one person did not wish to be further involved. Thus, 126 (90.7%) participants completed the study. Only incomplete data were available for two IBS patients. The analysis was, therefore, conducted on 124 participants. This means that the study was underpowered for the HCV and IBS group, as the estimated sample size of at least 50 patients in each disease group was not achieved in these two groups.

5.2.1. Baseline characteristics and patients' medical outcomes/response to standard medical treatment after 12 months

Both at baseline and after 12 months, 44% of participants were in relapse. Descriptive statistics for the relapse/remission status in all three groups at baseline and after 12 months are presented in Table 46. There were no significant differences in the tendency to relapse between the groups over time as evidenced by the results of logistic regression (Table 52).

Table 46: The distribution of active disease in HCV, IBD and IBS at baseline and after 12 months

	Baseline	At 12 months
	Relapse n (%)	
HCV (n=36)	19 (53)	13 (36)
IBD (n=59)	19 (32)	23 (39)
IBS (n=29)	17 (59)	19 (65)
Total (n=124)	55 (44)	55 (44)

At baseline, 40% of participants were anxious and 17% depressed (see Table 47 and Table 48). At 12 months, 37% of participants were anxious and 13% depressed. There was no

significant change over time either in anxiety caseness (χ^2 (1)=1.05 p=0.305) or in

depression caseness (χ^2 (1)=1.11 p=0.291).

Table 47: Anxiety cases (HADS Anxiety > 7) at baseline and after 12 months

	Baseline	At 12 months
	Anxious n (%)	
HCV (n=36)	16 (44)	12 (33)
IBD (n=59)	23 (39)	20 (34)
IBS (n=29)	16 (52)	15 (48)
Total (n=124)	55 (40)	47 (37)

Table 48: Depression cases (HADS Depression > 7) at baseline and after 12 months

	Baseline	At 12 months
	Depressed n (%)	
HCV (n=36)	12 (33)	4 (11)
IBD (n=59)	7 (12)	9 (15)
IBS (n=29)	3 (10)	3 (10)
Total (n=124)	22 (17)	16 (13)

Descriptive statistics for the HADS and the SF-12 subscales in all three groups at baseline

and after 12 months are presented in Table 49. There are no significant differences for any

of the HADS or SF-12 variables between the groups over time as evidenced by the results

of logistic regression (Table 52).

Table 49: Means and standard deviations on the HADS and the SF-12 subscales at

baseline and after 12 months in the HCV, the IBD and the IBS group

	Baseline Mean (SD)	At 12 months Mean (SD)
HADS Anxiety_HCV (n=36)	6.92 (4.15)	6.31 (4.11)
HADS Anxiety_IBD (n=59)	6.56 (3.58)	6.10 (4.83)
HADS Anxiety_IBS (n=31)	8.13 (3.00)	7.29 (3.50)
HADS Depression_HCV (n=36)	5.19 (4.52)	4.19 (3.86)
HADS Depression_IBD (n=59)	4.24 (2.92)	3.85 (3.98)
HADS Depression_IBS (n=31)	3.90 (3.30)	4.42 (3.69)
SF-12 Mental_HCV (n=36)	44.66 (12.67)	49.22 (11.34)
SF-12 Mental_IBD (n=59)	48.61 (11.03)	48.13 (12.61)
SF-12 Mental_IBS (n=31)	46.06 (10.42)	48.19 (10.23)
SF-12 Physical_HCV (n=36)	43.17 (11.67)	44.87 (10.68)
SF-12 Physical_IBD (n=59)	45.53 (11.19)	45.38 (10.72)
SF-12 Physical_IBS (n=31)	43.67 (11.09)	44.34 (11.31)

The descriptive statistics for the SCL90 subscales in all three groups at baseline and after

12 months are presented in Table 50. There are no significant differences on any of the

SCL90 variables between the groups over time as evidenced by the results of logistic

regression (Table 52).

Table 50: Means and standard deviations on the SCL90 subscales at baseline and

after 12 months in the HCV, the IBD and the IBS group

	Baseline	At 12 months
	Mean (SD)	Mean (SD)
Somatisation_HCV (n=36)	61.03 (12.87)	60.19 (12.16)
Somatisation_IBD (n=59)	55.56 (10.20)	56.58 (12.09)
Somatisation_IBS (n=31)	59.74 (8.52)	59.42 (9.24)
Obsessive-Compulsive_HCV (n=36)	61.75 (10.46)	61.31 (9.89)
Obsessive-Compulsive_IBD (n=59)	56.34 (8.46)	56.75 (11.63)
Obsessive-Compulsive_IBS (n=31)	58.97 (10.08)	56.52 (12.24)
Interpersonal Sensitivity_HCV (n=36)	60.42 (10.96)	57.81 (12.05)
Interpersonal Sensitivity_IBD (n=59)	55.64 (11.02)	55.51 (11.26)
Interpersonal Sensitivity_IBS (n=31)	56.94 (11.62)	56.61 (11.54)
Depression_HCV (n=36)	62.53 (12.07)	60.39 (11.84)
Depression_IBD (n=59)	58.31 (10.26)	57.56 (11.88)
Depression_IBS (n=31)	59.26 (10.13)	58.42 (11.71)
Anxiety_HCV (n=36)	57.94 (12.64)	57.36 (12.10)
Anxiety_IBD (n=59)	51.76 (9.96)	51.22 (11.86)
Anxiety_IBS (n=31)	56.77 (8.93)	54.26 (10.30)
Hostility_HCV (n=36)	57.89 (11.09)	54.58 (10.59)
Hostility_IBD (n=59)	53.05 (9.76)	52.90 (10.73)
Hostility_IBS (n=31)	55.03 (11.13)	53.68 (10.68)
Phobic Anxiety_HCV (n=36)	54.31 (11.30)	53.36 (11.85)
Phobic Anxiety_IBD (n=59)	51.24 (8.04)	50.61 (9.01)
Phobic Anxiety_IBS (n=31)	49.77 (8.14)	50.68 (9.23)
Paranoid Ideation_HCV (n=36)	55.72 (11.54)	55.17 (11.84)
Paranoid Ideation_IBD (n=59)	50.78 (10.32)	50.90 (10.61)
Paranoid Ideation_IBS (n=31)	51.23 (11.49)	50.35 (10.16)
Psychoticism_HCV (n=36)	57.97 (9.40)	57.61 (11.49)
Psychoticism_IBD (n=59)	54.51 (8.95)	53.86 (10.62)
Psychoticism_IBS (n=31)	55.39 (9.70)	54.52 (9.83)
GSI_HCV (n=36)	62.28 (11.22)	60.39 (11.51)
GSI_IBD (n=59)	55.93 (9.98)	55.93 (12.55)
GSI_IBS (n=31)	59.61 (10.02)	58.10 (11.67)
PST_HCV (n=36)	61.14 (10.32)	60.47 (11.29)
PST_IBD (n=59)	56.03 (9.83)	55.08 (11.32)
PST_IBS (n=31)	58.35 (9.36)	56.61 (11.25)
PSDI_HCV (n=36)	57.39 (8.87)	53.67 (12.24)
PSDI_IBD (n=59)	54.14 (9.86)	53.56 (10.81)
PSDI_IBS (n=31)	56.42 (8.55)	57.58 (7.15)

The descriptive statistics for all psychological variables in the whole cohort of patients are presented in Table 51. There are no significant differences regarding any of psychological variables over time for the whole cohort as evidenced by the results of logistic regression (Table 52).

Table 51: Means and standard deviations on the SCL90 subscales at baseline and after 12 months for the whole cohort of patients

	Baseline	At 12 months
	Mean (SD)	Mean (SD)
HADS Anxiety	7.05 (3.65)	6.45 (4.33)
HADS Depression	4.43 (3.54)	4.09 (3.85)
SF-12 Mental	46.85 (11.42)	48.46 (11.63)
SF-12 Physical	44.40 (11.27)	44.98 (10.78)
Somatisation	58.15 (10.88)	58.31 (11.51)
Obsessive-Compulsive	58.53 (9.67)	57.99 (11.42)
Interpersonal Sensitivity	57.33 (11.25)	56.44 (11.51)
Depression	59.75 (10.84)	58.58 (11.79)
Anxiety	54.76 (10.87)	53.72 (11.77)
Hostility	54.92 (10.61)	53.57 (10.62)
Phobic Anxiety	51.75 (9.20)	51.41 (9.95)
Paranoid Ideation	52.30 (11.10)	51.98 (10.37)
Psychoticism	55.71 (9.31)	55.10 (10.73)
GSI	58.65 (10.64)	57.74 (12.10)
PST	58.06 (10.02)	57.00 (11.44)
PSDI	55.63 (9.32)	54.58 (10.55)

Interactions between all psychological and demographic variables and the probability of relapse showed that male participants and older participants were significantly more likely to relapse than female and younger participants (p=0.039 and p=0.001, respectively) (Table 52). Furthermore, IBD participants were less likely to relapse than IBS participants (p=0.018). Those who were more anxious had a tendency to relapse more commonly than those with lower levels of anxiety (p=0.031). Those having better levels of physical quality of life were less likely to relapse than those with poorer physical quality of life (p=0.005). However, there was no statistically significant change over time on any of these variables (p=0.858).

Table 52: Interactions between all psychological and demographic variables and a

tendency to relapse

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	p
Sex_male vs. female	0.949	0.461	0.045	1.853	2.06	0.039*
Age	0.042	0.013	0.016	0.068	3.22	0.001*
Years since Diagnosis	-0.007	0.018	-0.044	0.029	-0.39	0.698
Baseline vs. 12 months	-0.044	0.250	-0.536	0.447	-0.18	0.858
Disease_HCV vs. IBS	-0.385	0.518	-1.400	0.630	-0.74	0.457
Disease_IBD vs. IBS	-1.059	0.448	-1.937	-0.181	-2.36	0.018*
HADSAnxiety	0.194	0.089	0.017	0.370	2.16	0.031*
HADSDepression	-0.031	0.069	-0.168	0.105	-0.45	0.651
SF12MSC	-0.006	0.022	-0.051	0.038	-0.27	0.788
SF12PCS	-0.051	0.018	-0.087	-0.015	-2.78	0.005*
SCL90SOM	0.024	0.027	-0.029	0.077	0.89	0.372
SCL90OC	-0.035	0.029	-0.093	0.021	-1.21	0.224
SCL90IS	0.009	0.029	-0.047	0.067	0.33	0.740
SCL90DEP	0.014	0.036	-0.057	0.086	0.39	0.694
SCL90ANX	0.000	0.034	-0.066	0.068	0.03	0.979
SCL90HOS	0.048	0.028	-0.007	0.103	1.71	0.086
SCL90PHOB	-0.040	0.025	-0.091	0.010	-1.56	0.118
SCL90PAR	-0.019	0.022	-0.062	0.024	-0.86	0.388
SCL90PSY	0.018	0.024	-0.029	0.066	0.77	0.441
SCL90GSI	-0.123	0.077	-0.274	0.028	-1.59	0.112
SCL90PST	0.042	0.068	-0.092	0.177	0.61	0.540
SCL90PSDI	0.013	0.023	-0.033	0.060	0.55	0.580

An additional contrast was conducted to observe a difference between HCV and IBD patients as part of the above model. This difference was not statistically significant (p=0.519) (see Table 53).

Table 53: The HCV and IBD disease group interactions with a tendency to relapse

Parameter	Estimate	Standard Error	95% Confidence Limits		Chi square	p
Disease_HCV vs. IBD	0.288	0.447	-0.588	1.166	0.42	0.519

When the analysis was rerun with significant and demographic variables only, older participants were still more likely to relapse than younger participants (p=0.005) (Table 54). IBD participants were less likely to relapse than IBS participants (p=0.008). Those with better physical quality of life were less likely to relapse than those with poorer physical quality of life (p=0.007).

Table 54: Interactions between significant variables and demographics and a tendency to relapse

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	p
Sex_male vs. female	0.556	0.380	-0.190	1.302	1.46	0.144
Age	0.033	0.012	0.009	0.056	2.76	0.005*
Years since Diagnosis	-0.009	0.016	-0.042	0.023	-0.57	0.566
Disease_IBD vs. IBS	-1.100	0.417	-1.918	-0.282	-2.64	0.008*
HADSAnxiety	0.072	0.045	-0.016	0.161	1.60	0.109
SF12PCS	-0.040	0.015	-0.070	-0.010	-2.66	0.007*

5.2.2. Interactions between psychological variables and a total number of relapses in IBD

No significant relationship was found between psychological problems such as anxiety/depression and a total number of relapses in the IBD group (Table 55). Interestingly enough, however, CD participants were found to be less likely to relapse than UC participants ($p < 0.0001$).

Table 55: Interactions between psychological variables and a total number of relapses in the IBD group

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	p
Sex_male vs. female	1	0.281	0.335	-0.376	0.939	0.70	0.401
Age	1	-0.012	0.011	-0.035	0.010	1.13	0.288
Years since Diagnosis	1	-0.002	0.015	-0.033	0.027	0.03	0.854
CD vs. UC	1	-1.235	0.336	-1.893	-0.576	13.52	0.000*
HADSAnxiety	1	0.068	0.065	-0.060	0.197	1.09	0.296
HADSDepression	1	0.077	0.076	-0.072	0.227	1.02	0.311
SF12MSC	1	0.039	0.029	-0.018	0.098	1.78	0.182
SF12PCS	1	-0.030	0.018	-0.066	0.004	2.94	0.086
SCL90SOM	1	0.022	0.019	-0.015	0.060	1.35	0.246
SCL90OC	1	-0.019	0.026	-0.071	0.031	0.58	0.446
SCL90IS	1	-0.004	0.024	-0.052	0.043	0.04	0.846
SCL90DEP	1	0.037	0.039	-0.039	0.114	0.91	0.341
SCL90ANX	1	0.043	0.027	-0.010	0.096	2.44	0.118
SCL90HOS	1	0.028	0.022	-0.016	0.073	1.56	0.212
SCL90PHOB	1	-0.021	0.020	-0.060	0.018	1.11	0.292
SCL90PAR	1	0.012	0.019	-0.025	0.051	0.43	0.512
SCL90PSY	1	-0.027	0.031	-0.089	0.035	0.73	0.393
SCL90GSI	1	-0.042	0.049	-0.139	0.054	0.74	0.388
SCL90PST	1	-0.008	0.069	-0.144	0.127	0.02	0.901
SCL90PSDI	1	-0.022	0.023	-0.068	0.024	0.88	0.348

When the analysis was rerun after removing all insignificant variables (excluding SF12PCS as this variable almost reached significance), CD participants were again found to be less susceptible to relapse (p<0.0001) (Table 56). Additionally, those participants with poorer physical quality of life were more likely to relapse than those with better physical quality of life (p=0.001). This is consistent with the above data for the whole cohort of IBD, IBS and HCV patients.

Table 56: Interactions between significant variables and a total number of relapses in the IBD group

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	p
Sex_male vs. female	1	0.298	0.214	-0.120	0.718	1.95	0.162
Age	1	-0.010	0.008	-0.025	0.005	1.62	0.202
Years since Diagnosis	1	-0.006	0.012	-0.030	0.016	0.33	0.562
CD vs. UC	1	-1.248	0.254	-1.746	-0.749	24.10	0.000*
SF12PCS	1	-0.035	0.011	-0.057	-0.013	9.93	0.001*

Hypothesis 4 testing

Even though the initial model suggested that anxiety was correlated with an increased likelihood of relapse, the later model did not confirm this observation. There was no temporal change observed in the tendency to relapse, either. Nor was there any significant difference between disease groups in their likelihood to relapse over time. Participants with higher levels of physical quality of life were less likely to relapse than those with lower physical quality of life (p=0.007). However, this tendency was not temporal and not specific to any particular disease group. Thus, psychological status at baseline did not explain medical outcomes after 12 months in this cohort of patients with chronic diseases of the digestive tract. In addition, no significant relationship was found between psychological problems such as anxiety/depression and a total number of relapses in IBD. Thus, Hypothesis 4 that patients with psychological co-morbidities are less likely to have a satisfactory response to standard treatment/better physical outcomes at 12 months was rejected.

<u>Summary of most significant results</u>

In general, older participants were more likely to relapse than younger participants (p=0.005). Those with better physical quality of life were less likely to relapse than those with poorer physical quality of life (p=0.007). IBD participants were less likely to relapse than IBS participants (p=0.008). There was no statistically significant change over time in the tendency to relapse. Thus, anxiety/depression at baseline did not explain medical outcomes after 12 months in this cohort of patients with chronic diseases of the digestive tract. Furthermore, there was no significant difference between disease groups in their likelihood of relapse over time. No significant relationship was found between psychological problems such as anxiety/depression and a total number of relapses in IBD. However, CD participants were found less likely than UC participants to relapse (p<0.0001).

5.3. Discussion

To the author's knowledge, this study was the first to prospectively evaluate the relationship between psychological problems and medical outcomes/response to standard medical treatment in patients with chronic gastroenterological conditions. While studies conducted with other disease groups (Lavoie et al., 2006; Rivelli & Jiang, 2007; Yates et al., 2004) showed a link between psychological status and somatic outcomes, this investigation has not confirmed this observation in a cohort of patients with chronic diseases of the digestive tract.

Interestingly, this cohort management study was only the fourth prospective and the first controlled investigation into the relationship between psychological status and medical outcomes in patients with inflammatory bowel disease (Andrews et al., 1987; Mittermaier et al., 2004; North et al., 1991). In contrast to the previous observations by Mittermaier et

al. (2004) and Andrews et al. (1987), but consistent with the conclusions of North et al. (19991), anxiety/depression at baseline was not associated with a total number of relapses over a period of time. Andrews et al., however, did not specify the timeline of their study and so accurate comparisons cannot be made. Interestingly, though, Andrews et al. have observed that psychological status adversely affected medical outcomes only in patients with Crohn's disease, but not with ulcerative colitis.

With respect to research by Mittermaier et al. (2004), their study lasted 18 months and included 60 participants in remission and was therefore six months longer than the present investigation. This might in part explain why the researchers found a positive relationship between depression at baseline and poorer medical outcomes after 18 months. On the other hand, North et al. (1991) observed their cohort of IBD patients for a period of two years and did not observe a link between depression and poorer medical outcomes. The latter study, however, included only 32 participants. It is clear that larger and longer lasting studies may help delineate these findings.

The sample size in the present study is comparable to that of Mittermaier et al. (n=59 vs. n=60, respectively). Thus, the difference is mainly in the time frame. Also, in Mittermaier et al.'s sample (2004), depression at baseline was found in 28% of patients whereas in this study only 12% of IBD patients were depressed, which makes these groups psychologically different and may explain the results. Interestingly, Mittermaier's patients were all in remission at baseline and thus, should have a low rate of psychological problems, while in this study 61% of IBD patients were in remission. In order to make this comparison more valid, the present study ought to have recruited patients in remission and future studies should tend to have as homogenous samples as possible. However, the largest limitation of the study by Mittermaier et al. (2004) is that the researchers used the

Beck Depression Inventory (BDI), which is not as precise as the HADS in diagnosing anxiety and depression in people with IBD. In fact, five items in the BDI overlap with symptoms of IBD: appetite, weight loss (two questions), general fatigue and worries about health. This, in turn, may mean that researchers overdiagnosed depression. North et al. (1991), on the other hand, avoided this flaw by removing the mentioned items from their version of the BDI. Thus, even though North et al.'s study involved a smaller sample size, its advantages are in the rigour of the procedure and the length of the trial. Thus, it may mean that there is, in fact, no link between psychological status and physical outcomes in patients with IBD as evidenced by the present study and the study by North et al. (1991).

As regards the HCV group, no other similar studies have been identified and any comparisons are therefore impossible. With respect to the IBS group, based on the conflicting data from available studies (El-Serag et al., 2004; Fowlie et al., 1992; Mearin et al., 2006), it is difficult to estimate whether anxiety and/or depression predicts worse physical outcomes. The present study, in contrast to previous investigations, suggests that there is no relationship, either positive or negative, between both anxiety and depression and medical outcomes/response to medical treatment after 12 months in patients with IBS. However, the present study did not achieve the estimated sample size in either the HCV or IBS group, which means that there is not sufficient power to observe whether such a relationship really exists. Moreover, all the three groups were not homogenous. It could be better if of all the patients had either been in remission or in relapse of the disease at baseline. Longer and larger prospective studies with more homogenous groups of patients are needed to better understand the relationship between psychological problems and relapse of somatic symptoms in these patients.

The greatest limitation of this study is its too short time frame. It is especially problematic in view of the fact that patients with all three studied conditions relapse less frequently than once a year. In fact, in five years time, 25% of HCV patients will clear the virus (Grebely et al., 2006) and the rest will still be carriers. Similarly in IBS, in a two-year period, 2-18% of patients have worse symptoms, 30-50% have unchanged symptoms and for the rest of patients, their symptoms either disappear or significantly improve (El-Serag et al., 2004). In IBD, in a 2-year period approximately 30% of patients relapse (Vidal et al., 2006). Thus, prospective investigations should probably last at least five years so that the relationship between psychological status and medical outcomes in these particular patient groups can be observed. Alternatively, research should focus on conditions with a similar remission/relapse pattern.

Moreover, the sole definition of remission/relapse and a method of its measurement in these three diseases may be varied. In HCV, for example, remission was considered to be a clearance of the virus as measured by the blood test. In the IBS case, there are no disease activity indices available and, thus, in this study very subjective and not previously standardised criteria (two questions on patients' perception of symptoms) were chosen to evaluate the remission/relapse status. Finally, in both subtypes of IBD, disease activity indices are in the form of a questionnaire and have been previously validated and widely used. One can, therefore, argue that comparisons of these three disorders in terms of their disease activity are not fully justified due to these methodological differences in the measurement of remission/relapse status.

Furthermore, the current study used the term 'physical outcomes' and 'response to medical treatment' interchangeably which has not been practiced in previous studies. The author is of the view that both terms relate to similar constructs. In particular, physical, medical or

somatic outcomes can be evaluated by applying disease activity measures and observing

whether patients are in remission or relapse and therefore whether their outcomes are better

or worse. Response to medical treatment is also measured on disease activity indices and

relates to whether patients feel better or worse on current treatment. The type of treatment

was, however, not examined in the present study as it was not of a particular interest to the

author. Thus, researchers conducting studies of similar designs perhaps should focus on

responses to particular treatments in patients with chronic gastroenterological conditions.

Additionally, even though initial comparisons identified several interesting interactions

between the variables of interest (i.e. more anxious participants had a tendency to relapse

more commonly than those with lower levels of anxiety (p=0.031)), further exploration of

data did not confirm these observations. However, some other interesting issues are noted.

In particular, older participants were more likely to relapse than younger participants

(p=0.005), which might be explained by the fact that older participants generally tend to

have poorer health and more co-morbid age-related problems. Furthermore, participants

with better physical quality of life were less likely to relapse than those with poorer

physical quality of life (p=0.007). This result is intriguing as it may mean that the patients'

psyche and the way patients feel about their lives may have an impact on their somatic

symptoms. However, this was not a temporal trend.

Moreover, the fact that IBD participants were less likely to relapse than IBS participants

(p=0.008), and this tendency was not temporal either, may mean that these groups were

different from the start. Ideally, similar prospective studies should include patients either in

remission or in relapse to be able to more rigorously observe the progress of the disease.

This study did not pre-set remission status as part of inclusion criteria which might be

perceived as a limitation, but which in truth resulted from the reality of conducting a PhD

project. In particular, the PhD study length did not allow for long-term investigations and

as a consequence reduced the recruitment period to a minimum. Thus, the inclusion criteria needed to be fairly broad to allow for obtaining an adequate sample.

Finally, the fact that CD participants relapsed less frequently than UC participants is not consistent with other available studies in which both groups of sufferers relapse with a similar frequency (Vidal et al., 2006). This finding can, however, be explained by the type of medication the participants received while in the study. In particular, 24 out of 31 CD patients versus only 12 out of 33 UC patients were on immunosuppressants, which are thought to be the most effective long-term therapy in IBD. Patients with CD were thus more effectively treated and because of that could relapse less often. The following chapter develops the problem of the relationship between patients' psyche and the course of their disease by observing in a randomised controlled design whether improved doctors' knowledge of patients psychological wellbeing may alter doctors' behaviour and/or influence patients' medical outcomes.

Chapter 6: Doctors' knowledge of patients' psychological status and patients' clinical outcome: A pilot randomised controlled trial (Study 4)

This chapter reports on Study 4, which was a sub-study within the previously described Study 1 (Chapter 3) and Study 3 (Chapter 5). Study 4 was a pilot randomised controlled trial conducted over 12 months on a subset of participants with inflammatory bowel disease. Here the experimental and control groups' baseline comparisons in terms of their demographic characteristics and psychological profiles are presented, as is the prospective analysis comparing patients' clinical outcomes (a total number of positive scores for IBD activity, anxiety and depression prevalence). The latter is stratified by whether the treating doctor was aware or unaware of each patient's psychological status. The chapter also provides a qualitative summary of data related to the trial (i.e. psychological/psychiatric treatments recommended by doctors) found in patients' casenotes. This methodology therefore tested the hypothesis that doctors' knowledge of patients' psychological status alters doctors' behaviours and/or improves patients' clinical outcomes (Hypothesis 5).

6.1. Introduction

Previous chapters demonstrated that psychological problems and anxiety in particular, commonly co-exist with chronic diseases of the digestive tract. Although the preceding data suggest that compared with chronic hepatitis C, IBD patients seem to be less burdened with psychological morbidity, comparisons with the general healthy population in terms of quality of life clearly show poorer outcomes in IBD patients. Therefore, interventions

directed at improving quality of life are warranted in these patients. Interestingly, there is a lack of good quality studies exploring psychiatric and psychological interventions in IBD.

Antidepressants have not been tested in any randomised control trial as a method of treatment for psychological problems in IBD (see Chapter 8 for the systematic review of available studies). There is also a lack of good quality data on the place of psychotherapy in treating psychological problems in IBD. In fact, as discussed in the Preamble, only four publications described randomised controlled trials exploring the effectiveness of psychotherapy in IBD, and two of them referred to one study (Jantschek et al., 1998; Keller et al., 2004; Schwarz & Blanchard, 1991; von Wietersheim et al., 2001). The reason behind this apparent lack of interest in studies on psychotherapy may include the high cost of such studies as well as the discouraging findings of the research conducted thus far with these patients (von Wietersheim & Kessler, 2006). Moreover, even if conducted, such studies may not alter the care of these patients in the Australian general community as many remote areas do not have access to psychological help due to either geographic, workforce or financial barriers in access to psychologists. Thus, this study examined a pilot intervention which, if successful, may be cost-effective and could be offered to patients for whom formal psychotherapy is not available.

Currently, South Australian gastroenterologists do not perceive taking care of patients' psychological health as primarily their responsibility (as evidenced by the interview study presented in Chapter 9). Yet, in the case of the current state of health services in Australia where the time per patient is limited, it is important that all doctors involved in the care of a particular patient are sensitive to a patient's psychological problems. Anxiety and depression can be difficult to detect and if a gastroenterologist suspects these problems may concern his/her patients, immediate action should be undertaken to prevent the

progress of psychological problems. It is especially so as there is a link between depression and medical non-compliance (DiMatteo, Lepper, & Croghan, 2000). Moreover, only a half of those affected by mental problems seek medical care (Andrews, Henderson, & Hall, 2001) and a good relationship between the treating doctor and his/her patient seems likely to contribute to quicker recognition of a patient's difficulties. Interestingly, in other diseases such as diabetes, it has been found that patients who positively experience the patient-doctor relationship had better outcomes, such as better glycaemic control (Viinamaki, Niskanen, Korhonen, & Tahka, 1993). Similar findings have been reported in studies with HIV-infected participants and showed that the quality of the patient-doctor relationship was associated with medication adherence in these patients (Schneider, Kaplan, Greenfield, Li, & Wilson, 2004).

The significance of the patient-doctor relationship has also been studied in the context of gastroenterology (Cheli, 1993), as well as with respect to inflammatory bowel disease (Sewitch et al., 2003). Sewitch et al. (2003) enrolled 153 patients with IBD and 10 gastroenterologists in a prospective study exploring determinants of non-adherence to medication. It was shown that a good therapeutic relationship significantly improved medication compliance. This finding is especially important considering the studies reporting very poor medication compliance (40-60% non-adherence rates) in patients with IBD (Kane, Cohen, Aikens, & Hanauer, 2001; Sewitch et al., 2003). Thus, interventions encouraging a good patient-doctor relationship between patients with IBD and their gastroenterologists are warranted to improve disease management.

The intervention described in this chapter was based on the assumption that increasing gastroenterologists' knowledge of their patients' psychological status is likely to improve the patient-doctor relationship and positively influence patients' clinical outcomes. This

conceptualisation was based on the biopsychosocial paradigm (Engel, 1980), which postulates that improved knowledge would make gastroenterologists more aware of potential psychological problems in their patients, make them more likely to discuss psychological difficulties with patients and connect with patients on a more personal level including patients' extramedical concerns. This, in turn, would enhance the relationship between a patient and a doctor. To the author's knowledge, such a study has not been previously conducted in patients with inflammatory bowel disease. Thus, the aim of this study was to determine whether physicians' knowledge of patients' psychological status might improve patients' clinical outcomes. The secondary aim of this pilot randomised controlled trial was to the estimate sample size necessary to detect significant differences for future studies. The following hypothesis is therefore under investigation in this study:

- Physicians' knowledge of patients' psychological status alters physicians' behaviour and/or improves patients' clinical outcomes (Hypothesis 5).

A summary of methods used in this study is presented in Figure 8 (for detailed description of methods see Chapter 2).

Study 4
A summary of methods

Aim:
To discover whether disclosure of the psychological status of patients with IBD to their physicians alters doctors' behaviour and/or influences patients' responses to treatment/their physical outcomes

Hypotheses tested:
Physicians' knowledge of patients' psychological status alters physicians' behaviour and/or improves patients' clinical outcome (Hypothesis 5).

Estimated sample size:
During relapses, 60% of patients with IBD suffer from psychological problems. During remission, about 30% of patients with IBD suffer from psychological problems. Patients visiting the RAH were thought to be mainly in relapse, thus, the assumption was made that at least about 60% would have psychological problems. As previously stated, the planned sample of patients with IBD was between 50 and 125. The sample of patients with psychological problems was expected to be between 30 and 65 patients. Half of these cases were to be randomly disclosed to the physician. A power calculation was not conducted in this case as the study was a pilot and the results are to be used for calculating more accurate sample sizes for a larger trial in the future.

Design:
A pilot randomised controlled trial was conducted on selected IBD participants. Patients were given a battery of psychological and disease activity measures three-monthly for a year.

Randomisation:
Random permuted blocks were used to create a randomization matrix. The "A" was regarded as disclosure of the score to the treating physician, and the "B" was considered non-disclosure of the score to the treating physician. No stratification was conducted and the ratio between the groups was 1:1.

Single-Blinding:
Patients were blinded to their trial allocation

Outcome measures:
•   Doctors' behaviour as assessed by documentation in patients' case-notes with respect to psychological issues;
•   The proportion of participants in the experimental group as compared to the control group in clinical remission of IBD after a year of standard therapy;
•   The proportion of patients in the experimental group as compared to the control group with an improved psychological status;
•   The proportion of patients in the experimental group as compared to the control group with improved quality of life.

Figure 8: A summary of methods used in Study 4

6.2. Results

Overall, 25 IBD patients qualified to participate in this sub-study by meeting the HADS criteria for caseness for either anxiety or depression. Thirteen patients were allocated to the experimental/disclosure group and 12 to the control/non-disclosure group (for detailed description of Methods see Chapter 2). One participant in the control group was withdrawn from the study in the middle of the trial as she was no longer contactable. At 12 months, 24 participants were evaluable, 13 in the disclosure group and 11 in the control group.

6.2.1. Baseline characteristics of the experimental/disclosure and the control group

A greater number of patients allocated to the experimental/disclosure group had CD whilst more patients in the control group had UC (see Table 57). However, this difference between the groups was not statistically significant (p=0.073).

Table 57: Number of CD and UC participants in the experimental/disclosure and the control group at baseline

Group	Experimental/Disclosure	Control
Number of participants/percent	N (%)	N (%)
CD	9 (69)	4 (33)
UC	4 (31)	8 (67)
Total	13 (100)	12 (100)

$\chi^2(1)$=3.22, p=0.073

There were numerically more female participants in each group, with ten (77%) females in the experimental/disclosure and seven (58%) females in the control group (see Table 58). However, this difference between the groups was again not statistically significant (p=0.319). Groups did not differ on the education variable, either (p=0.244).

173

Table 58: Sex and education frequencies in the experimental/disclosure and the control group at baseline

Variables		Experimental/Disclosure	Control
		N (%)	
Sex[1]	Male	3 (23)	5 (42)
	Female	10 (77)	7 (58)
Education[2]	Primary	1 (8)	1 (8)
	Secondary	8 (61)	4 (33)
	Trade/TAFE	3 (23)	2 (17)
	Tertiary	1 (8)	5 (42)

[1] $\chi^2(1)=0.991$, p=0.319
[2] $\chi^2(3)=4.167$, p=0.244

The mean age, years since diagnosis and years with symptoms were almost equal in each group (see Table 59). Although the control group was slightly younger than the experimental/disclosure group and the time since diagnosis in this group was slightly longer than in the experimental/disclosure group, neither of these differences were statistically significant (p>0.05).

Table 59: Age, years since diagnosis, years with symptoms at baseline in the experimental/disclosure and the control group

Variables	Experimental/Disclosure group Mean (SD)	Control group Mean (SD)	t (df)	p
Age $n_{Exp}= 13$ $n_{Contr}= 12$	47.69 (13.99)	45.75 (15.32)	0.331(23)	0.743
Years since diagnosis $n_{Exp}= 13$ $n_{Contr}= 12$	13.58 (8.77)	14.38 (9.95)	-0.211(23)	0.835
Years with symptoms $n_{Exp}= 11$[1] $n_{Contr}= 12$	14.92 (9.59)	14.42 (11.29)	0.114(21)	0.910

[1] One participant did not report the number of years with symptoms

Sixty-nine percent of participants in the experimental/disclosure group were in remission compared to 42% in the control group (see Table 60). However, the Chi^2 test revealed that the groups did not significantly differ in their disease activity (p=0.165).

Table 60: Disease activity in the experimental/disclosure and the control group at baseline

	Experimental/Disclosure group (n = 13)	Control group (n = 12)
	N (%)	
Active disease	4 (31)	7 (58)
Not active disease	9 (69)	5 (42)

$\chi^2(1)$=1.92, p=0.165

Comparisons in prevalence of anxiety and depression between the experimental/disclosure and the control group at baseline

Importantly, patients eligible to participate in this trial could either fulfil depression or anxiety criterion and thus, some people might have normal ranges of anxiety while meeting the HADS criterion for depression.

The distribution of severity of anxiety measured by the HADS was similar in both groups (Fisher's Exact Test p=0.110). Most participants had either a mild (8 – 10 points) or a moderate (11-14 points) level of anxiety (see Figure 9). No participants in either group were estimated to have severe (15-21 points) anxiety. The majority of participants (8 participants - 61%) in the experimental/disclosure group had moderate anxiety compared with 3 participants (25%) in the control group. The majority of participants in the control group were observed to have mild anxiety (8 participants - 67%).
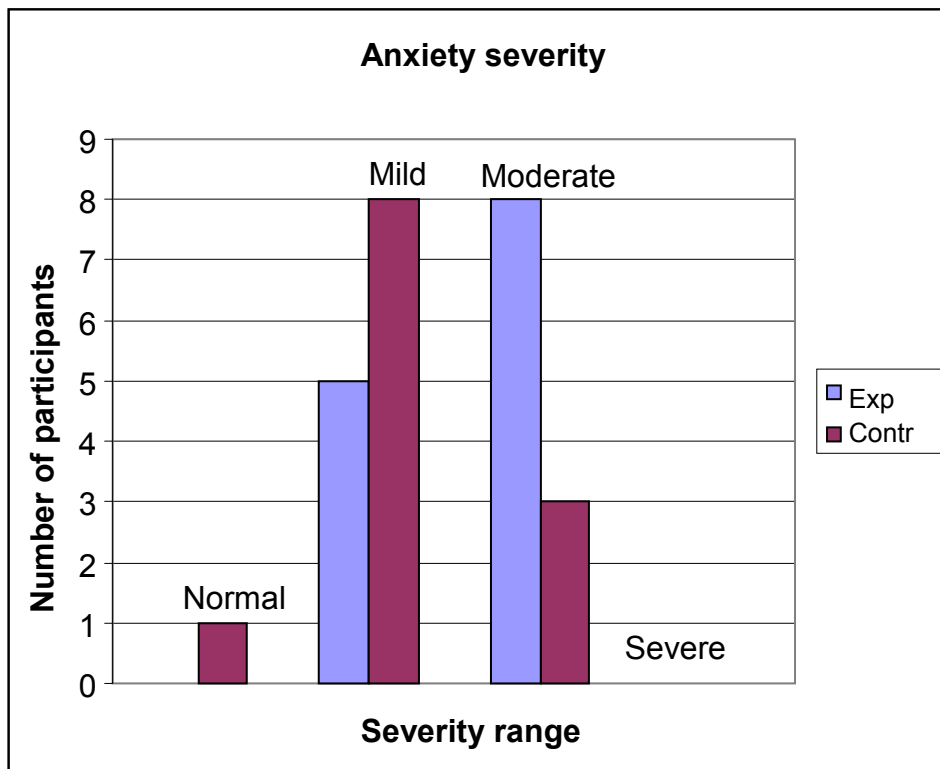
Figure 9: HADS Anxiety severity distribution in the experimental/disclosure group and the control group

The distribution of severity of depression was similar in both groups (Fisher's Exact Test p=0.242). The majority of participants' score was within a normal range (0-7 points) irrespective of which group they were allocated to. However, the severity of depression in those participants who were depressed did differ between the groups. Those in the control group were mildly depressed, whilst those in the experimental/disclosure group were either moderately or mildly depressed. Twenty-three percent of the experimental/disclosure group (3 participants) were moderately depressed compared with none in the control group. One participant (out of 13) in the experimental/disclosure group was mildly depressed compared with three (out of 12) in the control group.

Comparisons of baseline means on the HADS, the SF-12 and the SCL90 subscales between the experimental/disclosure and the control group

The groups did not differ significantly in the mean scores for anxiety and depression nor did they differ in quality of life (p>0.05) (see Table 61). However, the differences in the HADS Anxiety variable were close to significant (p=0.056). Similarly, there was no significant difference between the groups on any of the SCL90 subscales.

Table 61: Comparisons between the experimental/disclosure and the control group on the HADS, the SF-12 and the SCL90 subscales

Variables	Experimental/ Disclosure group (n=13) Mean (SD)	Control group (n=12) Mean (SD)	t(df)	p
HADS Anxiety	10.85 (1.72)	9.25 (2.22)	2.016 (23)	0.056
HADS Depression	6.38 (4.03)	5.50 (1.93)	0.690 (23)	0.497
SF-12 Mental component	39.34 (10.25)	42.97 (9.14)	-0.930 (23)	0.362
SF-12 Physical component	46.37 (11.17)	45.64 (7.98)	0.188 (23)	0.852
Somatisation	59.38 (11.10)	58.50 (7.26)	0.233 (23)	0.817
Obsessive-Compulsive	61.77 (7.36)	58.67 (9.37)	0.924 (23)	0.365
Interpersonal Sensitivity	59.62 (9.67)	63.50 (11.41)	-0.920 (23)	0.367
Depression	63.23 (7.68)	65.33 (8.94)	-0.632 (23)	0.534
Anxiety	60.92 (6.13)	56.50 (7.58)	1.609 (23)	0.121
Hostility	60.38 (10.26)	59.33 (8.50)	0.278 (23)	0.784
Phobic Anxiety	57.38 (9.24)	53.42 (9.12)	1.079 (23)	0.292
Paranoid Ideation	53.15 (8.67)	56.33 (13.56)	-0.704 (23)	0.488
Psychoticism	56.08 (7.92)	59.17 (11.37)	-0.793 (23)	0.436
GSI	63 (7.17)	61.25 (8.24)	0.567 (23)	0.576
PST	62.08 (7.05)	62.25 (7)	-0.061 (23)	0.952
PSDI	59 (6.80)	57.83 (8.26)	0.387 (23)	0.703

6.2.2. The experimental/disclosure and control groups differences over time on psychological variables and disease activity

As detailed above, the experimental/disclosure and controls group did not significantly differ in any demographic characteristics at baseline. Moreover, the groups did not differ on any of the HADS, the SF-12 and the SCL90 subscales, nor did they differ in disease

severity or in the severity of anxiety and depression over time. The repeated measure ANOVA revealed that the mean score for anxiety significantly dropped in both groups over the study period (p=0.0097) (Table 62). Figure 10 illustrates the trend of change in both groups.

Table 62: Mean comparisons between the five time points of the trial for all the participants

Variables	F (df)	Effect size	Power
HADS Anxiety	3.56(88)*	0.139	0.852
HADS Depression	1.49(88)	0.064	0.446
SF-12 Mental component	0.64(88)	0.028	0.203
SF-12 Physical component	0.68(88)	0.030	0.214
Somatisation	3.90(22)	0.151	0.471
Obsessive-Compulsive	3.11(22)	0.124	0.393
Interpersonal Sensitivity	0.33(22)	0.015	0.085
Depression	0.00(22)	0.000	0.050
Anxiety	0.61(22)	0.027	0.116
Hostility	0.05(22)	0.002	0.055
Phobic Anxiety	0.91(22)	0.040	0.149
Paranoid Ideation	0.12(22)	0.005	0.063
Psychoticism	0.02(22)	0.001	0.053
GSI	0.67(22)	0.030	0.123
PST	0.00(22)	0.000	0.050
PSDI	0.04(22)	0.002	0.054

* p<0.05
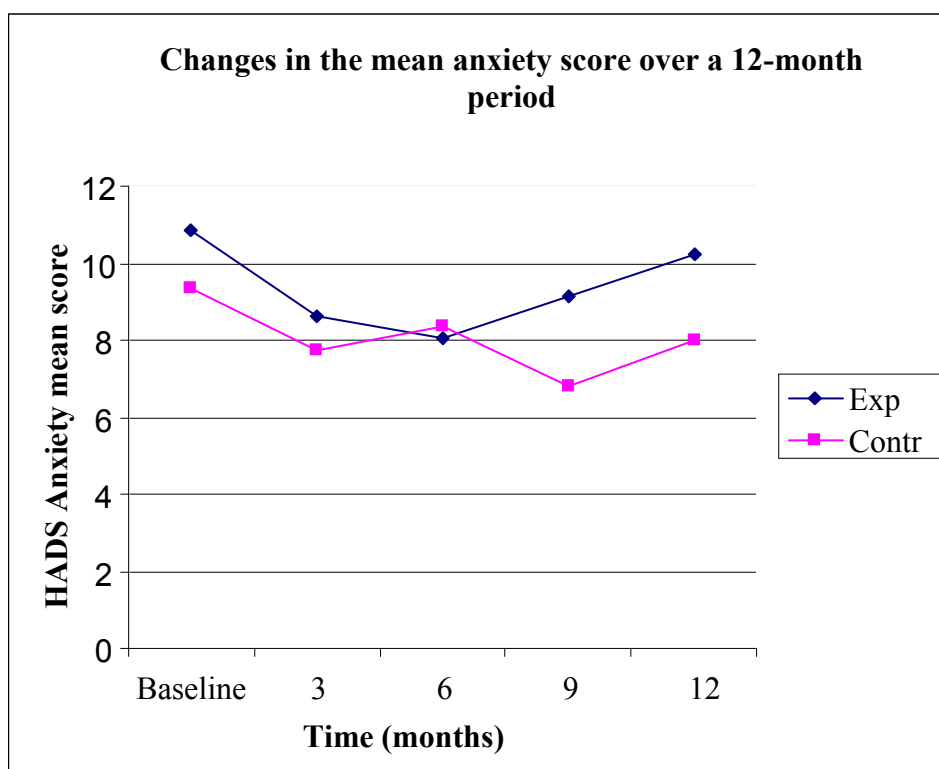
Figure 10: Changes in the mean anxiety score over a trial period (measured each three months for a period of 12 months) in the experimental/disclosure and the control group

The Holm's post hoc tests revealed three significant differences in the HADS Anxiety variable related to particular stages (see Table 63).

Table 63: Comparisons of HADS Anxiety mean changes over time adjusted with the Holm's adjustment for multiple comparisons

Assessment times	F (df)	p
baseline vs. 3 months	8.41 (88)	0.042*
baseline vs. 6 months	7.99 (88)	0.046*
baseline vs. 9 months	10.10 (88)	0.020*
baseline vs. 12 months	2.20 (88)	0.848
3 months vs. 6 months	0.01 (88)	1
3 months vs. 9 months	0.08 (88)	1
3 months vs. 12 months	2 (88)	0.848
6 months vs. 9 months	0.12 (88)	1
6 months vs. 12 months	1.80 (88)	0.848
9 months vs. 12 months	2.87 (88)	0.657

Specifically, in both groups, the level of anxiety dropped significantly between the baseline and three months (p=0.042), the baseline and six months (p=0.046) and between the baseline and nine months (p=0.020). However, the effect size of this difference was small[1], although with a good power level of 0.85 (see Table 62).

The largest effect sizes in the differences between the stages were observed on the SCL90 Somatisation variable (0.151), the HADS Anxiety variable (0.139) and the SCL90 Obsessive-Compulsive variable (0.124) (Table 62). However, all of these can be regarded as small. With respect to the power[2], only the effect size for the HADS Anxiety variable differences achieved the 0.80 level.

The effect sizes for the differences between the experimental/disclosure and the control group were less than 0.1 and the power was also found to be small (see Table 64). Therefore, due to this small power, it is impossible to estimate whether groups significantly differ on any other subscale over time, in relation to the participation in a particular trial group or in the interaction between them.

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[1] Typically, in social sciences, the effect size of 0.1-0.2 is considered small, 0.3-0.4 is considered medium and 0.5 and over is considered large (Cohen, 1988).

[2] Typically, power of at least 0.8 is considered adequate to detect a meaningful difference (Cohen, 1988).

Table 64: Mean comparisons between the experimental/disclosure (n=13) and the control group (n=11)

Variables	F (df)	Effect size	Power
HADS Anxiety	0.99(22)	0.043	0.158
HADS Depression	0.80(22)	0.035	0.137
SF-12 Mental component	1.62(22)	0.069	0.230
SF-12 Physical component	0.62(22)	0.027	0.117
Somatisation	0.15(22)	0.007	0.066
Obsessive-Compulsive	0.86(22)	0.037	0.144
Interpersonal Sensitivity	0.67(22)	0.029	0.122
Depression	0.14(22)	0.006	0.065
Anxiety	0.73(22)	0.032	0.130
Hostility	0.04(22)	0.002	0.054
Phobic Anxiety	1.02(22)	0.044	0.161
Paranoid Ideation	0.36(22)	0.016	0.089
Psychoticism	0.16(22)	0.007	0.067
GSI	0.18(22)	0.008	0.069
PST	0.01(22)	0.000	0.051
PSDI	0.07(22)	0.003	0.057

The effect sizes of the differences in interaction between the stages of the trial and the experimental/control group allocation were also very small (see Table 65). The largest effect size observed in this analysis was found in the SCL90 Psychoticism variable (0.117), yet the power was only 0.37. With such a small power in most of the effects, the small sample size may not allow detection of significant differences on most of the subscales over time, in relation to the participation in a particular trial group and the interaction between them. In addition, low levels of power in interactions between the trial allocation and temporal changes (Table 65) and no information on whether the differences between the groups over time were significant, means that it is impossible to say whether the intervention examined in this trial was effective.

Table 65: Mean comparisons between the time points of the trial and the experimental/control group interactions

Variables	F (df)	Effect size	Power
HADS Anxiety	1.31(88)	0.056	0.393
HADS Depression	0.69(88)	0.030	0.215
SF-12 Mental component	0.76(88)	0.033	0.234
SF-12 Physical component	1.18(88)	0.051	0.355
Somatisation	0.25(22)	0.011	0.076
Obsessive-Compulsive	0.06(22)	0.003	0.056
Interpersonal Sensitivity	2.27(22)	0.094	0.303
Depression	1.83(22)	0.077	0.253
Anxiety	0.20(22)	0.009	0.071
Hostility	0.01(22)	0.000	0.051
Phobic Anxiety	0.08(22)	0.003	0.058
Paranoid Ideation	0.85(22)	0.037	0.143
Psychoticism	2.93(22)	0.117	0.373
GSI	0.17(22)	0.008	0.068
PST	1.02(22)	0.044	0.162
PSDI	0.06(22)	0.003	0.056

With respect to the planned comparisons within the particular group analysis, no statistically significant difference on any of the subscales was detected (Table 66).

Table 66: Planned comparisons within particular group between the baseline and 12 months

Variables	Experimental group Mean difference (SE)	Experimental group t (df)	Control group Mean difference (SE)	Control group t (df)
HADS Anxiety	0.61 (0.90)	0.68(88)	1.36(0.98)	1.39(88)
HADS Depression	-0.46 (0.74)	-0.62(88)	0.63(0.81)	0.78(88)
SF-12 Mental component	2.52 (2.86)	0.88(88)	-2.15(3.11)	-0.69(88)
SF-12 Physical component	4.59 (2.57)	1.78(88)	-1.31(2.80)	-0.47(88)
Somatisation	-5.76 (3.16)	-1.82(22)	-3.45(3.43)	-1(22)
Obsessive-Compulsive	-3.69 (2.49)	-1.48(33)	-2.81(2.71)	-1.04(22)
Interpersonal Sensitivity	-3.23 (2.10)	-1.54(22)	1.45(2.28)	0.64(22)
Depression	-2 (2.04)	-0.98(22)	2.09 (2.22)	0.94 (22)
Anxiety	2 (2.20)	0.91(22)	0.54(2.39)	0.23(22)
Hostility	-0.53 (2.42)	-0.22(22)	-0.27(2.63)	-0.10(22)
Phobic Anxiety	1.15 (2.30)	0.50(22)	2.09(2.50)	0.83(22)
Paranoid Ideation	-3 (3.20)	-0.93(22)	1.36(3.48)	0.39(22)
Psychoticism	-3.38 (2.45)	-1.38(22)	2.81(2.66)	1.06(22)
GSI	-1.92 (2.11)	-0.91(22)	-0.63(2.29)	-0.28(22)
PST	-1 (1.40)	-0.71(22)	1.09(1.52)	0.72(22)
PSDI	-0.07 (2.19)	-0.04(22)	0.72(2.38)	0.30(22)

* $p<0.05$

Prevalence of anxiety over time

During the 12-month period, 69% of the experimental/disclosure group participants showed anxiety on either four or five occasions (Table 67). In the control group, 37% of participants met the anxiety criterion for caseness at one time only and another 36% on two or three assessments. However, the Gamma statistics showed that groups did not significantly differ in their total number of positive scores for anxiety (G=-0.358, p=0.226).

Table 67: A total number of positive scores for anxiety in the experimental/disclosure (n=13) and the control group (n=11)

Positive scores	Experimental group n (%)	Control group n (%)	Total n (%)
1	4 (31)	4 (37)	8 (34)
2	0 (0)	2 (18)	2 (8)
3	0 (0)	2 (18)	2 (8)
4	2 (15)	0 (0)	2 (8)
5	7 (54)	3 (27)	10 (42)

G=-0.358, p=0.226

When the number of patients who rated positive for anxiety was compared for each follow-up point, groups significantly differed at 12 months (Table 68). The experimental/disclosure group had a significantly higher anxiety positivity rate than the control group ($\chi^2(1)=4.19$, p=0.041). Groups did not significantly differ at baseline (Fisher's Exact Test p=0.357), after 3 months (Fisher's Exact Test p=0.630), 6 months (Fisher's Exact Test p=0.408) or 9 months ($\chi^2(1)=0.001$, p=0.973).

Table 68: Prevalence of anxiety in experimental/disclosure (exp) and control (cont) groups

	Baseline		at 3 months		at 6 months		at 9 months		at 12 months	
	Exp	Cont	Exp	Cont	Exp	Cont	Exp	Cont	Exp	Cont
Anxious	11	7	11	8	9	5	7	6	9*	3
N/anxious	2	4	2	3	4	6	6	5	4*	8

*p<0.05 (experimental versus control group)

Prevalence of depression over time

During the 12-month period, 38% of the experimental/disclosure group participants were not diagnosed with depression and 23% were observed to fulfil the depression criterion for caseness once only (Table 69). Another 23% fulfilled this criterion on five occasions. In the control group, the majority of participants (64%) did not fulfil the depression criterion

for caseness on any occasion. Groups did not significantly differ in their total number of positive scores for depression (G=-0.386, p=0.192).

Table 69: A total number of positive scores for depression in the experimental/disclosure (n=13) and the control group (n=11)

Positive scores	Experimental group n (%)	Control group n (%)	Total n (%)
0	5 (38)	7 (64)	12 (50)
1	3 (23)	1 (9)	4 (17)
2	0 (0)	1 (9)	1 (4)
3	1 (8)	1 (9)	2 (8)
4	1 (8)	0 (0)	1 (4)
5	3 (23)	1 (9)	4 (17)

G=-0.386, p= 0.192

When the number of depressed patients was compared for each follow-up point, the Fisher's Exact Tests revealed no significant difference between the groups at any of the time-points (p>0.05) (Table 70).

Table 70: Prevalence of depression in experimental/disclosure (exp) and control (cont) groups

	Baseline		at 3 months		at 6 months		at 9 months		at 12 months	
	Exp	Cont	Exp	Cont	Exp	Cont	Exp	Cont	Exp	Cont
Relapse	3	3	7	2	5	1	6	3	4	2
Remission	10	8	6	9	8	10	7	8	9	9

IBD activity over time

During the 12-month period, 62% of the experimental/disclosure group participants were either in remission from their IBD or fulfilled criteria for active disease at one time only (Table 71). In the control group, 45% of participants were either in remission or had active disease at one time only while the remaining 55% had active disease at two, four or five

time-points. However, the Gamma statistics showed that groups did not significantly differ in their total number of occasions of active disease (G=0.239, p=0.412).

Table 71: A total number of positive scores for IBD activity in the experimental/disclosure (n=13) and the control group (n=11)

		Experimental group n (%)	Control group n (%)	Total n (%)
Relapses	0	4 (31)	3 (27)	7 (30)
	1	4 (31)	2 (18)	6 (25)
	2	1 (8)	1 (9)	2 (8)
	3	1 (8)	0 (0)	1 (4)
	4	1 (8)	1 (9)	2 (8)
	5	2 (14)	4 (37)	6 (25)

G=0.239, p=0.412

When the number of patients with active disease was compared for each follow-up time, the groups significantly differed at 3 months (Fisher's Exact Test p=0.033) (Table 72). The experimental/disclosure group had a significantly lower IBD activity rate than the control group. However, groups did not significantly differ at baseline ($\chi^2(1)=0.001$, p=0.973), after 6 months (Fisher's exact test p=0.390), after 9 months ($\chi^2(1)=0.734$, p=0.444) or after 12 months (Fisher's exact test p=0.697).

Table 72: IBD relapse/remission status of patients in experimental/disclosure (exp) and control (cont) groups

	Baseline		at 3 months		at 6 months		at 9 months		at 12 months	
	Exp	Cont	Exp	Cont	Exp	Cont	Exp	Cont	Exp	Cont
Relapse	6	5	2*	7	3	5	6	7	6	4
Remission	7	6	11*	4	10	6	7	4	7	7

*p<0.05 (experimental versus control group)

6.2.4. Qualitative analysis of patients' case-notes content

During this stage, the data collected from the case-notes were qualitatively summarised (see Chapter 2 for the detailed description of methods). Within this sample of IBD sufferers, there were six doctors' interventions concerning psychological issues during the 12-month period of the trial. The interventions took place with five patients (38%) from the experimental/disclosure group and with one (9%) in the control group. The difference between the groups, however, was not statistically significant (Fisher's Exact Test p=0.166). The interventions included: advice about seeing a psychiatrist; advice about talking with a patient's GP about treatment with antidepressants; talking and counselling about stress; discussing the HADS results sent to the doctor by the author; talking about anxiety; and prescribing an antidepressant. Antidepressants were prescribed in three patients with good effects reported for sleep, mood disorders and general wellbeing. Antidepressants included doxepin (50mg) and mirtazapine (45mg). In one patient the exact name of the antidepressant was not recorded.

Hypothesis 5 testing

Hypothesis 5, that doctors' knowledge of patients' psychological status alters doctors' behaviour and/or improves patients' clinical outcomes, was therefore not proven. Due to the small power, it was impossible to estimate whether groups significantly differed on any subscale over time. There was no statistical difference between the groups in a total number of positive scores for IBD activity or total prevalence of anxiety and depression. Although five doctors (38%) in the experimental group changed their behaviour and initiated some psychological treatment with their patients compared to only one doctor (9%) in the control group, this difference was not statistically significant. On the other hand, after 12 months, the experimental group had higher prevalence of anxiety than the

control group and, after 3 months, the experimental group had a lower total number of positive scores for IBD activity than the control group. It may be argued, therefore, that the trial improved the experimental/disclosure group's physical outcomes in one instance. However, it may have worsened the propensity to be anxious in this group in one instance.

Summary of most significant findings

The experimental/disclosure and the control groups did not differ either in their baseline demographic characteristics or in their means on any of the scales (p>0.05). However, in both groups, the level of anxiety dropped significantly between baseline and three months (p=0.042), baseline and six months (p=0.046) and between baseline and nine months (p=0.020). The effect size of these differences, however, was small with 85% power to detect the difference. The small power did not allow detection of significant differences on most of the subscales over time in relation to participation in a particular trial group or the interaction between them. Groups did not differ in the total number of positive scores for anxiety (p=0.226) or depression (p=0.192) nor in the total number of positive scores for IBD activity (p=0.412). Finally, the qualitative analysis showed that five doctors in the experimental/disclosure group changed their behaviour and initiated psychological treatment with their patients compared with only one doctor in the control group. This difference, however, was not statistically significant (p=0.166).

6.3. Discussion

Randomised controlled trials examining the effectiveness of psychological interventions in IBD are still a rarity despite the fact that patients with IBD are highly anxious (as evidenced by results of Study 1 presented in Chapter 3). Interestingly, psychotherapy has been found to be ineffective in these patients in a recent literature review (von Wietersheim

& Kessler, 2006). Other psychological approaches should, therefore, be examined in order to improve patients' wellbeing. The impact of the treating doctor's knowledge of patients' psychological status on clinical outcomes in IBD has not been previously examined. Thus, this pilot research was undertaken to observe whether improving doctors' knowledge of their patients' psychological status would be acceptable and might improve these patients' outcomes.

The results clearly show that larger samples are needed to detect a difference in this regard. In particular, low levels of power in interactions between the trial allocation and temporal changes and no information on whether the differences between the groups over time were significant, meant that it is impossible to say whether the intervention examined in this trial was effective. However, the data do not rule out this intervention's efficacy and, consequently, further studies are recommended. Moreover, the non-significant difference of five (38%) psychological interventions in the disclosure group versus only one (9%) in the control group, suggests that this sort of approach may at least prompt doctors to act when psychological co-morbidities are identified. This action in turn has the potential to improve outcomes if this intervention itself is effective.

According to the interview study conducted with South Australian gastroenterologists (see Chapter 9), these specialists do not feel adequately trained to be primarily responsible for treatment of psychological problems of their patients. GPs, on the other hand, may think patients who are under gastroenterologist's care do not require as much of their attention. This situation may mean that patients with IBD are not commonly treated for their psychological problems. Campaigns informing GPs of the unrecognised needs of patients with IBD are thus needed. This study aimed to observe if making gastroenterologists aware of their IBD patients' psychological problems changed doctors' behaviour or patients'

outcomes. While the fact that five doctors in the experimental group initiated some treatment for their patients was not statistically significant, it is possible this change might be shown to be significant if the sample size was larger. This study was limited to those IBD participants who met the HADS anxiety or depression criterion for caseness and only 25 people out of 64 enrolled participants fulfilled the criteria. Clearly, larger prospective studies examining the impact of doctors' knowledge of patients' psychological problems on these patients' medical outcomes are needed to answer this question definitively.

The prevalence of anxiety and depression in patients with IBD may vary significantly depending on the setting and patients' demographics as well as their disease activity. Rates between 30-80 % are quoted as representative for IBD (Addolorato et al., 1997; Andrews et al., 1987; Guthrie et al., 2002; Mittermaier et al., 2004). In planning this study it was assumed that during relapses, 60% of patients with IBD suffer from psychological problems (Addolorato et al., 1997) and during remission, about 30% of patients with IBD suffer from psychological problems (Mittermaier et al., 2004). Patients visiting the RAH outpatient clinic were thought to be mainly in relapse. Thus, the assumption was made that at least about 60% would have psychological problems and the sample of patients with psychological problems was therefore expected to be between 30 and 65 patients based on the power calculation conducted for Study 3 (see section 2.5 in Chapter 2) with half randomly disclosed to the physician. In the cohort of IBD clinic outpatients, the prevalence of anxiety was later estimated at 37% and depression at 11% (see Chapter 3), both of which are substantially lower than usually reported. This may be because the majority of clinic patients were in remission (64% participants with inactive disease) and thus visiting doctors for a check-up or prescription only, or because of better local mental health care. Clearly, the prevalence estimates taken from other studies for the sample size calculation (Addolorato et al., 1997; Mittermaier et al., 2004) were not relevant to this South

Australian IBD group. Therefore, not surprisingly, the final sample was smaller than predicted and was clearly not enough to detect a significant difference. Ideally, investigators should not rely on data from other studies while doing power calculations but, rather, should have locally robust data on the prevalence of psychological co-morbidity to design an adequately powered study.

An interesting result of this study was that levels of anxiety in both groups significantly dropped over time up to nine months. As this was true for both groups, it can be suggested that mere participation in the trial and regular contact with the researcher reduced participants' anxiety. However, in the last three months of the trial the anxiety rate increased coming back to the level only slightly lower than that at the starting point. Consequently, this may indicate that even simple psychological interventions may improve patients' wellbeing. However, these interventions are not a long-term therapeutic solution and they should not replace a psychological therapy. Alternatively, this phenomenon can also be explained by the natural course of anxiety which periodically comes and goes (as described in the Preamble), sometimes in relation to disease activity and thus, this intervention could have no effect. Again, however, the results of this trial had only a small effect size. It is therefore strongly recommended to conduct similar trials on larger samples to observe whether similar tendencies can be identified.

Finally, consistent with findings presented in the next chapters, the qualitative analysis of patients' case notes showed that those three patients who received treatment with antidepressants appeared to benefit from this treatment. Specifically, doctors observed a positive effect on sleep, mood disorders and general wellbeing in patients who were given antidepressants. Similarly to other available studies on the use of antidepressants in IBD (see Chapter 8), these findings come from case observations and, as such, cannot be

generalised for the whole IBD population until confirmed by larger controlled trials. However, it has long been established that paper records may in general be inaccurate and of low quality (Mansfield, 1986). Thus, it is likely that case notes may have underreported information relevant to this research. It is evident that larger studies are needed as antidepressants may offer a yet unexplored pathway to management of IBD. This concept will be now more systematically explored in the second part of the thesis. The next chapter will present methods used in the final two studies of the thesis.

PART II: Antidepressants and the course of inflammatory

bowel disease

Chapter 7: Research methods used in Part II of the thesis

This chapter reports on methodology used in Part II of the thesis. It details the aims and objectives applied in Studies 5 and 6. It also discusses details of sampling, inclusion and exclusion criteria, measurements, outcome measures and further information regarding the methodology applied in the two studies. It concludes with the ethical considerations involved in Study 5 and the plan of analysis.

7.1. Aims and objectives

Part II of the thesis comprises two studies aiming to understand the current role of antidepressants in inflammatory bowel disease. Study 5 (Chapter 8) involved a systematic review of literature. It was designed to quantitatively and qualitatively explore the efficacy of antidepressants in IBD. However, because of the lack of reliable statistical data, it was only possible to undertake a qualitative analysis.

The aim of this study was:

- To discover whether the literature supports the efficacy of antidepressants in IBD.

Its objective was:

- To gather, organise and evaluate the current knowledge about the use of antidepressants in inflammatory bowel disease.

Study 6 (Chapter 9) involved standardised semi-structured interviews. This approach enabled in-depth exploration of specialists' experiences, opinions and attitudes about treating IBD patients with antidepressants. It also provided insight into whether doctors' attitudes towards the use of antidepressants influences their practice. Content analysis was

performed on the collected data, and the results added to knowledge about physicians' views on treatment and their understanding of psychological problems in IBD as well as their attitutes towards future randomised controlled trials.

The aim of this study was:

- To examine the attitudes of specialists (gastroenterologists) towards the use of antidepressants in patients with IBD.

Its objectives were:

- To collect specialists' opinions on their IBD patients taking antidepressants;

- To identify specialists' experiences with the use of antidepressants in patients with IBD;

- To discover what specialists'opinions are about a potential of randomised controled trial in this area.

7.2. Methodology used in Study 5

7.2.1 Inclusion and exclusion criteria

It is a common practice to include only controlled studies in systematic reviews (Alderson, Green, & Higgins, 2005). In this case, however, it was not possible due to the lack of such studies in the area of interest. All forms of research publications, describing any study design published between 1990 and 2005, which examined the use of antidepressants in inflammatory bowel disease, were therefore included in this review. Participants had to have a diagnosis of inflammatory bowel disease (either Crohn's disease or ulcerative colitis or not specified inflammatory disorder). Studies published before 1990 were not included, as the author was mostly interested in the newest antidepressants, introduced to the market in the 1990s. The author chose to focus on newer antidepressants only as some

studies indicated they may have potential to reduce inflammation (Varghese et al., 2006). All forms of research publications not related to the use of antidepressants in IBD or related to the use of antidepressants in IBD but published before 1990 were excluded from the analysis.

7.2.2. Design

Study 5 involved a systematic review of existing literature regarding the use of antidepressants in IBD. Its goal was to collect data from all types of accessible studies and investigate whether further research in this area are indicated.

7.2.3. Procedure

Data source

PubMed, CINAHL, Cochrane (Cochrane Depression, Anxiety and Neurosis Group and the Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders group), PsycInfo, and Embase databases were searched during July 2005 - September 2005 for any studies published between 1990 and 2005 in which antidepressants were used in inflammatory bowel disease patients. Follow-up searches were conducted in October and November 2005 to identify more recently published papers. Hand searches of the following journals: *Gastroenterology*, *Current Treatment Options in Gastroenterology*, *Psychosomatic Medicine*, and *General Hospital Psychiatry* were also conducted in September – November 2005.

The search terms used were: Inflammatory Bowel Diseases OR Inflammatory Bowel Disease OR Colitis, Ulcerative OR Ulcerative Colitis OR Crohn Disease OR Crohn*

Disease OR Granulomatous Colitis OR Granulomatous Enteritis OR regional Ileitis OR terminal Ileitis OR Ileocolitis OR ibd AND Antidepressive Agents OR antidepress* OR Thymoanaleptics OR Thymoleptics OR ssri OR mirtazapine OR bupropion OR paroxetine OR selective serotonin reuptake inhibitor* OR selective norepinephrine serotonin reuptake inhibitor*. There was no language restriction as the author is fluent in English, Polish and French. Articles in German and Spanish were translated by one of the supervisors and colleagues of the author. Searches for additional studies in the reference lists of identified articles as well as searches for unpublished theses stored at the University of Adelaide and in the whole of Australia through the National Library of Australia were also performed. Additionally, selected experts (18 South Australian gastroenterologists) were contacted.

Data Extraction

The systematic review identified no randomised controlled trials, cohort prospective studies or case-controlled studies. Nevertheless, an open-label study, case reports, reviews, a guideline, a discussion, and a letter were located. The quality of the selected studies was assessed using the *Cochrane Reviewers' Handbook* (Alderson et al., 2005). However, because all the identified studies were non-randomised the appendix to this manual prepared by the Cochrane Non-Randomised Studies Methods Group was also used (Olsen, 2002). The standard components of the quality assessment are: sample size, allocation concealment, clear description of treatment, representative source of subjects, use of diagnostic criteria or inclusion criteria, outcome measures described and the use of validated instruments. The Cochrane Non-Randomised Studies Methods Group has not specified the components of the quality assessment for non-randomised trials as yet. The author's own criteria therefore needed to be created. As this systematic review identified mainly case reports, reviews and one open-label study, in assessing their quality length of treatment, follow-up, clear description of a treatment, description of participants, and the

use of validated instruments were taken into account. The author is aware of these studies' various limitations. However, because no other published data exist in this field it is important to sum up the up-to-date literature as it may inform and facilitate future randomised trials in this area.

Data Synthesis

As statistical data were accessible only for one study, and even then were limited, conducting a meta-analysis was not possible.

7.2.4. Primary outcome measure

The primary outcome measure was the efficacy of antidepressants in maintaining or inducing remission of inflammatory bowel disease. Remission was defined as at least a 4-week period with disease activity at less than 150 points or a drop in a score of at least 70 points for Crohn's disease and a score < 2 points or a drop in a score of at least 3 points for ulcerative colitis, measured on the Crohn's Disease Activity Index and the Simple Clinical Colitis Activity Index, respectively OR at least a 4-week period with a complete lack of IBD symptoms (Best et al., 1976; Walmsley et al., 1998). Therefore, the effectiveness of treatment with antidepressants in patients with IBD was defined as the remission of the disease activity beyond the usual length of remission (different for a particular patient).

7.3. Methodology used in Study 6

7.3.1. Participants and sample

The study used purposive sampling where participants were selected based on their potential to provide data relevant to the research questions (Sarantakos, 1998). All

participants were board-recognised gastroenterologists with more than 5 years of professional experience as a specialist working in two major South Australian hospitals. None had training in psychiatry that exceeded the usual requirement for medical training. Interviews were conducted until the interviewer was satisfied that data saturation occurred.

7.3.2. Inclusion, exclusion and withdrawal criteria

Gastroenterologists who worked at the Royal Adelaide and Queen Elizabeth Hospitals at the time of recruitment, who responded to the invitation letter and gave informed consent, were included into the study. Those who were on leave and/or were not contactable as well as those involved in this study as supervisors were excluded from the study. Gastroenterologists were given the opportunity to withdraw from the study at any time.

7.3.3. Design

Semi-structured interviews were conducted with gastroenterologists. This approach enabled in-depth exploration of specialists' experiences, opinions and attitudes about treating IBD patients with antidepressants.

7.3.4. Procedure and measurement

Data for this exploratory study were collected in October and November 2005 in two major South Australian metropolitan teaching hospitals, the Royal Adelaide Hospital (RAH) and the Queen Elizabeth Hospital (QEH). The author advertised the study during research meetings at the Department of Gastroenterology and Hepatology, at the RAH in September 2005 and at the Department of Gastroenterology and Hepatology, at the QEH in October 2005. Interested gastroenterologists gave the author their contact details. The author

subsequently contacted these gastroenterologists by phone or email to set up a time and a venue for the interview. Sixteen participants were interviewed at their hospital offices, one participant was interviewed at his office at the University of Adelaide, and one participant wished to be interviewed at the researcher's office at the Discipline of General Practice, University of Adelaide. At the start of the interview all the participants were asked to read the study information sheet (see Appendix 12) and sign a written consent (see Appendix 13).

The author undertook digitally-recorded, standardised semi-structured interviews with the gastroenterologists using 12 open-ended questions (see Appendix 14). The interviewer clarified questions when needed and probed participants' views further when required. Demographic data were collected at the end of each interview. The interviews lasted up to half an hour with a median of 10 minutes. The recorded interviews were transcribed verbatim by the author (for transcripts of interviews see Appendix 15). The draft of each interview was subsequently read and checked against the recordings by a research assistant; no major areas of disagreement arose. Responses to each question were then collected and summarised by the author and where it was appropriate to do so, the author enumerated the responses. Finally, the general organisation of data and their interpretation was confirmed with a researcher experienced in qualitative research.

7.3.5. Variables of interest

The variables of interest included doctors' attituted towards and experiences with using antidepressants in IBD patients as well as their attitutes towards future randomised controlled trial in this area.

7.3.6. Ethical considerations

Ethics Committee approval

Ethical approval for conducting Study 6 was obtained from the Royal Adelaide Hospital Research Ethics Committee. The notification was sent to the University of Adelaide Human Ethics Committee.

Informed consent

Potential participants were informed that their participation in the study was voluntary and their confidentiality was assured. Participants were informed they could withdraw from the study at any time without any consequences.

Potential risk for participants

No risk for participants was identified.

Confidentiality and anonymity

All the information obtained in the study was treated as confidential. Reporting of results consisted only of aggregated data. Transcripts of interviews do not include any identifying data.

Data storage

In light of the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines, all data were identified by participant number only, thereby ensuring that identities were not disclosed ("ICH Topic E6 (R1) Guideline for Good Clinical

Practice," 2002). The only place where the participant's name appeared was on the consent form which was kept in a secure locked storage room in the Discipline of General Practice.

Reporting of results

Study results were reported as de-identified data. No confidential data were revealed. Study results were analysed and submitted for publication in peer reviewed journals.

7.3.6. Analysis

Data were analysed using standard qualitative content analysis (Marks & Yardley, 2004; Sarantakos, 1998). The author identified the words and sentences relevant to the given question. Responses to questions were divided into mutually exclusive categories where possible and subsequently coded. Participants' responses were then summarised.

The next chapter reports on the results of Study 5, which aimed to discover whether the literature supports the efficacy of antidepressants in IBD.

Chapter 8: Antidepressants and inflammatory bowel disease: a systematic review (Study 5)

This chapter reports on findings of a systematic review of literature concerning the influence of treatment with antidepressants on inflammatory bowel disease course and activity. The results of all relevant studies are presented, summarised and discussed.

8.1. Introduction

As previously stated, inflammatory bowel disease is an incurable condition. There is ongoing research to find a curative treatment and understand the aetiology of IBD in immunology (Fort et al., 2005), microbiology (Macfarlane, Furrie, Kennedy, Cummings, & Macfarlane, 2005), molecular biology (Plevy, 2005) and food science (Jowett et al., 2004). IBD is incompletely understood (and treated) and an individual patient's responses to treatment are variable. Until globally effective treatment is found, there is a need to decrease the number of relapses of the disease, lengthen remission and improve quality of life and psychosocial functioning of patients.

As already demonstrated, the psychology of patients with IBD has been of great interest to many investigators (Addolorato et al., 1997; Andrews et al., 1987; Guthrie, 2004; Guthrie et al., 2002; Helzer et al., 1984; Levenstein et al., 2000; Porcelli, Zaka, Leoci, & Centonze, 1995; Robertson et al., 1989). However, as also noted earlier, when psychological treatment in the form of psychotherapy is provided most randomised controlled trials in patients with IBD have found it to be ineffective (Jantschek et al., 1998; Keller et al., 2004; Schwarz & Blanchard, 1991; von Wietersheim et al., 2001). Thus, some investigators have

proposed that treating psychological co-morbidities with antidepressants might be of more utility to control disease activity and lengthen remission, particularly in Crohn's disease patients (Kane, Altschuler, & Kast, 2003; Kast, 1998; Kast & Altschuler, 2001; E. A Walker et al., 1996). Thus far, a systematic analysis of available studies assessing the efficacy of antidepressant therapy for the control of somatic symptoms in patients with IBD has not been undertaken. Therefore, this study examined whether the existing literature supports a role for antidepressants in managing inflammatory bowel disease. For a detailed description of methods see Chapter 7.

8.2. Results

A total of 106 articles were identified from electronic databases, most of which were not directly related to the entered keywords. Only 12 publications met the inclusion criteria. During hand searches of journals and during searches of reference lists of identified articles and unpublished theses, no new articles matching the inclusion criteria were found. The contact with selected experts also failed to identify new papers.

In order of design quality, articles that met the inclusion criteria were: one non-randomised open-label trial, six case reports, three reviews, one guideline, one discussion paper, and one letter referring to previous studies. The total number of IBD patients described was 20; eight participants were described in the open-label study and 12 in case reports. Antidepressants described included: paroxetine, bupropion, amitriptyline, phenelzine and mirtazapine. Paroxetine was used in three studies in 12 participants. Bupropion was used in two studies in six participants, and was recommended for use in patients with IBD in two reviews, one discussion paper and one letter. Amitriptyline was used in one study with one participant. Phenelzine was used in one study in one participant. Mirtazapine was not recommended in one review (see Appendix 16).

8.2.1. Positive impact of antidepressants on inflammatory bowel disease activity

Five research studies indicated a positive impact of treatment with antidepressants on inflammatory bowel disease activity. Four out of these five studies were case reports. One study out of the five was an open-label trial. There were 16 patients treated with antidepressants in these five studies and all were reported to have benefited from this treatment. Of 16 patients treated with antidepressants, there were four females, two males, and in the remaining 10 cases sex was not specified. Seven patients suffered from Crohn's disease, one from ulcerative colitis, and eight from unspecified inflammatory bowel disorder; all patients were adults. Examined antidepressants were: paroxetine (two studies), bupropion (two studies), and phenelzine (one study).

Two reviews, one discussion paper, and one letter also endorsed a positive impact of treatment with antidepressants on inflammatory bowel disease activity, despite the lack of provision of any new patient data. In all four of these papers bupropion was recommended for use in inflammatory bowel disease patients.

8.2.2. Negative or no impact of antidepressants on inflammatory bowel disease activity

One study, a case report, suggested a potential negative impact of an antidepressant on inflammatory bowel disease. Three patients were described and the antidepressant used was paroxetine. Prior to prescribing paroxetine, these patients had not been diagnosed with inflammatory bowel disease. Following treatment with paroxetine for depression, patients developed chronic diarrhoea and were subsequently diagnosed with inflammatory bowel disease, Crohn's disease in two patients and non-specified inflammatory bowel disorder in

one patient. There was no control group in the study, however, and the significance of this observation seems unclear.

In one paper, mirtazapine was not recommended for use in inflammatory bowel disease (see: Discussion for explanation). Another case report found no impact of antidepressants on inflammatory bowel disease. One adult male participant was described and the antidepressant used was transdermal amitriptyline gel. Amitriptyline did not help the patient with pain nor fully treat the depression. However, the patient noticed his mood did improve.

8.2.3. Quality of studies

Five quality criteria for analysis were set and included length of treatment with antidepressant; follow-up; clear description of treatment; description of participants; and validated instruments (see Appendix 17). Five studies met all or four out of five of the quality criteria. One article met three out of five of the quality criteria. Six publications met only one out of five of the quality criteria. The study by Kast et al. (2001) met all the quality criteria selected for this systematic review. The next best study was by Walker et al. (1996). However, the weakness of this study lay in the fact that the authors did not specify IBD type and did not use a disease activity index. The study by Scott et al. (1999) also met a majority of the quality criteria, however, the researchers did not use a validated instrument to measure inflammatory bowel disease activity, and they focused only on pain and depression, as their intention was to treat these disorders, rather than to influence IBD activity. Eirund et al.'s (1998) study addressed four out of five quality criteria but the authors failed to use an inflammatory bowel disease activity index. The study by Kast (1998) also met four criteria out of five, but again, the researcher did not use a validated instrument to measure inflammatory bowel disease activity. Kane et al.'s (2003) study

addressed three out of five criteria. The researchers did not provide any information about length of treatment nor did they describe patients' characteristics and further follow-up. The non-experimental papers (Ginsburg & Bayless, 2005; Kast, 2003, 2005; Kast & Altschuler, 2004, 2005) and the study by Torras et al. (2003) did not meet the quality criteria. Moreover, although their recommendations were of interest and may help in understanding the issue, they added no new data.

8.3. Discussion

This systematic review is the first structured attempt to explore the hypothesis that the clinical course of IBD may be influenced by specifically treating psychological co-morbidities with antidepressants. Despite widespread acknowledgement that IBD is not a "6 week illness" (Lichtenstein, Hanauer, Kane, & Present, 2004), its psychological dimension has been largely ignored in standard treatment paradigms. Unfortunately, because of the paucity of published data – both quantitative and qualitative – this review is unable to provide a definitive answer on whether IBD can be improved by antidepressant therapy. However, it has highlighted a significant "evidence gap" in the literature, supporting the author's premise that psychological co-morbidities in patients with inflammatory bowel disease are often unrecognised and in general remain under-treated and under-researched.

While the author acknowledges the poor methodological quality of the collected studies, their results do, however, indicate that antidepressants appeared not only to help certain individual patients with IBD cope with their emotional problems, but also improved their quality of life. The published observations also intriguingly suggest that antidepressant therapy may have specifically influenced the course of their inflammatory disease. This novel therapeutic possibility warrants further consideration.

To date, researchers with an interest in the impact of a patient's psyche on disease activity in IBD have conducted little formal research on the use of antidepressants in this condition, with most published data being uncontrolled and anecdotal. As noted, only 12 relevant articles were identified, and five of these did not include new data. However, the three case reports (Kane et al., 2003; Kast, 1998; Kast & Altschuler, 2001), two reviews (Kast, 2003; Kast & Altschuler, 2005), and the discussion paper (Kast, 2005) did explore the potential for influencing disease activity in IBD with antidepressants from a novel perspective.

Kast (1998) presented a medical history of an anxious and depressed patient with Crohn's disease who was treated with phenelzine and subsequently achieved remission from IBD. In further reports, Kast and Altschuler (2001) describe two additional patients who achieved long-lasting remission of Crohn's disease whilst using bupropion. These investigators hypothesise that this may have resulted from decreased tumor necrosis factor-alpha (TNFα), which is known to play a vital role in Crohn's disease. Both phenelzine and bupropion increase intracellular cAMP (Talmadge et al., 1993) which, in turn, decreases TNFα. As phenelzine may cause a hypertensive crisis, bupropion is suggested as a safer therapeutic option. Interestingly, phenelzine and other monoamine oxidase inhibitors have also been noted to induce remission of rheumatoid arthritis, a disease in which - as in Crohn's disease - TNFα has a central role (Lieb, 1983). Kast (2003), compared the use of bupropion and mirtazapine in patients with Crohn's disease. He speculated that both these antidepressants have the potential to affect inflammatory responses: bupropion by lowering TNFα and mirtazapine by increasing its level. Therefore, according to his hypothesis (Kast, 2003), there are theoretical reasons for recommending bupropion and cautioning against mirtazapine when treating depression in patients with Crohn's disease. Although Kast's explanations appear logical and are supported by other investigators (Kane et al.,

2003), their practical effectiveness needs to be experimentally confirmed in appropriate clinical studies.

The largest study in this systematic review, which most closely matched the standard quality criteria (see section 7.2.3 Chapter 7), was that by Walker, Gelfand et al. (1996). Whilst comparing patients with IBD with and without current psychological problems, the investigators noticed that depressed patients (n=8) who were given paroxetine in an open label design showed significant improvement in relation to functional disability. The researchers had expected an improvement only in depression, however, patients' scores on SF-12 also improved in the area of physical limitations, occupational role, emotional role, social function, pain, mental health, vitality, and health perception, with higher scores associated with increased quality of life (E. A Walker et al., 1996). Although the importance of this result seems unquestionable, significant weaknesses in the study need to be stated. These include the small sample size, open label design and the fact that the investigators did not differentiate between patients with Crohn's disease and ulcerative colitis. However, given the potential importance of this observation, larger studies addressing these methodological issues are clearly needed.

In discussing the possible effects of antidepressant therapy on IBD as revealed by this systematic review, the author acknowledges that all the analysed studies were characterised by various limitations. Specifically, these limitations included: lack of randomisation or control groups; potential lack of relevance to ulcerative colitis as most data pertain to Crohn's disease; non-homogenous participants; failure to consistently apply standardised instruments; and lack of routine follow-up tests. Similarly, because of the uncontrolled nature of the observations, all studies are open to selection, performance, attrition and

detection bias. Moreover, seven out of 12 publications emanated from the same research group, and four of these were discussions that did not contain any new data.

The fact that there is little good quality data in this area does not mean it is unworthy of further study. Our present state of knowledge regarding interaction between psychological co-morbidities and IBD resembles that of our knowledge of the pathogenesis of IBS twenty years ago. At that stage, IBS was thought to be predominantly a psychological condition, whereas we now have clear-cut, well accepted evidence of pathological abnormalities in the gut (Barbara et al., 2004; Gwee et al., 1999). Currently, IBD is generally thought to be purely inflammatory, but clinical observations in individual patients make it hard to dismiss the potential role of psychological factors (Ringel & Drossman, 2001). Moreover, it is well accepted that IBS frequently co-exists in patients with IBD (Pace et al., 2003; Simren et al., 2002) and that both patient groups suffer similar impairment in physical and psychological domains (Pace et al., 2003), making rigid distinctions between psychological versus inflammatory mechanisms more difficult to uphold. As antidepressants are widely used in IBS (Jackson et al., 2000), and because doctors are already known to treat anxiety, depression and pain in IBD using guidelines for IBS (Ginsburg & Bayless, 2005; Ringel & Drossman, 2001), creating informed discussion and hopefully prompting further research in this area is therefore likely to improve our understanding of IBD and patient care. The following chapter develops this line of enquiry by describing the interview study with gastroenterologists, which explores the role of antidepressants in inflammatory bowel disease.

Chapter 9: "It doesn't do any harm, but patients feel better": a qualitative exploratory study of gastroenterologists' perspectives on the role of antidepressants in inflammatory bowel disease (Study 6)

Like the previous chapter, this chapter explores the role of treatment with antidepressants in inflammatory bowel disease. However, it examines this problem from a different angle by analysing practitioners' opinions, experiences and attitudes regarding the use of antidepressants in this disease. Participants' responses are collected, analysed through content analysis and discussed.

9.1. Introduction

As can be seen from the previous chapter's findings, the literature on the role of antidepressants in inflammatory bowel disease lacks properly designed controlled studies. Even though data from the available research suggests a beneficial effect of antidepressants on the course of IBD, their paucity makes it impossible to draw any firm conclusions. Nevertheless, Chapter 8 clearly emphasises the gap in current knowledge about this problem.

As one of the major barriers to implementing a change in disease management is the attitudes and habits of relevant clinicians, the author sought to conduct a qualitative exploratory study into clinicians' views and practices. The semi-structured interviews were designed to: identify gastroenterologists' attitudes to the use of antidepressants in IBD; investigate, on a preliminary basis, gastroenterologists' observations of the effects of

antidepressants on IBD; and explore gastroenterologists' attitudes towards further research in this area, especially towards possible randomised controlled trials. For the detailed description of methods see Chapter 7.

9.2. Results

All approached doctors agreed to take part in this study. Eighteen participants were recruited, with nine gastroenterologists participating at each site. Two gastroenterologists associated with these departments did not participate due to their direct involvement in the study. This sample represents 78% (18 out of 23) of the gastroenterologists working in these two hospitals, 66% (18 out of 27) of them working in the Central-Northern Adelaide Health Services, and 36.7% (18 out of 49) working in South Australia. Seventeen of the 18 participants were male, which is consistent with the sex mix for gastroenterologists in SA; 10 were born outside Australia. Their ages ranged from 33 to 64 years, with a median of 44. Their experience in gastroenterology ranged from two to 30 years, with a median of 16 years. Fifteen doctors completed their undergraduate studies in Australia. Ten doctors completed their postgraduate studies in Australia, five conducted them partly in Australia and partly overseas, and three completed postgraduate studies overseas. Participants treated between one and 12 IBD patients per week (with a mean of five patients). They worked both in public and private practices.

Twelve questions were asked (see Appendix 14), and the analysis presented below summarises the most important findings. For full transcripts of the interviews see Appendix 15.

9.2.1. The role of antidepressants in chronic disease and in IBD

All participants agreed that antidepressants were a useful medication for depression, IBS and various pain syndromes. The gastroenterologists often used antidepressants in treating chronically ill people because, as many participants reported: "in patients with a chronic disease depression is more common" [than in healthy people]. Two gastroenterologists believed antidepressants were overused, yet another two believed them to be underused. One participant said, "They are underused because we, gastroenterologists, rarely have time to ask about depression". One gastroenterologist, however, reported that he was "always keen to look at non-drug options for enhancing physical health and well-being" and used antidepressants only when necessary, i.e. with organic depression.

All participants were in agreement that antidepressants cannot be used as effective primary therapy in IBD and that no evidence exists in published research that antidepressants have an influence on the level of inflammatory markers. Most gastroenterologists, however, reported having successfully used antidepressants as an adjunct therapy. Interestingly, some gastroenterologists stated that psychological problems in IBD are easy to overlook and that in a number of patients, psychological issues are a significant concern.

9.2.2. Reasons for using/not using of antidepressants in patients with IBD

Fourteen of eighteen participants had prescribed antidepressants or suggested using antidepressants in patients with IBD. Reasons given for treating IBD patients with antidepressants were: pain; evidence of depression or significant mood disorder, which might include anxiety; depression; sleep problems; and gut symptoms despite being in a quiscent phase (gut irritablity, IBS in IBD). Seven out of 14 gastroenterologists who had prescribed antidepressants had specifically treated anxiety or depression. Most (12 out of 14) of the participants who prescribed antidepressants to patients with IBD, however,

prefered referring depressed patients to their GP or to a psychiatrist rather than being the initiators of this treatment. On the other hand, gastroenterologists felt comfortable with using antidepressants for pain, disturbed sleep pattern, and IBS symptoms in IBD. Those gastroenterologists who did not use antidepressants in patients with IBD reported that this was either because they had not treated a depressed patient; did not believe depression was a significant problem in these patients; or did not see their role as detecting depression.

Four of eighteen gastroenterologists did not use antidepressants or endorse using antidepressants in patients with IBD. Two of these participants reported that this was because they had not treated a depressed patient. The third stated that there was no need to treat patients with IBD with antidepressants because, "when the inflammation is treated the psychological well-being improves". The fourth participant summarised his experience with antidepressants with the following words: "I don't get involved in treating depression. I don't see my role as detecting depression, I don't prescribe antidepressants for depression, that's somebody else's [role]".

9.2.3. Type of antidepressants used and results of treatment

Participants had used classic tricyclics (e.g. amitriptyline, dothiepin, prothiaden, doxepin, imipramine, nortriptyline), selective serotonin reuptake inhibitors (SSRI) (citalopram, sertraline) and serotonin and noradrenaline reuptake inhibitors (SNRI) (mirtazapine) antidepressants in patients with IBD. However, with tricyclics they reported mainly focusing on treating somatic aspects of the disease e.g. pain, gut irritability, urgency of defecation. Tricyclics are, according to most participants, better researched in this area and have been found to be effective for IBS-like symptoms in patients with IBD. Gastroenterologists often reported using the same antidepressants that they prescribe in patients with IBS. Only a few had tried treating anxiety and/or depression in their patients

with IBD with the newer antidepressive agents. Those who had used the newer agents felt that psychological problems responded well to this treatment.

9.2.4. Treatment with antidepressants and the course of IBD

Ten of the 14 gastroenterologists who had prescribed antidepressant therapy did not perceive that antidepressants had any influence on the course of IBD and they tended to agree with the following quote from one participant: "There is no impact on IBD, but patients feel better". However, one of them explained his opinion in the following way: "I don't think it influences the activity of the IBD. The IBD is occurring in an individual and the individual's ability to manage the disease can clearly be improved by managing the accompanying mood disorder". Despite their opposition to the idea that antidepressants directly affect the course of the disease, many argued that the treatment with antidepressants seemed to improve patients' quality of life.

In general, antidepressants were thought to help patients with IBD in managing their disease, cope with unpleasant symptoms, improve patients' sleep patterns, reduce pain and gut irritability and help them look after their nutrition and diet. Moreover, the benefits of the treatment with antidepressants might be more visible on disease activity indices rather than on inflammatory activity markers. Two gastroenterologists who thought treatment with antidepressants had influenced the course of IBD reported that antidepressants helped in controlling exacerbations of IBD and reduced symptoms of IBD. These two gastroenterologists used amitriptyline, nortriptyline, citalopram, and sertraline.

Most participants who had used antidepressants in patients with IBD (12 out of 14) believed that there was no difference in the effect of antidepressants on the disease

between CD and UC patients. However, three doctors noticed that they had mainly treated CD patients with antidepressants, and not UC. One participant hypothesised that this was because of the earlier onset of CD compared to UC. He said, "CD often has a bias towards a younger age of onset than UC that is in a broader age" and because of that are more likely to be depressed and subsequently given antidepressants. On the other hand, one doctor treated only UC patients with antidepressants as they "have often got rectal involvement" and "this rather constant alertness at night [that] makes them hear things in the night and wake up and want to go for a wee". In general, CD patients seemed to be treated with antidepressants for their psychological problems and pain whereas UC patients for pain and sleep disturbances. Nevertheless, the tendency was not very strong, as most participants did not differentiate between CD and UC in terms of their co-occurrence with anxiety and/or depression.

9.2.5. Psychological treatment in patients with IBD

Nine out of 18 participants reported suggesting psychological treatment for their patients with IBD. Some gastroenterologists reported that they referred their patients to psychologists, counselors, psychiatrists or general practitioners for psychotherapy. One doctor revealed he conducted some form of psychotherapy with his patients. Gastroenterologists also suggested hypnotherapy, relaxation and physical exercises to patients with IBD. Gastroenterologists reported that they sought psychological treatment for their patients with IBD when patients had symptoms of anxiety and/or depression, had chronic pain syndrome, psychosexual problems and problems with body image, or were opioid-dependent. The results of these treatments were, by and large, unknown as the gastroenterologists did not specifically follow up the patients with respect to psychological co-morbidities. However, one doctor remarked, "On a couple of occassions I have suggested relaxation therapy and hypnotherapy but have had very limited success".

Another doctor was of a different opinion: "I am sympathetic to the idea of psychosocial issues being crucial, important".

9.2.6. Gastroenterologists' opinion on the feasibility of a trial with antidepressants in patients with IBD

All gastroenterologists would approve of their IBD patients' decision to enter a trial consisting of antidepressant therapy. However, gastroenterologists reported that they would like to: receive some information about the study; check the inclusion criteria and the hypothesis of the research; analyse the protocol of the research; see the evidence that antidepressants may work in IBD if the medication is given to people without psychological problems; discuss the trial with patients; receive assurance that during a trial standard treatment remains unchanged; receive assurance that anxiety and/or depression are properly diagnosed; evaluate the risk for patients, and explain to patients about randomisation and blinding.

9.2.7. Additional comments

At the end of the interview, gastroenterologists were asked to add any comments. Four gastroenterologists demonstrated their particular interest in the psychological status of their patients with IBD, telling the author about their own studies of the mental health status of patients with IBD. Interestingly, one participant referred to developmental psychology and attachment theory. Gastroenterologists also emphasised the role of stress as an exacerbating factor in some patients. One participant reported that co-occurrence of IBD with IBS symptoms was a predictor of psychological problems in patients with IBD.

9.3. Discussion

This qualitative exploratory study was designed to investigate and describe the attitudes and practices of specialist gastroenterologists with respect to antidepressant and other psychological therapies in patients with IBD. Based upon this study, gastroenterologists are well aware of a high burden of anxiety and depression in patients with IBD, although they do not routinely evaluate their patients for psychological co-morbidities. Many are open to the premise that treating anxiety and depression may improve patients' quality of life. The participants were, however, quite sceptical that psychological problems and/or antidepressant therapy had a central role in the clinical course of IBD.

Although it is controversial, some investigators have proposed that the psyche may play a pivotal role in the causation of IBD (Engel, 1955; Lieberz, 1991; Sheffield & Carney, 1976), whilst others have proposed that psychological co-morbidities, especially anxiety and depression, may influence the clinical course of IBD (Mittermaier et al., 2004). As yet the literature is unable to answer the question of whether treatment of IBD with antidepressant therapy is of benefit (Chapter 8), mostly due to the quality of available data: non-randomised, non-blinded, and non-controlled studies. Nevertheless, there is some evidence that antidepressants may have an impact on the inflammatory activity by lowering or increasing TNF alfa (Kast, 2003) and there is also evidence of the impact of stress on inflammation in IBD (Mawdsley et al., 2006). However, no trial devoted solely to the use of antidepressants in IBD has ever been conducted. Thus, one of the main aims of this investigation was to assess gastroenterologists' likely acceptance of a properly conducted clinical trial in this area. Indeed, the content analysis revealed that although the interviewed gastroenterologists used antidepressants in IBD to minimise symptoms and to treat insomnia, anxiety and depression, they would require strong evidence of specific benefit prior to accepting their potential role in modifying the course of IBD.

In previous works on anxiety and depression in IBD, certain antidepressants have been suggested to have a specific benefit on the clinical course of IBD (Eirund, 1998; Kane et al., 2003; Kast, 1998; Kast & Altschuler, 2001; E. A. Walker, M. D. Gelfand, A. N. Gelfand, F. Creed, & W. J. Katon, 1996). Unfortunately, none of gastroenterologists participating in the current study had used these antidepressants, which included paroxetine (Eirund, 1998; E. A. Walker et al., 1996), bupropion (Kane et al., 2003; Kast & Altschuler, 2001) and phenelzine (Kast, 1998). As the gastroenterologists were unable to confirm or refute the previously reported observations, the choice of an antidepressant for the evaluation in future trials is still unclear. Taking into account the opinions of the surveyed gastroenterologists, future research into the role of antidepressants in IBD should focus on both the physical and psychological impact of antidepressants on patients with IBD. If antidepressant therapy was shown to improve the clinical course of IBD, further questions would need to be addressed. If all antidepressants were equally effective, one may infer that the psyche plays a major role in the course of IBD. On the other hand, if a specific antidepressant (or class of antidepressants) was more efficacious, our understanding of the inflammatory cascade in IBD itself may change.

Interestingly, during this study the author also observed that some gastroenterologists had treated IBD patients with antidepressants in the same way they had treated IBS patients. This is not surprising given the symptomatic similarities of these two conditions (Barratt et al., 2005) and the increasingly well documented overlap between these two diseases (Simren et al., 2002). As already discussed in Chapter 8, 20 years ago IBS was thought to be a predominantly psychological condition with no inflammatory element, whereas we now have some evidence of pathological abnormalities in the gut (Barbara et al., 2004; Gwee et al., 1999). By contrast, IBD is currently thought to be purely inflammatory,

however, clinical observations in individual patients render it difficult to completely exclude psychological factors (Ringel & Drossman, 2001). Moreover, even the "objective" measures of severity such as the Crohn's Disease Activity Index (CDAI) are well known to be affected by the psyche in influencing ratings for "abdominal pain" and "general wellbeing". Furthermore, as IBD and IBS commonly coexist, it is difficult to make categorical distinctions between psychological versus inflammatory mechanisms. It is, therefore, very important to explore various treatment options in the hope that informed discussion will prompt further research and improve standard medical care of these patients and therefore their quality of life. The fact that these surveyed gastroenterologists generally endorsed the concept of conducting a properly designed trial on the role of antidepressants in IBD, which would encourage their patients to participate in such research, is an important result in this regard. The last chapter summarises and discusses the most significant findings of the thesis. It also documents their implications for practice and policy.

Conclusion

This chapter provides an overview of the most important findings of the six studies comprising the thesis. The chapter also summarises proposed future research resulting from findings of the present studies. Moreover, recommendations for clinical and research practice resulting from findings of conducted studies are also provided as well as recommendations resulting from the experience of conducting psychological research in the gastroenterology practice.

I. Overview of findings

This interdisciplinary thesis highlights the need for a biopsychosocial approach to the management of patients with chronic gastrointestinal and hepatologic disorders. In particular, the thesis describes several studies on the relationship between psychological problems and physical outcomes/response to medical treatment in patients with inflammatory bowel disease and other common chronic gastroenterological disorders. The thesis makes significant original contributions to knowledge in three respects. Firstly, it demonstrated that anxiety is highly prevalent in people with chronic gastroenterological disorders and, particularly, in HCV. Secondly, it demonstrated potential for simple cost-effective treatment of anxiety and, thirdly, it revealed that psychological problems do not alter the course of the disease in patients with IBD. However, importantly, the results of this thesis cannot be generalized to patients who are not managed clinically by gastroenterologists. Patients with less severe disease who are treated by General Practitioners could have different rates of psychological problems and dissimilar levels of quality of life.

The most significant results are presented in the order they appear in the thesis.

First, two cross-sectional studies (Chapters 3 and 4) were conducted to estimate and compare the prevalence of psychological problems in the three disease groups. In contrast with Hypothesis 1 (Patients with IBD are most affected by psychological problems as compared to patients with IBS and HCV), the first study showed that the HCV group had the highest psychological morbidity as measured by the SCL90. Patients with HCV also had significantly higher prevalence of depression than the remaining groups. Moreover, this study demonstrated high levels of anxiety in all three disease groups, with a total of 42% of participants fulfilling the anxiety criterion for caseness.

The further cross-sectional study (Chapter 4) tested Hypothesis 2 (patients with IBD and patients with IBS with the greater number of co-morbid functional gastrointestinal disorders have higher levels of depression and anxiety and poorer quality of life than those with smaller number of functional disorders) and found it to hold for the IBD but not the IBS group in terms of the physical quality of life measure. In contrast to IBS patients, those IBD participants with fewer functional disorders had better physical quality of life than participants with a greater number of functional disorders. Interestingly, though, there was no relationship between the number of functional disorders and anxiety and depression in either group of patients.

This study further tested Hypothesis 3 (Patients with IBD and with co-morbid IBS have higher rate of psychological problems and poorer quality of life than patients with IBD without IBS). It found that the two groups were in fact no different in terms of their psychological co-mobirdities and mental quality of life. However, concurrent IBS was found to predict poorer physical quality of life in IBD sufferers.

The next cohort prospective study disproved Hypothesis 4 (Patients with psychological co-morbidities are less likely to have a satisfactory response to standard treatment/better physical outcomes at 12 months), revealing that anxiety/depression at baseline did not explain medical outcomes after 12 months in this cohort of patients with chronic diseases of the digestive tract. There was no significant difference between disease groups in their likelihood to relapse over time, either. Moreover, no significant relationship was found between psychological problems such as anxiety/depression and the total number of relapses in IBD.

The subsequent randomised controlled trial evaluated Hypothesis 5 (Physicians' knowledge of patients' psychological status alters physicians' behaviour and/or improves patients' clinical outcomes). The trial was successful in terms of reducing anxiety in IBD patients over a period of nine months. However, due to the small power, it was impossible to estimate whether groups significantly differed on any subscale over time. Further qualitative analysis showed, interestingly, that five doctors (38%) in the experimental group changed their behaviour and initiated psychological treatment with their patients compared with only one doctor (9%) in the control group. However, this difference was not statistically significant. Hypothesis 5 was, therefore, found not to hold.

The subsequent systematic review on the role of antidepressants in IBD demonstrated that although most reviewed papers suggested a beneficial effect of treatment with antidepressants on the disease course, due to the lack of reliable data, it is impossible to judge the efficacy of antidepressants in IBD.

The last study, a qualitative interview study, showed that gastroenterologists commonly treat IBD patients with antidepressants for pain, anxiety and/or depression, and insomnia.

Antidepressants were reported to be useful in improving psychosocial well-being, quality of life, and self-management of the disease by patients. However, gastroenterologists were found to be sceptical towards psychological problems themselves, or antidepressant therapy having a central role in the clinical course of IBD. Nevertheless, properly designed trials were found to be justified and necessary based upon the available uncontrolled data described in the systematic review, and based on gastroenterologists' receptiveness to the idea of conducting a trial on the role of antidepressants in IBD.

In summary, thus, three hypotheses out of five were fully rejected and two hypotheses were partly rejected. The reasons behind this were most likely sampling issues. The studies were underpowered due to problems with recruitment. This could especially affect the results of Study 2 where the relationship was found between the greater number of functional gastrointestinal disorders and quality of life in IBD but not in IBS. The cohort prospective study and the randomised controlled trial were equally affected by the small sample size of HCV and IBS patients with psychological problems. Moreover, groups were not homogenous as patients' disease activity and time since diagnosis varied. This could potentially impact the results of Study 1 (hypothesis 1) and 3 (hypothesis 4) where more homogenous samples could change the results. However, this was dealt with at the analysis level and did not show to be the case. Finally, many other variables (e.g. personality or coping styles) not assessed in this thesis could be responsible for the results. In the future, these issues could be addressed by conducting exploratory hypothesis-driven research.

II. Future research

The literature review (Chapter 1) revealed the need for well-designed and properly controlled research, and more specifically, for longitudinal prospective studies on the psychological aspects of IBD and on the temporal relationship between these

psychological co-morbidities and the disease course in particular. This area of knowledge was found to be full of conflicting data and subsequent controversies regarding psychological co-morbidities. The review suggested that psychological disturbances such as anxiety and/or depression are difficult to discretely assess in patients with IBD due to the lack of disease specific instruments to measure psychological problems, which might explain conflicting results of the available studies. Many currently used instruments (e.g. Beck Depression Inventory) have items that may be influenced by active or poorly controlled disease. On the other hand, IBD activity indices also contain many subjective items that may be influenced by psychological factors rather than purely gastrointestinal inflammation. Therefore, research focused on the development of better instruments to quantify both the psychological and inflammatory aspects of IBD is clearly needed.

Moreover, a comprehensive literature review (see Preamble and Chapter 1) indicated the need for more systematic studies exploring the most appropriate approach to psychological treatment. Cognitive-behavioral therapy has been proposed to be a promising path in this area. However, CBT has not been adequately investigated in good quality studies as yet and such studies were therefore suggested.

The cross-sectional comparative study (Chapter 3) on the prevalence of anxiety and depression in IBD, IBS and HCV revealed only moderate or even small levels of depression in these three groups of patients compared with the data for other chronic diseases. It was proposed that this may be a result of adequate care and gastroenterologists' interest in their patients' psyche. Studies comparing standard care in terms of the practitioners' interest in mental health in gastroenterological outpatient clinics in other Australian and international hospitals were suggested to be useful to better understand this finding. On the other hand, anxiety was found to be high in all the patients and while this

was unproblematic to understand in patients with IBD and IBS, the reasons for the high rates in the HCV group were less clear. It was proposed that studies exploring the problem of guilt in patients with HCV could shed some light on this premise. Moreover, qualitative studies exploring HCV patients' perspectives on their psychological co-morbidities are also warranted.

The subsequent cross-sectional research study (Chapter 4) into the relationship between the number of co-morbid functional gastrointestinal disorders in IBD and IBS patients showed that the number of functional gastrointestinal disorders did not predict the rate or severity of psychological co-morbidities or patients' quality of life in IBS. This was explained by the fact that as functional gastrointestinal disorders commonly co-occur, patients with IBS do not perceive multiple symptoms as a sign of many disorders, but rather as several manifestations of a single disorder with which they have been diagnosed. Future studies examining whether disclosing the additional diagnoses to IBS patients leads to a measurable change in psychological co-morbidities or quality of life were recommended. Larger studies were also suggested in this respect as this result might have occurred due to the small sample consisting of only 32 participants.

Furthermore, this study has also noted a discrepancy between clinician and research-based (the BDQ) diagnoses of IBS. As this finding is likely to affect the efficiency of future translations of research advances into clinical care, larger studies to better define where clinicians and the criteria fail to concur would be helpful in this regard. Population-based series, for the purpose of re-examining the potential link between the number of functional gastrointestinal disorders and psychological co-morbidities in IBS, were also suggested.

The findings of the cohort prospective study (Chapter 5) indicated the need for larger and longer studies with more homogenous samples on the temporal relationship between psychological status and medical outcomes of patients with IBD. Similarly, in the two remaining groups, larger studies are warranted to better understand whether anxiety/depression at baseline can predict physical outcomes after a period of time. Moreover, in these three disorders, the time frame for trials should fit their remission/relapse pattern and it has been proposed that this should not be less than five years. Alternatively, research should focus on conditions with a similar remission/relapse pattern, because IBD, IBS and HCV differ with this respect. In order to make more methodologically accurate comparisons between the three disorders, finding disease activity index relevant to all the three conditions is also recommended. Finally, similar prospective studies should include patients either in remission or in relapse in order to more rigorously observe the progress of the disease.

The results of the subsequent randomised controlled trial (Chapter 6) again identified the need for larger prospective studies to observe whether improving doctors' knowledge of their patients' psychological status might improve these patients' outcomes. The promising results of this intervention, even though not significant due to low levels of power in interactions between the trial allocation and temporal changes, do not rule out its efficacy and, because of this, further studies are recommended.

The qualitative part of the randomised controlled trial as well as the systematic review (Chapter 8) and the interview study (Chapter 9) showed that most of those IBD patients who received treatment with antidepressants benefited. The findings arise, however, mainly from case observations and, as such, cannot be generalised for the whole IBD population until confirmed by larger trials. It is clear that larger good quality studies are

needed as antidepressants may offer a yet relatively unexplored path to management of IBD.

III. Recommendations

Recommendations for clinical and research practice resulting from findings of conducted studies

The most important recommendation for clinical practice resulting from studies reviewed and conducted as part of this thesis is that patients with chronic gastroenterological conditions should be thoroughly screened for psychological problems and could benefit from specific psychological treatment targeting these disorders. However, a universal and effective psychological treatment that would work for the majority of patients has not been identified as yet.

Anxiety, which has been found to be highly prevalent among participants, seems an unrecognised problem and methods of reducing it should attract the attention of practitioners and researchers working in the area. It is clear from the randomised controlled trial results that mere participation in a trial and regular contact with the researcher reduced patients' anxiety. Consequently, this may indicate that even simple psychological interventions may improve patients' wellbeing. Moreover, patients with HCV should be commonly monitored and psychologically treated for their anxiety and depression as this group is the most affected by psychological problems compared with IBD and IBS patients. Additionally, the reasons behind the high prevalence of psychological problems in this group are not well understood and should be further examined.

In the area of research practice, a recommendation should be made with respect to obtaining an appropriate sample size in studies on psychological problems in IBD. The disease per se is not very prevalent and identifying an appropriate number of patients with psychological co-morbidities may be a problem in studies with short recruitment periods. Due to differences in the prevalence of psychological problems in IBD patients depending on setting and country, investigators should not rely on data from other studies while investigating sample size. In order to avoid underpowered studies, collecting locally robust data on the prevalence of psychological co-morbidity is recommended.

Furthermore, based on the low response rate noted in some of the studies comprising this thesis, different methodological approaches and recruitment strategies should be applied in studies in similar settings. It is advisable that the time burden of completing questionnaires is reduced. Furthermore, if possible, patients should be invited into studies while they are waiting for their doctor's appointment and not after this appointment. The involvement of the clinic's staff in inviting patients into studies instead of the researchers, who are unfamiliar to potential participants, is also suggested.

Another issue to be considered in research and clinical practice pertains to the accuracy of a clinical versus questionnaire or criteria based approach to the diagnosis of functional disorders. From the cross-sectional study (Chapter 4) regarding the prevalence of functional gastrointestinal disorders in IBD and IBS, it might be suggested that the new criteria are not as sensitive in detecting IBS as the previous ones, particularly the Rome I criteria. However, in the current study, the new Rome III criteria have been demonstrated to have excellent sensitivity in detecting any functional bowel disorder, although there is poor agreement between clinicians and the new criteria as to the specific subtype of functional bowel disorder (that is, IBS, functional bloating and functional constipation).

This "inaccuracy" needs to be acknowledged in any interpretation of criteria-based clinical trial data in the clinical setting. With continuing advances in the understanding of the pathophysiology underlying functional gastrointestinal disorders, the accurate classification of these subtypes of functional bowel disorders may be more important in light of more specifically targeted therapies becoming available.

Recommendations resulting from the experience of conducting psychological research in a gastroenterology clinic

The most important recommendation resulting from the conduct of psychological research in a gastroenterology clinic is that psychologists with special expertise in the management of patients with gastrointestinal (GI) conditions should become regular members of multidisciplinary gastroenterology teams in Australia.

As stated in the Preamble, the association between gastrointestinal conditions and psychological problems (Drossman, 1999) goes far beyond the fact that chronic diseases make people more vulnerable to anxiety and/or depression (Rodin et al., 1991). In fact, the gut, while responding to environmental and physiological factors, is also directly interconnected to the brain via the so called "brain-gut axis" (Jones et al., 2006), creating additional susceptibility for gastroenterology patients to develop psychological problems and vice versa. Because of this, the understanding and treatment of GI disorders should also incorporate their psychological aspects. Furthermore, investigations into the prevalence and nature of psychological difficulties and the design of interventions to prevent and treat them should become part of the day-to-day management of all chronic conditions, as such interventions may have the potential to directly improve patient outcomes (Kuchler, Bestmann, Rappat, Henne-Bruns, & Wood-Dauphinee, 2007) and reduce healthcare utilization (Deter et al., 2007).

In reality, gastroenterology clinics in Australia only rarely employ psychologists on a regular basis to participate in these tasks. Moreover, apart from the recognition that functional disorders may coexist with psychological problems and as such should be treated, the psychological management of most other gastroenterological problems is not, at present, part of standard medical practice in gastroenterology in Australia. In some overseas units with an interest in this area, doctors have started incorporating both physical and psychological symptoms into their diagnosis and management (Drossman, 1998b; Gerson & Gerson, 2003; Moser, 2000) and are becoming increasingly aware that ignoring patients' psyche during treatment has the potential to result in treatment failure because of the association between depression and medical non-compliance (DiMatteo et al., 2000). Because of this, a change in the patient-doctor relationship has been recommended in recent years towards more open communication and greater patient involvement in treatment decisions (Bensing et al., 2006). As a consequence, patients are likely to feel less reluctant in discussing their psychological problems with their doctors. However, generally, South Australian gastroenterologists continue to believe that the psychological difficulties of their patients are neither their direct or primary concern (Chapter 9), and feel ill equipped to deal with these issues.

Moreover, South Australian gastroenterologists regard the patient's General Practitioner (GP) as more expert in diagnosing and treating mental health issues. Thus, if a patient wishes to discuss his/her psychological difficulties, the advice offered by gastroenterologists is typically limited to recommending the patient visits their usual GP (Chapter 9). Although this may seem inefficient from a health utilisation view-point, structural reasons concerning patient reimbursement also drive this practice. As psychological support is currently not available for these patients in the hospital outpatient

setting, they would typically be referred to an outside/private psychologist. Patients referred directly to a psychologist outside the public hospital setting by their gastroenterologist are unable to obtain any Medicare reimbursement, whereas those referred by a GP are reimbursed for the psychological treatment. Thus, even if willing to act promptly, gastroenterologists are forced to refer their patient back to their GPs.

There is no doubt that clinics both in gastroenterology and general practice, are generally busy and the time ascribed to particular patients often limited. The fact that dealing with mental health problems is more time consuming than dealing with a viral infection additionally aggravates the situation. Thus, greater use of psychologists could directly contribute to improving patient care by relieving time pressures, shifting the principal responsibility for patients' mental care away from both gastroenterologists and GPs, who for different reasons may not be fully equipped to deal with such issues (for example, because of the lack of time and training to conduct psychotherapy such as CBT), and filling the gap in communication between the two groups of doctors about patients' psychological needs. Additionally, a psychologist in the clinic would be a valuable resource person for patients, doctors and nurses wishing to up-skill themselves in effective, brief psychological interventions.

The Australian and New Zealand guidelines for treatment of depression issued in 2004 have consistently recommended that treatment of depression should involve a co-operation of the GP and a mental health professional (Ellis, 2004). More recent policy changes and the introduction of the "Better Access to Mental Health Care Initiative" in November 2006 are considered to provide better access to clinical psychologists, psychologists, social workers and occupational therapists who are registered with Medicare Australia ("Better Access to Mental Health Care Initiative," 2006). However, the fact is that there is no direct

link between gastroenterologists and psychologists. This remains a problem because in order to achieve the best results in treating mental health problems, and because early detection and intervention has been shown to reduce the severity, duration, complexity and the cost of such problems as depression (Bilsker, Gilbert, Myette, & Stewart-Patterson, 2005), it is crucial to target these problems early. Thus, if a patient has trusted a gastroenterologist with their difficulties, and only half of those affected by mental problems seek medical care (Andrews et al., 2001), gastroenterologists should be able to refer a patient directly to a psychologist who in the best case scenario works at the same clinic, without the patient suffering a cost penalty.

Australian gastroenterology teams have in recent years been enriched by dieticians and extended role nurses as a way of bolstering care. The author proposes that there should also be a role for a co-located psychologist among these patients' carers. The author also strongly suggests that Medicare refunds for psychological care are extended to include specialists' referrals for this treatment. Furthermore, the value of employing psychologists as part of teams in gastroenterology clinics seems an economically and socially sound solution when one accounts for the financial and social costs of reduced worker productivity, benefits payments, employee retention, absenteeism, and disability resulting from psychological problems such as depression (Goetzel, Ozminkowski, Sederer, & Mark, 2002). According to estimates from the World Health Organization, by the year 2020, depression will become the second most common cause of disability in the developed world, and so these already high costs will additionally increase (WHO, 2007). Therefore, psychologists' knowledge and experience should be more commonly utilised by the Australian health system, especially because psychological interventions can focus not only on treating existing problems, but also on screening and early prevention. The results of this thesis showed clearly that psychological problems, and particularly anxiety, are not

rare in gastroenterology practice in Australian tertiary clinics. Effective interventions targeting these problems in the gastroenterology setting are still to be proposed.

This thesis has therefore indicated a need for interdisciplinary approaches to the management of chronic diseases of the gastrointestinal tract. In fact, as a result of the author's work at the Royal Adelaide Hospital gastroenterology clinic, the clinic offered a number of placements for future health psychologists to support doctors in the management of their patients. It is clear that in order to manage chronic conditions effectively, and to better understand and treat gastrointestinal diseases, teams consisting of gastroenterologists, GPs, psychiatrists, and psychologists should work more closely. Only in this way can the requirements of the biopsychosocial paradigm (Engel, 1980) be fully applied to standard medical care. Moreover, the different educational and disciplinary backgrounds of the team members can better enable problem solving that takes into account the important psychological aspects of gastroenterological conditions. Thus, the inclusion of psychologists in gastroenterology teams, and the creation of a subdiscipline called Psychogastroenterology, in line with overseas best practice, is an important step towards providing a more holistic approach to gastroenterological problems, including their significant psychological component. This thesis will, hopefully, contribute to this process.

IV. Final comments

This thesis has highlighted the need for the biopsychosocial model to be applied to managing chronic gastroenterological conditions. Interdisciplinary approaches to the management of these conditions are also needed in Australian gastroenterology clinics to better understand and treat patients. Depression in the examined sample of IBD, IBS and HCV patients was found to be less prevalent than usually reported in studies on similar

participants and well managed. Anxiety, however, was established as a significant

challenge. Thus, anxiety targeted interventions and research in this setting are urgently

needed, especially with respect to patients with HCV. Moreover, larger studies exploring

the influence of gastroenterologists' knowledge of patients' psychological problems on

these patients' medical outcomes are recommended as they may have the potential to

improve standard care with a little or no cost involved. Furthermore, longer and larger

prospective studies with more homogenous samples of patients are needed to confirm the

nature of the relationship between psychological problems and relapse of somatic

symptoms in patients with chronic digestive diseases, and especially in HCV and IBS. In

addition, randomised controlled trials exploring the efficacy of antidepressants in IBD are

warranted to categorically answer the question of whether they can change the course of

IBD. Finally, psychologists with special expertise in the management of patients with

gastrointestinal conditions should become regular members of multidisciplinary teams in

gastroenterology clinics in Australia, and the Medicare refund policy on access to

psychologists should include gastroenterologists' referrals.

Appendices

Appendix 1

Table: Features of 17 studies describing the co-morbidity of psychological problems with IBD in alphabetical order

Name of the study	Sample and source of subjects	Methods	Results
Addolorato et al. 1997 (Italy)	79 consecutive patients with IBD (43 CD and 36 UC) tertiary referral centre, no steroid therapy, no previous surgery + 36 healthy controls matched for sex, residence, marital and socioeconomic status.	Case-control study; disease activity: sCDAI for CD and Truelove-Witts criteria for UC and a clinical rating scale (CRS); psychological assessment: STAI, Zung self-rating depression scale.	The percentage of subjects with state anxiety significantly higher in the CD ($P < 0.001$) and UC ($P < 0.001$) than in controls. The percentage of subjects with depression significantly higher in the CD ($P < 0.05$) and UC ($P < 0.05$) than in controls. State anxiety and depression significantly associated with physical morbidity and correlated with malnutrition in CD and UC patients.
Andrews et al. 1987 (UK)	162 consecutive patients (91 CD and 71 UC) attending IBD clinic, no controls.	Cohort prospective study; physical morbidity measured with CRS; psychological assessment: HADS; in addition a sample interviewed for DSM-III by a psychiatrist blinded to the HADS results.	Prevalence of psychiatric illness (DSM-III) in UC and CD was 34% and 33% respectively. No statistically significant association between the presence of psychiatric illness and the present physical illness in UC. Psychiatric illness more common in the physically ill CD patients compared with those who were well: 50% v 8% ($p < 0.01$), using HADS criteria 66% v 37% ($p < 0.001$). The presence of psychiatric illness adversely affected physical recovery. Seventeen percent recovered when psychiatrically ill v 53% when psychiatrically well ($p < 0.025$).

Name of the study	Sample and source of subjects	Methods	Results
Drossman et al. 1991 (USA)	997 members of the Crohn's and Colitis Foundation of America (320 UC and 671 CD), no controls.	Cross-sectional random survey; self-administered questionnaire measuring IBD symptoms, psychosocial health, medication use, daily functional status, perceptions of health, and coping styles. Survey included: SIP, SCL-90, and the Ways of Coping-Revised questionnaire.	The health status of this population is generally good and may be a result of effective coping styles. Patients with CD have more psychosocial difficulties, which appear related to greater symptom severity. Both psychosocial and physical health variables are related to number of physician visits, while primarily physical health variables are related to number of hospitalizations and surgeries.
Guthrie et al. 2002 (UK)	116 consecutive patients (75 CD, 37 UC, 4 unspecified) attending GI clinic with a special interest in IBD. No controls.	Cross-sectional survey; IBD-related factors questionnaire developed by Drossman et al. (see above), a modified disease activity index, a measure of the severity of IBD symptoms, HADS, and SF-36.	Thirty patients (25.9%) had a probable psychological problem; 55% (47.4%) had possible psychological problem (measured by HADS). Both psychological symptoms and disease severity or activity contributed independently to impaired health-related quality of life. After severity of disease taken into account, no significant differences between CD and UC in depression scores and health-related quality of life.
Helzer et al. 1982 (USA)	50 consecutive CD patients obtained either from the university clinic (22) or a private internist clinic (28) + 50 consecutive controls with chronic medical illnesses of various kinds excluding gastrointestinal disorders obtained from the same sources.	Case-control study; gastroenterological assessment: CDAI, psychiatric assessment: the Renard Research Interview, EPI, and the Paykel Life Events Inventory.	Compared with controls, a significantly greater number of the patients with CD met criteria for some psychiatric disorder at some time in their lives, and a significantly greater number had a diagnosis of depression. A greater number of CD patients than controls reported obsessional or phobic symptoms, and the mean number of obsessional symptoms was higher in CD patients than in controls. No evidence of an interaction between psychiatric disorder and CD.

238

Name of the study	Sample and source of subjects	Methods	Results
Helzer et al. 1984 (USA)	50 consecutive UC patients obtained either from the university clinic of gastroenterology (15) or a private internist clinic (37) + 50 consecutive controls with chronic medical illnesses of various kinds excluding gastrointestinal disorders obtained from the same sources.	Case-control study; gastroenterological assessment: barium enemas or x-rays or colonoscopy with biopsy; psychiatric assessment: structured psychiatric interview, EPI, a 90-item self- administered personality inventory, and the Paykel Life Events Inventory.	No greater frequency of diagnosable psychiatric problem in UC patients than in controls. Those with UC and a psychiatric illness did not appear to have more serious gastrointestinal involvement, nor did severity of the UC predict more frequent or more serious psychiatric problem. Personality profiles similar in UC patients and controls. No correlation between the frequency of potentially stressful life events within the six months prior to interview and severity of UC at the time of interview. Despite the fact that more than a quarter of the UC patients had some diagnosable psychiatric illness, the occurrence of psychiatric problem was rarely documented.
Kurina et al. 2001 (UK)	First study included 12,499 patients with IBD (7268 UC and 5231 CD) and 800,000 controls with minor medical conditions not related to the conditions of interest, obtained from the ORLS database of southern England reporting general hospital admissions. Second study included 41,324 patients with depression and 12,687 patients with anxiety and approximately 800,000 controls.	Retrospective nested case-control studies; using a database of linked hospital record abstracts to test whether UC or CD co-occurred with depression or anxiety more often than expected by chance.	Both depression and anxiety preceded UC significantly more often than would be expected from the studies with controls. The associations were strongest when the depression/anxiety was diagnosed shortly before UC. The association between depression and UC was also significant when depression preceded UC by five or more years. Neither depression nor anxiety occurred before CD more often than expected by chance. Depression and anxiety were significantly more common after CD; the associations were strongest in the year after the initial record of CD. UC was followed by anxiety, but not by depression, more often than expected by chance and the association was strongest within one year of diagnosis with UC.

Name of the study	Sample and source of subjects	Methods	Results
Levenstein et al. 1994 (Italy)	79 UC patients attending hospital IBD clinic. No controls.	Cross-sectional double-blind study comparing patients with and without symptoms of the disease; disease activity: Truelove and Witts criteria, by endoscopy with biopsy and by barium enema. Psychological assessment: the Paykel Interview for Recent Life Experiences, STAI, CES-D, and PSQ. Six days after psychological testing unprepared rigid proctoscopy performed by the physician blinded to earlier results.	Among asymptomatic patients, the level of stress over the past 2 yr on the General Perceived Stress Questionnaire was higher in the 11 with mucosal abnormalities than in the 35 with a normal rectal mucosa (p = 0.004). Among the entire population, symptomatic patients were more likely to recall major life events in the previous 6 months than the asymptomatic group (p = .02). The association of perceived stress with rectal mucosal abnormalities in asymptomatic patients is strongly suggestive of a true link between psychological factors and ulcerative colitis activity. Symptomatic patients had higher level of perceived stress, trait and state anxiety and depression.
Magni et al. 1991 (France and Italy)	50 consecutive UC patients tertiary referral centre + 50 controls with urolithiasis or symptomatic varicocele matched with UC patients for sex, age and marital status.	Case-control study; disease activity: Edwards & Turnlove's classification. Psychological assessment: SAD-L and SCL-90.	History of psychiatric disturbance found in 11 UC patients (22%) and 8 controls (16%). At the time of the interview a psychiatric disturbance was present in 31 UC patients (62%) and four controls (8%). The most frequent diagnoses in UC patients were minor depression and generalized anxiety disorder. Patients with UC scored significantly higher than the controls on all the different SCL-90 subscales.

Name of the study	Sample and source of subjects	Methods	Results
Mittermaier et al. 2004 (Austria)	60 consecutive patients with IBD (47 CD and 13 UC) in remission obtained from tertiary clinic. No controls.	Cohort prospective study with follow-up tests every 3 months for 18 months. Disease activity: CDAI and CAI. Psychological status: BDI, STAI, IBDQ, PSQ, and RFIPC.	At baseline, depression found in 17 of 60 (28%) patients. Thirty-two patients (59%) experienced at least one relapse during the 18 months of follow-up. BDI scores at baseline significantly correlated with the total number of relapses after 12 ($p < .01$) and 18 months ($p < .01$) of follow-up. Depression scores at baseline correlated with the time until the first recurrence of the disease ($p < .05$). Anxiety and low HRQOL also related with more frequent relapses during follow-up ($p < .05$ and $p < .01$, respectively).
Nordin et al. 2002 (Sweden)	492 patients with IBD (161 CD and 331 UC) identified by a registry at the university IBD clinic. A population-based sample. No controls.	Cross-sectional self-administered postal questionnaire comprising: SF-36, IBDQ, and HADS. Disease history collected from the register.	Patients with UC reported higher levels in all dimensions of health-related and disease-specific quality of life than did patients with CD. CD patients reported more anxiety and depression than did patients with UC. Patients with ileoanal anastomosis were more anxious and depressed than those with ileostomy.
North et al. 1994 (USA)	Twelve articles with > or = 10 subjects (10 out of 12 studies were controlled) on which statistical data were reported from standardized instruments of measure included.	Systematic review of the literature on psychiatric factors in CD with special attention to research methodology.	Most studies reported a significant association between CD and psychiatric factors. Many of the investigative groups reporting such an association in CD had also studied UC and failed to find a similar association in that disease. Published data indicate that CD, unlike ulcerative colitis, may be statistically associated with lifetime psychiatric disorders. This association appears to be more modest than in IBS, in which far higher rates of psychiatric disorders are reported than in CD.

Name of the study	Sample and source of subjects	Methods	Results
Robertson et al. 1989 (UK)	80 consecutive patients with IBD (44CD and 36 UC) + 22 consecutive new referrals with suggested IBD (16 CD and 6 UC) + 40 controls with diabetes.	Case-control study; disease activity assessment not specified; psychological status: the questionnaire designed to assess patients' adjustment to IBD and their quality of life, EPI, and HADS.	High neuroticism and introversion scores in patients with IBD (both before diagnosis and in established cases) than in controls (p less than 0.05). Introversion scores increased with the duration of disease (r = 0.51). Depression was uncommon, occurring only in patients with active chronic disease. Patients believed there was a close link between personality, stress and disease activity. Forty two patients with IBD thought the disease was initiated by a stressful life event or a 'nervous personality'.
Schwartz et al. 1982 (USA)	46 CD patients seen in psychiatric consultation at the public clinic and hospital.	Cross-sectional retrospective review of clinical records. The researchers analysed: demographic data, reason for psychiatric visit, duration of contact, history of IBD, current and past medication, history of significant stress (excluding this associated with IBD), and history of traumatic childhood.	The most common reason that psychiatric consultation was requested was depression, followed by pain and narcotic-related problems. Factors which appeared to contribute to psychiatric morbidity were: duration of CD, frequent hospitalizations and surgical procedures, presence of an ostomy, history of proctocolectomy, current psychosocial stress unrelated to Crohn's disease and a history of traumatic childhood experiences.

Name of the study	Sample and source of subjects	Methods	Results
Simren et al. 2002 (Sweden)	242 patients with IBD (110 CD and 132 UC) from the university clinic + controls (normal values for the PGWB, GSRS, and HADS derived from the Swedish population; results of STAI compared with American working adults).	Case-control study; disease activity: by colonoscopy, rigid sigmoidoscopy, and blood tests. Psychological assessment: GSRS, HADS, STAI and PGWB.	The psychological well-being in patients with IBD in long-standing remission similar to that of the general population. CD patients reported more psychosocial dysfunction, reduced well-being, and GI symptoms than UC patients. Thirty-three percent of UC patients and 57% of CD patients had IBS-like symptoms. The group with IBS-like symptoms (both UC and CD) had higher levels of anxiety and depression and more reduced well-being than those without. Anxiety and reduced vitality were found to be independent predictors for IBS-like symptoms in these patients.
Tanaka et al. 2005 (Japan)	77 UC consecutive patients obtained from the university internal medicine clinic. No controls.	Cross-sectional survey; assessment: questionnaire measuring patients' perception of difficulties of life, POMS, Jalowiec Coping Scale, the Emotional Support Network Scale, and with the use of clinical records.	A relatively large number of patients perceived a 'decline of vitality or vigour' despite being in the remission phase. In the presence of IBS-like symptoms, the scores for 'difficulties of life in society' or 'difficulties concerned with bowel movements' were high.
Tarter et al. 1987 (USA)	53 consecutive patients with IBD (26 CD and 27 UC) tertiary clinic + 28 normal controls obtained by advertisements.	Case-control study; disease activity: clinical examination; psychiatric assessment: DIS	Compared to normal controls, CD patients manifest an increased prevalence of anxiety, depression and panic disorder occurring at any time in their life. Only panic disorder had an excess prevalence in CD relative to community dwelling normals prior to the time of disease onset. Individuals with UC did not demonstrate an increased prevalence of psychiatric disorder before or after disease onset.

Legend:

BDI – Beck Depression Inventory

BMI – body mass index

CAI- Colitis Activity Index

CD – Crohn's disease

CES-D – the Center for Epidemiological Studies Depression Scale

CRS – Clinical Rating Scale

DIS – the Diagnostic Interview Schedule

EPI – the Eysenck Personality Inventory

GSRS – Gastrointestinal Symptom Rating Scale

HADS – the Hospital Anxiety and Depression Scale

IBD – inflammatory bowel disease

IBDQ – Inflammatory Bowel Disease Questionnaire

IBS – irritable bowel syndrome

PGWB – Psychological General Well-Being Index

POMS – Profile of Mood States

PSQ – the Perceived Stress Questionnaire

RFIPC – Rating Form of Inflammatory Bowel Disease Patient Concerns

SADS-L – the Schedule for Affective Disorders and Schizophrenia

sCDAI – simplified Crohn's Disease Activity Index

SCL-90 – the Symptom Check List 90

SIP – the Sickness Impact Profile

STAI – the State and Trait Anxiety Inventory

UC - ulcerative colitis

Yr – year

INFORMATION SHEET FOR RESEARCH PARTICIPANTS version 1
(version for patients with ulcerative colitis or Crohn's disease)

Dear Patient,

The Department of Gastroenterology at the Royal Adelaide Hospital and the Departments of Psychology and of General Practice at the University of Adelaide would like to invite you to participate in a study looking at ways to better manage inflammatory bowel disease (IBD).

Purpose of this study
The purpose of this study is to understand how psychological and quality of life issues may affect your experience of inflammatory bowel disease.

Your rights
This is a research project and you do not have to be involved. If you do not wish to participate, your usual medical care will not be affected in any way. You can also withdraw from the study at any time. If you decide to participate, your personal data will be treated confidentially and you will not be personally identified in any published results.

Description of the procedure
During this study you will receive your usual treatment. However, on 5 occasions, during 1 year, we will approach you to complete questionnaires about your health, psychological wellbeing and quality of life. This may be done either in the hospital or via post. Answering these questionnaires may take you about 40 minutes each time. The researcher will provide you with a reply paid envelope so that you can send them back. If you forget about filling in and sending your questionnaires back, the researcher will call you three times to remind you about our study. The researcher who will read your questionnaires is not involved in your medical treatment. Therefore, you should feel free to give frank responses to all the questions, as accurate answers are important. Your doctor will also provide the researcher with information about the activity of your inflammatory bowel disease and your treatment during this period, and give the researcher the access to your case-notes.

Randomization
The questionnaires may indicate that some patients have psychological problems (in addition to their inflammatory bowel disease). In this study, a half of patients who are diagnosed with psychological problems will have the results of their questionnaires revealed to the treating doctors. The other half of participants will be a control group and doctors will not be informed about each patient's scores on the psychological questionnaires. However, your doctor may still treat you for any psychological problems if he/she feels it to be necessary. If the study unexpectedly reveals that you suffer from a serious psychological problem, your doctor will be told irrespective of whether you are in a study or a control group, and you will be informed about your treatment options, so your usual care will not be affected.

Your safety
As this study involves neither medication nor painful procedures, there is no foreseeable physical risk for you. However, you should be aware that you will have to devote about 40 minutes of your time for filling in questionnaires on 5 occasions during 1 year.

Possible benefits
Your participation in this trial may help us to understand the psychological aspects of inflammatory bowel disease and to improve medical care for IBD patients in the future. However, you should be aware that you may not directly benefit from the study.

If you have any questions, you can contact:
Antonina Mikocka-Walus, main researcher, work: (08) 8303 5829 or (08) 8303 3460, after hours: (08) 8332 9450, or email: antonina.mikockawalus@adelaide.edu.au
Prof. Deborah Turnbull, Primary Supervisor, work: (08) 83035738
Dr Nicole Moulding, Supervisor, work: (08) 8303 3456
Dr Jane Andrews, Supervisor, work: 0417 814 828
Prof. Gerald Holtmann, Director of the Department of Gastroenterology and Hepatology, the Royal Adelaide, Hospital, work: 8222 2412, after hours: 0400107754
Treating Doctor's contact number

If you wish to speak to someone not directly involved in the study about your rights as a volunteer, or about the conduct of the study, you may also contact the Chairperson, Research Ethics Committee, Royal Adelaide Hospital on 8222 4139.

If you wish to take part in this study please call Ms Antonina Mikocka-Walus on (08) 8303 5829 or (08) 8303 3460 or send your name in the attached paid envelope.

Thank you,

Treating Doctor's
name……………………………………………………………………………….

<h1 style="text-align:center">INFORMATION SHEET FOR RESEARCH PARTICIPANTS version 2
(version for patients with hepatitis C)</h1>

Dear Patient,

The Department of Gastroenterology at the Royal Adelaide Hospital and the Departments of Psychology and of General Practice at the University of Adelaide would like to invite you to participate in a study looking at ways to better manage hepatitis C (HCV).

Purpose of this study
The purpose of this study is to understand how psychological and quality of life issues may affect your experience of your disease.

Your rights
This is a research project and you do not have to be involved. If you do not wish to participate, your usual medical care will not be affected in any way. You can also withdraw from the study at any time. If you decide to participate, your personal data will be treated confidentially and you will not be personally identified in any published results.

Description of the procedure
During this study you will receive your usual treatment. However, on 2 occasions during 1 year we will approach you to complete questionnaires about your health, psychological wellbeing and quality of life. This may be done either in the hospital or via post. Answering these questionnaires may take you about 40 minutes each time. The researcher will provide you with a reply paid envelope so that you can send them back. The researcher who will read your questionnaires is not involved in your medical treatment. Therefore, you should feel free to give frank responses to all the questions, as accurate answers are important. Your doctor will also provide the researcher with information about the activity of your hepatitis C and your treatment during this period, and give the researcher the access to your case-notes.

Your safety
As this study involves neither medication nor painful procedures, there is no foreseeable physical risk for you. However, you should be aware that you will have to devote about 40 minutes of your time for filling in questionnaires on 2 occasions during 1 year.

Possible benefits
Your participation in this trial may help us to understand the psychological aspects of hepatitis C and to improve medical care for HCV patients in the future. However, you should be aware that you may not directly benefit from the study.

If you have any questions, you can contact:
Antonina Mikocka-Walus, main researcher, work: (08) 8303 5829 or (08) 8303 3460, after hours: (08) 8332 9450, or email: antonina.mikockawalus@adelaide.edu.au
Prof. Deborah Turnbull, Primary Supervisor, work: (08) 83035738
Dr Nicole Moulding, Supervisor, work: (08) 8303 3456
Dr Jane Andrews, Supervisor, work: 0417 814 828
Prof. Gerald Holtmann, Director of the Department of Gastroenterology and Hepatology, the Royal Adelaide, Hospital, work: 8222 2412, after hours: 0400107754
Treating Doctor's contact number

If you wish to speak to someone not directly involved in the study about your rights as a volunteer, or about the conduct of the study, you may also contact the Chairperson, Research Ethics Committee, Royal Adelaide Hospital on 8222 4139.

If you wish to take part in this study please call Ms Antonina Mikocka-Walus on (08) 8303 5829 or (08) 8303 3460 or send your name in the attached paid envelope.

Thank you,

Treating Doctor's signature……………………………………………………………….

INFORMATION SHEET FOR RESEARCH PARTICIPANTS version 3
(version for patients with irritable bowel syndrome)

Dear Patient,

The Department of Gastroenterology at the Royal Adelaide Hospital and the Departments of Psychology and of General Practice at the University of Adelaide would like to invite you to participate in a study looking at ways to better manage irritable bowel syndrome (IBS).

Purpose of this study
The purpose of this study is to understand how psychological and quality of life issues may affect your experience of your disease.

Your rights
This is a research project and you do not have to be involved. If you do not wish to participate, your usual medical care will not be affected in any way. You can also withdraw from the study at any time. If you decide to participate, your personal data will be treated confidentially and you will not be personally identified in any published results.

Description of the procedure
During this study you will receive your usual treatment. However, on 2 occasions during 1 year we will approach you to complete questionnaires about your health, psychological wellbeing and quality of life. This may be done either in the hospital or via post. Answering these questionnaires may take you about 40 minutes each time. The researcher will provide you with a reply paid envelope so that you can send them back. The researcher who will read your questionnaires is not involved in your medical treatment. Therefore, you should feel free to give frank responses to all the questions, as accurate answers are important. Your doctor will also provide the researcher with information about the activity of your irritable bowel disorder and your treatment during this period, and give the researcher the access to your case-notes.

Your safety
As this study involves neither medication nor painful procedures, there is no foreseeable physical risk for you. However, you should be aware that you will have to devote about 40 minutes of your time for filling in questionnaires on 2 occasions during 1 year.

Possible benefits
Your participation in this trial may help us to understand the psychological aspects of irritable bowel syndrome and to improve medical care for IBS patients in the future. However, you should be aware that you may not directly benefit from the study.

If you have any questions, you can contact:
Antonina Mikocka-Walus, main researcher, work: (08) 8303 5829 or (08) 8303 3460, after hours: (08) 8332 9450, or email: antonina.mikockawalus@adelaide.edu.au
Prof. Deborah Turnbull, Primary Supervisor, work: (08) 83035738
Dr Nicole Moulding, Supervisor, work: (08) 8303 3456
Dr Jane Andrews, Supervisor, work: 0417 814 828
Prof. Gerald Holtmann, Director of the Department of Gastroenterology and Hepatology, the Royal Adelaide, Hospital, work: 8222 2412, after hours: 0400107754
Treating Doctor's contact number

If you wish to speak to someone not directly involved in the study about your rights as a volunteer, or about the conduct of the study, you may also contact the Chairperson, Research Ethics Committee, Royal Adelaide Hospital on 8222 4139.

If you wish to take part in this study please call Ms Antonina Mikocka-Walus on (08) 8303 5829 or (08) 8303 3460 or send your name in the attached paid envelope.

Thank you,

Treating Doctor's
signature…………………………………………………………………….

Appendix 3
Royal Adelaide Hospital consent form No 1 (IBD patients)

PROTOCOL NAME: Psychological and quality of life issues in inflammatory bowel disease

INVESTIGATORS: Antonina Mikocka-Walus (PhD student), Prof. Deborah Turnbull, Dr Jane Andrews, Prof. Gerald Holtmann, Dr Nicole Moulding, Prof. Ian Wilson

The nature and purpose of the research project has been explained to me. I understand it, and agree to take part.
I understand that I may not directly benefit from taking part in the trial.
I understand that, while information gained during the study may be published, I will not be identified and my personal results will remain confidential.
I understand that the researcher may review my case-notes for the study purpose.
I understand that I can withdraw from the study at any stage and that this will not affect my medical care, now or in the future.
I have had the opportunity to discuss taking part in this investigation with a family member or friend.

Name of Participant: --

Signed: --

Dated: ---

I certify that I have explained the study to the patient/volunteer and consider that he/she understands what is involved.

Signed: -- Dated: ----------------------------
                    (Investigator)

Royal Adelaide Hospital consent form No 2 (IBS and HCV patients)

PROTOCOL NAME: Psychological and quality of life issues in irritable bowel syndrome and hepatitis C

INVESTIGATORS: Antonina Mikocka-Walus (PhD student), Prof. Deborah Turnbull, Dr Jane Andrews, Prof. Gerald Holtmann, Dr Nicole Moulding, Prof. Ian Wilson
The nature and purpose of the research project has been explained to me. I understand it, and agree to take part.
I understand that I may not directly benefit from taking part in the trial.
I understand that, while information gained during the study may be published, I will not be identified and my personal results will remain confidential.
I understand that the researcher may review my case-notes for the study purpose.
I understand that I can withdraw from the study at any stage and that this will not affect my medical care, now or in the future.
I have had the opportunity to discuss taking part in this investigation with a family member or friend.

Name of Participant: ---

Signed: ---

Dated: ---

I certify that I have explained the study to the patient/volunteer and consider that he/she understands what is involved.

Signed: -- Dated: -----------------------------
              (Investigator)

Appendix 4
A letter to treating gastroenterologist

Doctor's room address

Date

Dear Doctor ……,

This letter is intended to inform you that your patient………has agreed to participate in a study entitled "Psychological factors and response to medical treatment: Do psychological factors determine the outcome in patients with inflammatory bowel disorders and other common gastrointestinal and hepatologic disorders?"*.

As a part of this study we are assessing anxiety and depression scores in all patients, and provide you with this information. …….. scored …….on the Hospital Anxiety and Depression Scale Anxiety Subscale and this outcome may be interpreted as a possible/probable clinical disorder.

In this trial we are assessing the long-term outcome of patients with a number of conditions. Within this trial there is no specific treatment and your routine management should not be affected by this study.

The member of the study group and their contact details are listed above. Again, this letter is only for you information and does not require any specific actions from your side. Your routine clinical management should not be altered. If there are any questions, please do not hesitate to contact me on 83035829.

Sincerely yours,

Antonina Mikocka-Walus
Doctoral Research Candidate

* The study protocol has been approved by the Royal Adelaide Hospital Research Ethics Committee (protocol no 051009) and is being organised by the Department of Gastroenterology, Hepatology and General Medicine, the Royal Adelaide Hospital (Prof. Gerald Holtmann, Dr Jane Andrews, Ms Antonina Mikocka-Walus), and by the School of Psychology (Prof. Deborah Turnbull, Ms Antonina Mikocka-Walus), and Discipline of General Practice (Dr Nicole Moulding, Prof. Ian Wilson, Ms Antonina Mikocka-Walus) of the University of Adelaide.

Appendix 5
Survey for inflammatory bowel disease patients

Name:………………………………………………………………………………...

Address:………………………………………………………………………………

Age:…………………………date of birth…………………………..

Sex:………………………………………………………………………….
Education:……………………………………………………………………….

How many years with IBD symptoms:………………………………………………..
How many years with diagnosed IBD:………………………………………………..
What is your main concern with having IBD?:……………………………………
………………………………………………………………………………………..
………………………………………………………………………………………………
………………………………………………………………………………..
Other chronic diseases (gastrointestinal and psychiatric):……………………………
………………………………………………………………………………………………
………………………………………………………………………………………………
………………………………………………………………………………..
Any operations:………………………………………………………………………
………………………………………………………………………………………………
Current medication:(prescription + other):……………………………………..
………………………………………………………………………………………………
………………………………………………………………………………………
Previous medications for IBD:………………………………………………………..
………………………………………………………………………………………….
How long since last remission:…………………………………………………………
CDAI / SCCAI:…………………………………………………………………………
CRP………………………………………………………………………………….
Any other recent results (CT colonoscopy etc)………………………………………

Appendix 6
Survey for irritable bowel syndrome patients

Name:………………………………………………………………………………...

Address:…………………………………………………………………………………

Age:……………………….Date of birth……………………………………………….

Sex:………………………………………………………………………………..

Education:………………………………………………………………………………

How many years with diagnosed IBS:……………………………………………………

How many years with IBS symptoms …………………………………………………….

What is your main concern with having IBS?……………………………………………..

Other chronic diseases (gastrointestinal and psychiatric)…………………….......……..

……………………………………………………………………………………………

……………………………………………………………………………………..

Any operations:………………………………………………………………..

……………………………………………………………………………………………

…………………………………………………………………………………..

Current medication (prescription + other)………………………………………………

……………………………………………………………………………………………

How long on this medication:……………………………………………………………..

Previous medications for IBS…………………………………………………………...

……………………………………………………………………………………………

What are your predominant symptoms?

Diarrhoea

Constipation

Both

How long since last remission:……………………………………………………………

Have you got satisfactory control of your IBS symptoms over the last 3 months?

Yes   No

Are you now feeling better or worse when compared to your last visit in the clinic?

Better   Worse

Appendix 7
Survey for hepatitis C patients

Name:……………………………………………………………………………...

Address:……………………………………………………………………………

Age:……………………….Date of Birth……………………………………….

Sex:………………………………………………………………………..

Education:……………………………………………………………………….

Year of diagnosis with HCV:……………………………………………………

Year you contracted HCV (if known):……………………………………………

How contracted:………………………………………………………………….

Other chronic diseases (gastrointestinal and psychiatric):……………………………

……………………………………………………………………………………………

………………………………………………………………………………

What is your main concern regarding your HCV infection?……………………………

……………………………………………………………………………………

Any operations:……………………………………………………………………

……………………………………………………………………………………

Current medication:(prescription + other):……………………………………………

……………………………………………………………………………………

Previous treatment for HCV:………………………………………………………

………………………………………………………………………………………………

………………………………………………………………………………..

Do you also suffer from hepatitis B?:…………………………………………………..

If yes please give:

HbsAg.…………………………………………

HbeAg.…………………………………………….

Anti-HCV anti-body:……………………..………………………………………..

rt-pcr HCVRNA:………………………………………………………………..

Liver function tests (from notes)………………………………………………………

Ascites

Absent

Slight

Moderate

Bilirubin.…………………………………………………………………………….

Albumin.…………………………………………………………………………..

INR (or Prothrombin time)………………………………………………………………

Encephalopathy

None

Grade 1-2

Grade 3-4

Blood count.…………………………………………………………………………

Haemoglobin.………………………………………………………………………

Platelets.……………………………………………………………………………

MCV.………………………………………………………………………………

Appendix 8
Crohn's Disease Activity Index (CDAI)

The CDAI score is derived from summation of information collected from a diary card completed by the patient for the preceding 7 days, together with current clinical data.

Days 1 to 7	Sum	X factor	Score
Number of liquid or very soft stools in one week	____	2	____
Sum of 7 daily abdominal pain ratings (0 = none; 1 = mild; 2 = moderate; 3 = severe)	____	5	____
Sum of 7 daily ratings of general well-being (0 = generally well; 1 = slightly under par; 2 = poor; 3 = very poor; 4 = terrible)	____	7	____
Symptoms or findings presumed related to Crohn's disease: 1 point for each set that corresponds to patient's symptoms: Arthritis or arthralgia (inflammation of the joints); Iritis or uveitis (inflammation of the eye); Erythema nodosum, pyoderma gangrenosum or aphthous stomatitis (inflammation of the skin); Anal fissure, fistula or abcess; Other bowel-related fistula; Febrile episode of over 37 degrees C in the past week	____	20	____
Taking opiods for diarrhoea (0 = no; 30 = yes)	____		____
Abdominal mass (0 = none; 20 = questionable; 50 = definite)	____		____
Haematocrit (%) Males: 47 – 'crit Females: 42 – 'crit	____	6	____
Body weight (kg) 100 x [(standard weight for height – actual body weight)/standard weight for height]	____ kg		____cm
Total CDAI			____

Appendix 9
Simple Clinical Colitis Activity Index

Symptom   Score

Bowel frequency (day)
0
1
2
>9   3

Bowel frequency (night)
1
2

Urgency of defecation
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

Range 0-16
< 2 remission or a reduction of more than 3 points
> 5 relapse

Hospital Anxiety and Depression Scale

1. I feel tense or 'wound up':

Most of the time
A lot of the time
From time to time, occasionally
Not at all

2. I still enjoy the things I used to enjoy:

Definitely as much
Not quite so much
Only a little
Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen:

Very definitely and quite badly
Yes, but not too badly
A little, but it doesn't worry me
Not at all

4. I can laugh and see the funny side of things:

As much as I always could
Not quite so much now
Definitely not so much now
Not at all

5. Worrying thoughts go through my mind:

A great deal of time
A lot of the time
From time to time but not too often
Only occasionally

6. I feel cheerful:

Not at all
Not often
Sometimes
Most of the time

7. I can sit at ease and feel relaxed:

Definitely
Usually
Not often
Not at all

8. I feel as if I am slowed down:

Nearly all the time
Very often
Sometimes
Not at all

9. I get a sort of frightened feeling like 'butterflies' in the stomach:

Not at all
Occasionally
Quite often
Very often

10. I have lost interest in my appearance:

Definitely
I don't take as much care as I should
I may not take quite as much care
I take just as much care as ever

11. I feel restless as if I have to be on the move:

Very much indeed
Quite a lot
Not very much
Not at all

12. I look forward with enjoyment to things:

As much as ever I did
Rather less than I used to
Definitely less than I used to
Hardly at all

13. I get sudden feelings of panic:

Very often indeed
Quite often
Not very often
Not at all

14. I can enjoy a good book or radio or TV programme:

Often
Sometimes
Not often
Very seldom

Now, please check that you have answered all the questions.

Thank you!

Appendix 11

Bowel Disease Questionnaire (BDQ)

NOTE: This appendix is included on pages 261-278 in the print copy of the thesis held in the University of Adelaide Library.

Dear Colleague,

The Department of Gastroenterology in the Royal Adelaide Hospital and the University of Adelaide would like to invite you to participate in a study regarding psychological aspects of inflammatory bowel disease (IBD).

Stress and inflammatory bowel disease
Many patients and researchers have thought that there may be a relation between stressful life events and activity of IBD. Moreover, it is known that a significant number of IBD patients suffer from psychological disorders such as depression and anxiety. These disorders affect patients' personal lives, but may be effectively treated with antidepressant medication. Some scientific observations and studies have suggested that IBD improves after therapy with antidepressants.

Purpose of this study
We therefore wish to examine your and other doctors' opinions and experiences as regards the use of antidepressants in patients with IBD. We would like to discover whether you feel there is any influence on the course of IBD in patients who are specifically treated for co-morbid psychological disorders.

Possible benefits
Your attendance in this trial may help us to discover whether there is enough of a body of anecdotal clinical evidence to justify further research into the role of antidepressants in IBD. This is a research PhD student project and you are not obliged to be involved, as you will not directly benefit.

What you will be asked to do
If you agree to participate, a member of our research team will interview you. The interview will be a short questionnaire comprising 16 questions. Your answers will be treated confidentially. Data will be analysed in a de-identified fashion, and only group data will be reported. You may withdraw from the study at any stage.

If you had any questions do not hesitate to call:
Antonina Mikocka-Walus, the main researcher, work: (08) 8303 5829, after hours: (08) 8232 2423 (psychological questions)
Dr Jane Andrews, gastroenterologist, work: 82225918, after hours: 0417 814 828
Prof. Gerald Holtmann, Director of the Department of Gastroenterology and Hepatology, the Royal Adelaide, Hospital, work: 8222 2412, after hours: 0400107754

If you wish to speak to someone not directly involved in the study about your rights as a volunteer, or about the conduct of the study, you may also contact the Chairman, Research Ethics Committee, Royal Adelaide Hospital on 8222 4139.

Thank you,

Antonina Mikocka-Walus (PhD candidate)………………………………………………….

 Prof. Deborah Turnbull (Principal Supervisor)………………………………………………...

PROTOCOL NAME: Do antidepressants have an impact on the course of inflammatory bowel disease?

INVESTIGATORS: Antonina Mikocka-Walus (PhD student), Prof. Deborah Turnbull, Dr Jane Andrews, Prof. Gerald Holtmann, Dr Nicole Moulding, Prof. Ian Wilson

The nature and purpose of the research project has been explained to me. I understand it, and agree to take part.
I understand that I may not directly benefit from taking part in the trial.
I understand that, while information gained during the study may be published, I will not be identified and my personal results will remain confidential.
I understand that I can withdraw from the study at any stage.

Name of Participant: --

Signed: --

Dated: ---

I certify that I have explained the study to the Gastroenterologist and consider that he/she understands what is involved.

Signed: -- Dated: ----------------------------

PROTOCOL NAME: Do antidepressants have an impact on the course of inflammatory bowel disease?

INVESTIGATORS: Antonina Mikocka-Walus (PhD student), Prof. Deborah Turnbull, Dr Jane Andrews, Prof. Gerald Holtmann, Dr Nicole Moulding, Prof. Ian Wilson

Questionnaire

1. What is your experience of treating inflammatory bowel disease patients?

- How comfortable do you feel with treating IBD patients?

2. How many patients with IBD have you treated?

This week

This month

This year

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

If yes:
3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?

3c. What was the result of this treatment?

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?

If no:
3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?

4. What is your opinion of the use of antidepressants in IBD in general?

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

6. What is your opinion of the use of antidepressants in general?

7. Have you ever suggested using other psychological treatment in IBD patients?

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

9. Would you like to add any comments?

10. Would you like to receive a copy of results of this study?

11. What is the cause of IBD?

Demographics:

Age:
Sex:
Undergraduate studies where:
Postgraduate studies where:
How many years in gastroenterology:
Were you born in Australia:
Do you speak other languages:
In high school did you graduate in sciences or humanities:

Participant 1

Thursday 6 October

Age: 40
Sex: ▮▮▮
Undergraduate studies where: ▮▮▮▮▮▮▮▮▮
Postgraduate studies where: ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮
▮▮▮▮
How many years in gastroenterology: 6 years full-time and 3 years part-time doing PhD
Were you born in Australia: No
Do you speak other languages: Yes, ▮▮▮▮▮▮
In high school did you graduate in sciences or humanities: More Science. 4 out of 5
subjects in Sciences.
Patients per week: 5-10
Work: RAH

1. What is your experience of treating inflammatory bowel disease patients?

I guess full-time 6 years and part-time 3 years

- How comfortable do you feel with treating IBD patients?

I feel comfortable

2. How many patients with IBD have you treated?

I guess it is about 5 to 10 per week.
Ok, so I can count it. Generally, 5-10 patients per week?
You mean new patients?
Yes. Generally.

This week	5-10
This month	20-40
This year	300

3. Have you ever used antidepressants or suggested using antidepressants in these patients
for any reason?

Yes.

If yes:
3a. Did you notice any difference in the effect of antidepressants on the disease between
CD and UC patients?

Can't say I really can answer this question. I tend to use antidepressants in Crohn's. I think
the pain is more severe in Crohn's disease. I am not sure about the difference between
Crohn's and ulcerative colitis.

- Did you use antidepressants mainly for pain or for depression?

Mainly for pain.

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order?
Amitriptyline usually.
- What were your reasons? Why not SSRI?

I prefer tricyclics from SSRI because of the pain modulation.

3c. What was the result of this treatment?

I don't know. No idea. I guess in patients I used to treat probably half patients benefited.

- Was it effective?
In about 50% of cases.

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?

No.

If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?
NA

4. What is your opinion of the use of antidepressants in IBD in general?

I guess they have two roles. One is for treating depression and then for pain modulation. SSRIs for treating depression, and tricyclics for pain modulation.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

On inflammatory avtivity I am not aware of any impact.

6. What is your opinion of the use of antidepressants in general?

Well, I guess in patients with a chronic disease depression is more common. So there are areas where they can be very useful. For the patients I see often, population with hepatitis C they can be very useful. So I commonly prescribe SSRI and other antidepressants in these patients. Mainly for depression.

7. Have you ever suggested using other psychological treatment in IBD patients? Psychotherapy? Stress programs? Relaxation?

I have suggested hypnotherapy.

- Was it effective?
I do not know whether it was an effective treatment. I did not see the patient again. Sorry, did you say IBD or IBS?
- IBD.
That was patient with IBS. So I haven't used antidepressants in IBD.

- Why hypnotherapy?

There is a group in UK which has used hypnotherapy very successfully in IBS.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

Pretty good.
9. Would you like to add any comments?

Sounds like an interesting idea for PhD.

10. Would you like to receive a copy of results of this study?

That would be good.

11. What is the cause of IBD?
Yyyyyy

- In your opinion? I know there are different opinions.

Well, I don't know. I guess it appears to be an immunological mechanism. It seems to be important in developing CD. Defect of immunity. In UC I just have no idea.
Thank you very much.

Participant 2

Wednesday 12th October 2005

Age: 53
Sex: ███
Undergraduate studies where: ████████████
Postgraduate studies where: ████████████████████████████
███████
How many years in gastroenterology: 24
Were you born in Australia: Yes
Do you speak other languages: Not very well, ██████████████████████
██████

In high school did you graduate in sciences or humanities: Sciences
Patients per week: 5
Work: RAH

1. What is your experience of treating inflammatory bowel disease patients?

Well, it is a 25-year experience of treating IBD patients. That is in clinical practice, in private and public sector. And let's see, that involved patients with Crohn's disease, ulcerative colitis and indetermined colitis.

- How comfortable do you feel with treating IBD patients?

No problems at all.

2. How many patients with IBD have you treated?

This week probably 5, month 20, year 200.
This week   5

This month   20

This year   200

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

Certainly.

What were the reasons?

Evidence of depression or significant mood disorder which might include anxiety as well.

If yes:

3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?

No.

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?

It's changed over the years as the new generation of drugs have come through. So in the early stages it was predominantly dethyphyn, that was the preferred antidepressant 20 years ago. In more recent years it's been citalopram and mirtazapine that are my favourite ones.

- And why did you choose those antidepressants?

In terms of dethyphyn it was the preferred antidepressant as I said 15-20 years ago. In terms of SSRI, citalopram, I guess, it's just one that I became familiar with. It certainly has its drawbacks. Its benefits are that it has a bit of an anxiolitic effect as well as antidepressant effect. The drawback is particularly in male patients, for it has very significant sexual disfunction associated with it. So I have sort of moved to mirtazapine, which is non-SSRI, because it does not have this sexual disfunction, it has a similar sort of scope in terms of anxiety and depression and its appropriate management. Finally, it has an appetite stimulant effect which is sometimes quite useful in patients with IBD.

3c. What was the result of this treatment?

Well, I think you have to look at it in that I use the drug because somebody has a mood disorder. I do not use the drug because they have inflammatory bowel disease. So I would hope that the treatment for the mood disorder is effective. Otherwise, I wouldn't keep them on the treatment. I would look for other strategies to deal with their anxiety and depression. In terms of the underlying disease, I don't think that I can comment as to whether the treatment for the mood disorder actually improves the inflammatory bowel disease. What I undertake to do in treating mood disorder is improve the ability the person to cope with their disease. I often put it to them that I am yet to be totally convinced that mood disorders actually affect disease activity. But that the way they perceive themselves and the way their mood is certainly makes a difference to how they manage their disease. I can use analogy: If you just drop a brick on your toe and you are depressed, it hurts a lot. When you drop a brick on your toe and you have just won taxlotto, it doesn't hurt so much. They seem to be able to understand that.

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?

I don't think it influences the activity of the IBD. The IBD is occurring in an individual and individual's ability to manage the disease can clearly be improved by managing the accompanying mood disorder.

If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?

NA

4. What is your opinion of the use of antidepressants in IBD in general?

Well, I think that you have to keep an ear to the ground for mood disorder. It's very easy to overlook it. But you always need to remind yourself that there is a patient there who happens to have inflammatory bowel disease and that you need to keep your mind on the patient, and if there are significant issues, environmental issues, you might have to help them deal with those, or help let their general practitioner deal with those.

And if there are significant mood disorders then they may require pharmacotherapy as well. I don't order psychotropic medication because I think it's going to improve the disease.

OK.

5. To what extent do you think antidepressants can have an impact on the disease? What impact? So we say that not so big.

No, I don't think it has.

Only managing of the disease?

Yes, it's only managing of the patient who has the disease rather than managing the disease.

6. What is your opinion of the use of antidepressants in general?
█████████████████. We know that adults in Australia have a 30% incidence, lifetime incidence, of significant mood disorders. So I'm here to help people deal with those and lot of them I think is situational. So you have to try again with the General Practitioner and other avenues to help people with situational circumstances that lead to mood disorders, particularly if they are vegetative symptoms of organic depression, and I think it is very important that antidepressants are considered as part of that management program. But some patients don't want to take them. So you could use other strategies to help them.

6a. There are also patients who cannot stop. They take antidepressants lifelong. What do you think about side effects in the long distance? Because this is a new I think problem. I don't embark on the antidepressant tablets with the understanding that it will be life-long. I would generally use them for 4-6 months and review. And in many instances I would try to withdraw the medication. And then in the fullness of time I understand whether they may be it longer term.

6b. I know that there is a theory, now some doctors believe that 5 years is a period to treat depression so ceasing antidepressants before this period is really pointless because there usually be a comeback of the disease.

Well, I think when you look at people who have depression and a chronic illness sometimes the depression is triggered by the chronic illness. That they have a flare of their inflammatory bowel disease and they become depressed, and between the interactions with your patient you decide that antidepressants can be a part of the management of this, and you get their disease under control and I don't think that's necessary the depressive illness is going to recur. Unless of course the organic disease is a problem. So I don't see them as

a five-year treatment, undertaken necessarily. There are different ranges of depressive illness.

7. Have you ever suggested using other psychological treatment in IBD patients?

Well, apart from the short psychotherapy that I undertake as a part of the consultation, I personally don't use other techniques. If it looks as if other techniques may be necessary then I would arrange for a referral to a psychiatrist. Rather than a psychologist. To the psychiatrist. And other strategies may be available to them but they are not really available to me so if I want to do CBT or hypnosis or things like that, relaxation therapies. I don't actually have the ability, the competence in any of these areas. So I would have to ask someone else to get involved.
Ok.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

More than happy.

More than happy.

I think one of other questions asked about long-term side effects. I don't think we need to be too concerned about long-term side effects with most of the current range of antidepressants. Oh, I haven't said that of course. We haven't had SSRIs around for very long, we haven't had mirtazapine around for very long. We don't really know what the long term toxicity might be. But I don't have any particular concerns about long-term toxicity.

9. Would you like to add any comments?

No. Except that you know, I think clearly any chronic disease and the psyche interact. And there is a constant interaction between those two things that changes, so if you have a significant physical illness and you can treat that successfully, then clearly it will have an impact on the psyche. So, I always like to think that I know a patient not just with respect to their disease but also with respect to the environment of the individual in which this disease is occurring. I think that's terribly important.

Other important thing worth while knowing is that in my postgraduate gastroenterology training we used to have a weekly session with a psychiatrist and our GI patients. So I've always had interest in it really. So we were exposed more than probably anyone else has ever been exposed in gastroenterology in this country, to mental health issues in association with gastroenterology.

So it can be different in other places?

I don't think you will find another teaching institution in Australia which puts an hour aside every week for gastroenterologists and their trainees to be exposed to mental health. And I consider myself privileged to have this experience.

10. Would you like to receive a copy of results of this study?

Sure.

11. What is the cause of IBD in your opinion?

A perturbation of the body's immune system within the gastrointestinal tract, the trigger for which is unknown.

- Thank you!

Participant 3

Wednesday 12th October 2005

Age: 35
Sex: ▇
Undergraduate studies where: ▇▇
Postgraduate studies where: ▇▇
How many years in gastroenterology: 5 years
Were you born in Australia: No
Do you speak other languages: Yes
In high school did you graduate in sciences or humanities: Sciences
Patients per week: 2
Work: RAH

What is your experience of treating inflammatory bowel disease patients?

What is my experience? How extensive?
- How comfortable do you feel with treating IBD patients? And how many years do you work in gastroenterology?

I have been in gastroenterology since 2001. Since that time I have been managing patients with IBD.

Do you feel comfortable?

Yes.
- Ok.

How many patients with IBD have you treated?

New cases I would say 2 for the last week. Month would be probably… New cases?

- Doesn't matter. Generally how many patients.

Because, you know if you have severily sick patients in the last month I would have seen them maybe 4 – 5 times.

- Ok. So then maybe new cases.

This week	2 new cases
This month	2 new cases
This year	half a dozen, 6 new cases

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?
No. Unless they were obviously depressed or have significant neurovegetative symptoms.
- But did you actually prescribe them or did you use them?
If there were but in my experience over the last month or years no.

Did you hear about that if doctors prescribe antidepressants to IBD patients or from your experience, or from literature, did they notice any difference between UC and CD patients?

I am not aware of it.

OK.
If yes:

3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?

NA
3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?
NA

3c. What was the result of this treatment?
NA

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?
NA

If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?

Did not have a depressed patient.

4. What is your opinion of the use of antidepressants in IBD in general?

I don't think I have an inclination to worry. If they are obviously depressed, I would have no hesitation in starting it. I mean this is a condition that can be of significant morbidity and proportion of these patients will get depressed as a result of inability to work and inability to function the usual way. And if that was significant I would use either pharmacotherapy or other forms of therapy like CBT.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?
May have some impact. What you mean?

- That there are some somatic changes. Not only to treat mood disorders but that you also influence the disease.

I am not aware of this information.

6. What is your opinion of the use of antidepressants in general?

No problems.

7. Have you ever suggested using other psychological treatment in IBD patients?

If they were obviously depressed, I personally not. The answer is no.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

For what reason?

- If there were evidence that antidepressants may cure or partly influence the disease, the somatic part of the disease?

Well, to be honest I am not aware that has been reported. If that was a case, I would be keen to receive some information about this and see what the protocol is.

- Ok.

9. Would you like to add any comments?

Yes, I am not quite sure what you're hoping to achieve. Sorry, I didn't read carefully. (*starts to read an info sheet aloud*)

What is the literature on this?

- There is not sufficient generally. But there are case studies and one study only with 9 participants stating that antidepressants influence also…

What group of antidepressants?

- There are different groups. Studies I know, there were paroxetin, mirtazapine, bupropion is the most…

So only SSRIs? No tricyclics?

- No. In studies I know, however there are a few of them. There is really a gap in knowledge in this area.

It would be difficult to say about their effectiveness because patients would be under the treatment for IBD at the same time.

- You need to have them all in remission.

But how? If they are already in remission.

- Ideally, it would be a randomised controlled trial but it's not possible in my case. It would be to to have patients with psychological disorders in remission, which happens.

Psychological disorders?

- Depression or anxiety, but in remission from IBD and then starting to treat mood disorder but at the same time to observe reactions of the body. It may lenghthen the remission.

Ok.
- But it's difficult to discuss it because I can't do it at the moment.
Ok.

10. Would you like to receive a copy of results of this study?

Yes.

11. What is the cause of IBD?

Autoimmune.

- Thank you very much.

You're welcome.

Participant 4

Wednesday 12th October 2005

Age: 42
Sex: ▮▮▮
Undergraduate studies where: ▮▮▮▮▮▮▮▮
Postgraduate studies where: ▮▮▮▮▮▮▮▮▮
How many years in gastroenterology: 10 as a consultant and 5 years as a registrar
Were you born in Australia: No, ▮▮▮
Do you speak other languages: Yes
In high school did you graduate in sciences or humanities: Sciences
Patients per week: 3
Work: RAH

1. What is your experience of treating inflammatory bowel disease patients?

How big is my experience?

- Generally, do you treat these patients and for how many years?

Almost 15 years.

- Do you feel comfortable with treating IBD patients?

Yes.

2. How many patients with IBD have you treated?

This week   3

This month   13

This year   100

OK.

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

No.

- No. Ok.

You mean as a treatment or as a treatment for the depression?

- Not necessary for the depression. For any reason. I know there are doctors who use antidepressants for pain.

Yes. I know.

So did you use antidepressants for any reason in IBD patients?

No. I don't think so.

If yes:

3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?
NA

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?
NA
3c. What was the result of this treatment?
NA

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?
NA

If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?

I treat patients on the basis of evidence. I haven't seen any evidence that antidepressants reduce number of therapies in inflammatory bowel disease.

OK.

4. What is your opinion of the use of antidepressants in IBD in general?

I would see them as useful if there was evidence of depressive symptoms, if I made a diagnosis based on DSM-III criteria for depression. In that sort of respect I would be happy to treat a patient with this sort of treatment. But if the nature of the question is, do I see the role for antidepressants in people with IBD without depression, no I have never used it.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

I suppose they may have a benefit and my experience is with the old generation of antidepressants. I don't have huge experience with SSRI. I would use more tricyclics rather than SSRI. But in number of patients with inflammatory bowel disease I have used tricyclic antidepressants to control pain and for sleep. But once again my experience is very limited.

- That's ok.

6. What is your opinion of the use of antidepressants in general?

Extremely usuful from the result I see in patients with the diagnosis of depression. I also find them useful in patients with IBS, and also for various pain syndromes, particularly abdominal pain syndrome. In the situations such as chest pain of noncardiac origin I found that traditional tricyclics may be of a benefit.

7. Have you ever suggested using other psychological treatment in IBD patients?

I have never treated a patient with antidepressants or psychotherapy primarily for IBD. I am not sure that I understand the question right.

- If the patient with IBD had depression and if you had such patient would you treat them with psychotherapy or order going to the psychotherapist.

Absolutely.

- So you did it?

Yes.

What was the result?

Gradual improvement. With SSRI if patient with IBD were depressed…

- Yes. But I am asking now about psychotherapy or meditation, relaxation.

Yes. But patients I direct don't come back to me for a follow-up.
- OK.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

Just clarify that. With the current therapy for IBD or only antidepressants and a washout period?

- No, Let's say that a patient would be in remission and would suffer from psychological disorders because we cannot treat with antidepressants a patient without psychological disorders. And the trial would look at how antidepressants influence their disease, to see whether remission would be longer and of course treating psychological disorders which appear.

If there were psychological issues yes, but I would like to see the evidence for treating IBD patients without psychological issues with antidepressants.

- Ok.

9. Would you like to add any comments?

So, I still remain uncertain about the direction of this study. This is to manage the patients with IBD without psychological symptoms.

No. It depends which study we are talking about. This study is about exploring doctors' opinions about antidepressants and IBD. My other study will be only focused on IBD patients with psychological disorders. At this stage it is only interviewing doctors about what they think.

Ok.

10. Would you like to receive a copy of results of this study?

Yes.

11. What is the cause of IBD?
Unknown.

Participant 5

13 October 2005

Age: 58
Sex: ███
Undergraduate studies where: █████████████
Postgraduate studies where: █████████████████████████
How many years in gastroenterology: 30
Were you born in Australia: No
Do you speak other languages: Yes, █████████████████████████
In high school did you graduate in sciences or humanities: both, mainly sciences (████████
█████████████)
Patients per week: 12
Work: RAH

1. What is your experience of treating inflammatory bowel disease patients?

Mine's pretty extensive. I did my training █████████████ where we had a strong
interest. When I was trained I worked for a guy called ████████ ██████████
██.
And I have been interested ever since then. I now work as ████████████ for the
RAH and ████████████████████████ within our specialist
IBD clinic. ██
███
███
███
███
███
███
███. So I have been
involved over the years.

- So you feel comfortable with IBD patients if they visit you.

I enjoy the area. I like the idea of doctors having long term involvement with patients
rather than just being, you know, one of hits like intensive care physicians or anaesthetists
must tend to be. So I quite enjoy that kind of engaging battle of the mind as well as the
body. Cause you've got to obviously relate to people, and desperately persuade them that
sometimes having boring long-term diseases they have to have boring long-term doctors,
boring long-term treatments. So that's half the battle, is really getting patients to be
prepared to take their medications if they got enough problems.

2. How many patients with IBD have you treated?

This week   12

This month   30-40 at least

This year   200 (private practice majority, RAH)

I didn't tell you about any of my Crohn's studies or whatever. We also have been doing lots of studies here; they organise it and I do it. I have been the principal investigator on the (*not clear*) and other new forms of (*not clear*) -silicilate, like the new (not clear).

How many years have you worked in gastroenterology?

███. I have now been working for 30 years primarily in gastroenterology.

OK.

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

Yes.

For what reason?

Mainly for their anticholinergic effect in tricyclics which are really useful. People with urgency of defecation and tendency to strain often have problems with nocturnal defecation. When you talk with them about their sleep pattern, they obviously have disturbed sleep and people are wakeful and anxious. As long as you can control inflammation you can sometimes get on top of that but in those who persist in wanting to get up and go to the toilet, I find it really useful to give a bed time dose of doxepin for example. Small doses, 10, 25, sometimes 50mg as an evening dose. Partly for its sedative properties. I suspect not much of a antidepressant properties at that level. Although I think subtle mood disturbances probably are partly involved in their anxiety about the whole process of getting up at night. They don't wish to be heavily sedated because they are frightened of incontinence. But it certainly is nice to try smooth out their sleep. So you have to pay attention to inflammation but I find that tricyclics are useful adjunct therapy. I am not quite experienced with the SSRIs. I have used the few things but I don't think I feel really comfortable with them partly cause I am antique now. And they've come in the last 5-10 years. And it's not an area I feel quite so familiar with. Partly because mainly I think I am focused on treatment so to pay attention to the organic side of inflammation, supression and if I've wanted to use, if I thought patient was seriously depressed and I've found a few, then I tend to just involve a psychiatrist and go to help rather than do all the prescribing myself.

If yes:

3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?

Well, I tend to use it in patients with UC because they're the ones that have often got rectal? involvement. And I've got 2 or 3 Crohn's patients who might have used them, but the majority would have UC. And it's probably only ten or dozen per couple of hundred that I've got who would be taking a night time dose of a tricyclic. But I tend to use that not just in patients with IBD because I ask many patients about their sleeping habits and if they

300

have got this rather constant alertness at night that makes them hear things in the night and wake up and want to go for a wee, I am quite keen to try to calm down them a little bit by using a mild sedative anti-cholinergic rather than getting up to do a wee or go to the toilet.

But was it any influence of antidepressants on the disease, on the somatic part of the disease?
It certainly helps some people and I can introduce you to a few patients who said they feel more comfortable taking them. Whether it's for the reasons that I think I have given them or whether it's for other reasons.

Placebo?

Yes, I can't be too dogmatic. But I think there are certainly some of them who when I suggest that you know it's not mandatory: if you feel you don't have to take them, you don't have to. But they come back and say: alright.

But did you find that for example that for example CD or UC patients benefit more than other groups of patients or you didn't?

I am not sure they have a major impact on the course of the disease. Having said that I have not really explored it in any scientific way. So I think my anecdotes are probably not frightfully worthwhile.

You know in scientific knowledge there are mainly case reports.

So I wouldn't put a lot of weight. I don't place a lot of weight on the idea that we should be treating people primarily with mood altering drugs. I think they can be a useful adjunct but they're not the main game.

Another question: what kind of antidepressants (brand name) did you order? What were your reasons?

In tricyclics I've got familiar with doxepine which comes as Sinequan? Or deptram.

So you've never tried SSRI or the newest like mirtazapine?
Not on a systematic basis.
What was the result of this treatment of antidepressants? And we may say that they benefited from this calming effect?

I think so. A little bit. People who have got sleep disturbance, getting a good night sleep and not rushing off to the toilet as often as they did. It's not always perfect. But you know there really are some people have to get up a number of times at night and that's very disruptive to your whole life if you're really not sleeping well.

Did you notice any influence of the treatment with antidepressants on the course of IBD?

I think I have not really tempted to answer that. So I don't believe so but then I've never studied this in the way that would allow me to really explore that. Like anything with the most vague anecdotes you really can't, I don't think. In diseases that are uniformly lethal and you save a few patients you can say wow an anecdote is important. For diseases where the natural history is fluctuating then it's very hard to know what causes those fluctuations.

And to identify the triggering factors or the factors that cause clinical improvement. You really have to do more than anecdote.

If no:
3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?

NA

4. What is your opinion of the use of antidepressants in IBD in general? Do you see any role?

I don't know of strong evidence that suggests they have a primary role. So I've not used them on a routine basis. If there are good, you know, Cochrane collaboration randomised controlled trials that really show us that, then I am always prepared to learn but I am not sure there are really large studies that have given us definitive answers. I have not really sought to use them as a primary therapy. I get the impression still that I mean it's quite clear that people with IBD have got many psychological disturbances. In my own broad view has always been many of them are secondary to the problem of having anxiety about their incontinence, about their bellyache, their diarrhoea, whether they can function socially, what they smell like, whether people are looking at their loins' generating capacities, whether it's wind or rumbling. There are many insecurities that people with diarrhoea and abdominal pain, I guess it's a common symptom of Crohn's, that make them anxious and potentially depressed. But I had largely felt in general that most of their mood disturbance was secondary to the physical problems that are certain to appear. And the social, and medications and all the other things that make their lives potentially difficult. But they're secondary problems rather than the primary.

5. To what extent do you think antidepressants can have an impact on the disease? What impact? You don't belive they have an impact?

I am a healthy sceptic. You show me the evidence and I am pleased to refute it. I am not aware of good strong evidence that suggest that's the primary way forward. Yes, I think they can be useful, that you have to be aware of anxiety and depression, and insecurity and the rest of it. Because they are important parts of the disease and the individual's reaction to it. But I think if you can get their bowels functioning normally and their life then more under control without too many medications or with convenient medications rather than inconvenient ones. Maybe not taking things up their backside the whole time? Taking just a few tablets. Then usually people's moods have picked up enormously and their fears and worries about cancer and the rest of it tend to evaporate as their health is improved.

Yes. There is still quite significant number of patients who suffer from psychological disorders during remission.

That's right. How do they compare with the controlled population?

I think the problem in this is that many patients with IBD have also IBS so it may be IBS in the remission of IBD and as we know IBS is really highly correlated with psychological disorders. This is one of my opinions about this. Because the number of these psychological disorders is still higher than in a normal population.

Well, I guess you would expect that, you might expect that in people who have had serious illnesses, but just as I'm sure that people who have had cancer or disasters you probably feel a bit insecure about the rest of their life so you would expect some difference but how striking it is from comparison populations I don't know. Because it's always very hard to talk about IBD and IBS in the same patient. We know that scarring of the rectum might produce a small reservoir so people might have to go more frequently, more urgently. Then rather their mucosa looks like in remission, they may still have symptoms. That could fit under the umbrella of urgency and whatever that might call it. IBS, but might be due to physical changes, secondary to the underlying inflammatory process. So it is always just a little difficult trying to draw the line between them. The symptom is due to acute inflammation versus chronic mild hard to identify inflammation versus some completely idiopathic motility disturbance that might proffer? as IBD.

6. What is your opinion of the use of antidepressants in general?

I am impressed that they can be useful as a short term measure. But that I am always very keen to look at non-drug options for enhancing physical health and well-being. I am a great believer in healthy mind and healthy body. So people who are, you know, down and depressed for whatever reason, that may be reacting to some of their life situations but they're often smoking and not exercising and doing things that make many normal people healthy, feel healthy and feel good about themselves. So it's difficult for some individuals if they are socially disadvantaged to feel good about themselves. Somehow we've got to find a way to do that and I am very keen if we can on looking at obesity, getting people to exercise if they can, to lose weight if they can, to stop smoking if they can, to do all these other physical things. That they can see as herbals? It's hard to tell people, you can't tell them not to be depressed but you can say: let's look at ways of improving the way you feel. By physical means not just drugs? So I am quite keen on antidepressants but I think there's got to be something else as well for the long term. And you wouldn't really want to keep people on large doses forever if it really wasn't important. If it could be avoided. I mean I think that about drug medication in general, the smallest doses and the shortest periods of therapy that is going to do the job. The trouble is that a lot of diseases we deal with are pretty chronic. But I am keen always to look at options that involve physical health. It is something you can tell people you can't say go away and sleep better but you can say: look, set the alarm clock and get up at 8:00am and go for a walk. You can set them a task that you know if they do that they are likely to feel then more tired at night and maybe get off to sleep. You know you can change things with a little advice. You can offer sensible, very simple advice.

7. Have you ever suggested using other psychological treatment in IBD patients?

Oh, I use psychiatrists occasionally as seeing patients who have major disturbances with mood or other reasons that I feel they really need help that I'm not feeling confident to offer them.

Did you order for example going to or attending psychotherapy or relaxation or something like that?
Quite a few of patients that I would work with would have had some attempts by their family doctors. Certainly in the private sphere. And I've used the psychologist a couple of times, not very much. I think maybe because I tend to be a tertiary referral doctor so the people I see, half of them, have already seen another gastroenterologists and have been unhappy with their progress or unhappy with the individual doctor and have come for the further help so it's quite often a pretty straight forward big physical problem. I would have

a few of them with clinically major problems, with opiodependancy, chronic abdominal pain associated with very severe psychological dysfunction. Some of the Crohn's patients in particular, opiodependancy and chronic pain syndromes and I just feel I have to involve the psychiatrist and other people and I saw a woman a month ago who was referred for another opinion and it was clear when I said: tell me about your smoking. She said: "I'm not going to tell you about it. I'm not going to change". And I said: "You are asking me to do something with my hands tied behind my back and I'm not sure I can do that very easily". When I enquired about her parents she said: "I am not going to tell you about them. I don't talk to them". I said: "This is really difficult for me because if there are big problems in your life that you can't talk about how am I expected to help?". You know so, it's all very well to say this is loof-limits but how can we look forward? ███████ But I suspect the pain problem is only under the CD that she certainly had, really only incidentally related. Yet she's got CD, yet she has got pain problem but I suspect that psychiatric, and psychosocial and psychosexual issues are huge perpetuators of the problem. And you know, if she won't even consider dealing with them, then (laughs)

She will probably have to.

Well, I hope so. For her sake. And I am really not sympathetic because the one thing people say to me quite often is: are you sure you're a gastroenterologist? Are you not a psychiatrist? Why are you asking me all these questions about my family? So for me, I think, history taking is paramount in trying to sort out people's problems. Physical examination is important but a relatively minor component. We did some studies on this ██ ████████████████ that showed that if you looked at a couple hundred outpatients, you could really get most of the answers on history taking. And the physical exam, gave you a few hernias and thyroid lumps and things, blood testing and routine x-rays gave you 1-2% additional bonuses, high calcium, this or that, that you haven't predicted on the clinical history. But in 90% of the time if you are a really experienced clinicians you get better than the registrars or the students and you can get most of the final diagnosis out of the clinical history and I've always emphasised that to medical students. That history taking is the supreme art and what distinguishes experienced doctors from inexperienced ones. And I think taking a good family history, the social sort of the history rather than just focussing on what is the pain, how often the bowel opens and so forth. What really gives you insight into people's lives if they're willing to give it. So for me that's always been a kind of broader view of patients and their lives. That's been very very important. So I am sympathetic to the idea of psychosocial issues being crucial, important. I'm not quite so convinced that drug therapies in the…

That's one of the choices.

is such a useful approach, primarily for inflammatory bowel disease.

You know the problem is that psychotherapy doesn't really work in these patients according to the many studies and some of them are really good, with good samples and it's quite a mystery …

I think it's only a part of the story. People who might seem to know that they have ……. severe stomach cramps and vomiting, and whatever it is, although it's important that you are empathetic and sympathetic when they say they can't come because they have got two small kids and don't want to do a lot of driving. And other endless factors that make life difficult. You still have to deal primarily I think with, it's a bit of a paradox, because there are many drugs that would help with IBD.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

Good. I have always been very proactive scientifically in general sense about trying to problem solve and I would be delighted for them to do anything that might help or might give you better insight, and me better insights in …I would be delighted. I don't have any.. I always encourage. If you ask other people around the department who is providing patients to study x, you will find that most people feel reasonably sympathetic towards me because although I might not be interested in their area, I am quite happy to burrow around and ask patients to help. And that's partly because of my sort of training background;

I did similar studies so that I can see the results now – the phenomenal success of some of these drugs. It's not because they have in particular psychotherapeutic benefits but because they have various specific and clear cut physical benefits and are ideal for patients that they treat and secondarily you can stop heartburning, or regurgitation. All sorts of things that have often been talked about, the tendency to retch or vomit, has been talked about as a psychological illness. But you can see how the whole thing disappears when you treat the severe reflux disease, especially in kids for example in whom its often harder to get good histories from to clarify exactly what the problem is.
So I'm a great beliver. Go for it if you want to carry out studies I would be thrilled to be involved and providing patients.

Thank you.

9. Would you like to add any comments?

No. I think I have said enough.

10. Would you like to receive a copy of results of this study?

Of course, of course. I want it.

11. What is the cause of IBD?

CD or UC?

If they are different in your opinion.

They're both multifactorial diseases. There're partial genetic risk factors that we've clarified a little bit recently. There are clearly immunological abnormalities, they are clearly microbiological bacterial abnormalities. They too play a part. And changing frequency in CD in the recent years testifies to the fact that there are some important environmental factors. As to physiological and psychological I'm not too sure. It's risen quite dramatically over a 20 year period. Now that to me says that there's something in the physical environment. We could argue that urbanisation has imposed its own pressures psychologically, but I suspect it's something not quite as mysterious as that. So I think a quite a bit is environmental factors. So I think it's this overlap of conditions that somehow (*not clear*).

Participant 6

October 2005

Age: 37
Sex: ███
Undergraduate studies where: ████████
Postgraduate studies where: ████████████████
How many years in gastroenterology: 8
Were you born in Australia: Yes
Do you speak other languages: ████████
In high school did you graduate in sciences or humanities: sciences predominantly
Patients per week: 3
Work: RAH

1. What is your experience of treating inflammatory bowel disease patients?

Inflammatory bowel disease?

Yes.

You mean occupational history as far as the IBD goes?

Yes.

Ok. I guess as a trainee having exposure to inpatients and outpatients in clinic in my clinical training. Probably my most in-depth experience is that I did some postdoctoral research ████████████████████, not directly related to IBD but that's a center where a lot of IBD is treated. So I did a weekly outpatient clinic there. In which probably 2/3 of patients had IBD.

And how many years have you worked in gastroenterology?
How many years? ████████████████████████
████████████████████████████████████
████████████████.

How many patients with IBD have you treated?
This week   3
That would be more than usual. I should add that a large bit of my time is in research and academic activities. So my patient ……. is relatively small.
This month   6

This year   20

Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

Not in many. I suspect that will be a small number that I might have and they would be people in who objectively the inflammation was quiescent. And yet they still had gut symptoms which might be a picture of functional gut symptoms. And in that case there may be a small number, maybe 2-3 people, that I might have seen where I've used antidepressants.

Ok. But it would be mainly for IBS?

I use it much more often for IBS.

If yes:
3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?

I don't think I have got enough experience with IBD patients to make a comparison.

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?

The most common I use is amitriptyline.

Why amitriptyline?

I find tricyclics over SSRIs because I don't think it is much evidence in SSRI in functional bowel disease. A lot of the people that I have seen with functional gut disease have associated sleep problems. And I think it is useful to take advantage of the sedating effects of tricyclics in a low dose by giving it at night.

3c. What was the result of this treatment?

I think globally that I would maybe get about 50% of people might find treatment beneficial and would have stayed on it.

Do you remember how long they stayed on this medication? Was it longer than normally or permanently?

A lot of them I don't have long follow-up date and a part of the reason for this is that many of the patients would commence therapy and then returned to care of their GP so I wouldn't necessary have long term follow-up with lot of patients who had tricyclics. So as to the duration of the therapy I find hard to comment on how long they would continue.

Ok.
3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?

For IBD, as I said, I think my experience with antidepressants there is too small.

If no:
3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?
NA

4. What is your opinion of the use of antidepressants in IBD in general?

I think that they have a place, I think there is a proportion of patients with IBD who also have a pain disorder related to the gut as well as inflammation. And that's the group of

people that I would consider treating even if I am not experienced with that and that group is small.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

I think they have the potential to improve the quality of life. I am not sure that there's much evidence to suggest that they would alter the course of the inflammatory process. But they could certainly have benefits on symptoms and that would have an impact on objective scores that are used for IBD such as CDAI. So they could have an impact on the activity index with these diseases.

6. What is your opinion of the use of antidepressants in general?

I think that they're useful drugs in the appropriate setting. I think they value is probably underrecognised by the large number of GPs in this area. But I think that their use with patients needs plenty of time of discussion with the patient to explain the reasons for their use.

7. Have you ever suggested using other psychological treatment in IBD patients?

I would certainly consider recommending those sort of tratments and in particular suggest that some patients might like to explore hypnotherapy where functional gut pain is a particular gut problem. Although I don't have personal experience with patients who have taken up that option.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

I think I would want to look at the inclusion criteria for the trial closely. And I think that probably I …….the number of patients that I would have to contribute to such trial would be relatively small. But I would certainly consider recommending individual patients for the trial.

9. Would you like to add any comments?

I don't think about anything specifically.

10. Would you like to receive a copy of results of this study?

Yes, that would be interesting. Thank you.
11. What is the cause of IBD?

I would view the cause as say an abnormal immunological response to antigens that are encountered in the gut. Be they bacterial or otherwise.

Participant 7

October 2005

Age: 43
Sex: █████
Undergraduate studies where: █████████████
Postgraduate studies where: RAH
How many years in gastroenterology: 12
Were you born in Australia: yes
Do you speak other languages: ████████
In high school did you graduate in sciences or humanities: predominantly sciences
Patients per week: 10
Work: RAH

What is your experience of treating inflammatory bowel disease patients?

██
████████████████████████████████████).

- How comfortable do you feel with treating IBD patients?

Quite comfortable.

Yeah? Ok.

2. How many patients with IBD have you treated?

This week   10

This month   40

This year   400

3. Have you ever used antidepressants or suggested using antidepressants in these patients
for any reason?

I have used tricyclic antidepressants. Mainly with intention to treat IB type disorders
aswell as I think that they have overlap with irritable bowel, so I use it for that. In terms of
treating underlying depression I haven't been an initiator of this treatment in these patients.
So specifically to treat depression I haven't actually initiated the treatment.

Did you use them for pain for example?

Certainly for pain. Yes. Certainly. It gets back to the IBS types scenario.

If yes:

3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?

Can't say I see any difference.

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?

Specifically being concerned about mood disorder. I used Sipiden (*not clear*) one of the new anti-depressants. If it's more for pain I use pacthypin, desyphen, or amitriptyline.

Ok. In the patients that you used exactly you mainly used tricyclics?

For pain? Yes.

Did you use SSRI in any patient for any reason?

Not recently.

3c. What was the result of this treatment?

I think it's generally quite good for the pain.

And you didn't think about observing mood changes I would say under the influence of antidepressants? Because you observed the influence on the pain.

I think patients generally feel better when their pain goes down. I think most patients did not have underlying disorder in my perception any way. In most cases it was related to the disease activity. So when the disease was under control their mood generally tend to improve. Apart from those who have other long-standing complicating Crohn's results.

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?

I can't say I have seen anything with the connection between them.

If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?

NA

4. What is your opinion of the use of antidepressants in IBD in general?

I think certainly if someone is clinically depressed…?….I think you can't always pick that up; we focus on the acute illness, perhaps we need to take a step back and take a look at what the patterns have on patients, but I think those who I have treated tend to feel better. I am not sure whether it actually has an influence on their disease as such.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

I don't think it's good evidence that they actually have an impact on the inflammatory activity. They help people to cope better with their symptoms, and if sleeps a problem, they can help.

6. What is your opinion of the use of antidepressants in general?

I think they have a role in patients with clinical depression. It's quite often reactive depression that's involved as we deal with the circumstances relating to the mood disorder, whether its acute illness or acute exacerbation of IBD, I think that often helps. I think in patients it works on having an effect on sleep and motivation, I think it has a significant effect.

7. Have you ever suggested using other psychological treatment in IBD patients?

I certainly referred some patients, younger patients to have counselling. And one or two that I've thought that have been clinically depressed to see the psychiatrist. Certainly psychological counselling (mumble).

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

Purely as treatment to their IBD?

Generally, if there is evidence that they have some role?

Yeah.

9. Would you like to add any comments?

No. I think that because IBS is, there's a lot taught about psychological factors and the impact as it is on the disease itself, we do tend to focus a lot on psychological factors. Because you're meeting people, and dealing with that, psychological factors are perhaps overlooked? I think it's fair to say that the whole process… stress and psychological factors are taught … in some textbooks…(*not clear*).
I've seen some patients who feel their symptoms, their Crohn's or IBD tends to flare at times when there's an increase in stress, so I think there's a role to play there, even if it's a patient perception, I think it is important to try to understand that aswell.

10. Would you like to receive a copy of results of this study?

Sure.

11. What is in your opinion the cause of IBD?

I think it is to play the environmental factors with its bacterial etiology. Obviously there is immune disregulation, probably has something to do with it aswell. I see it as an immune disorder if you like of the gut triggered by as yet unknown environmental agent. I suspect it's most likely going to be some sort of bacterial pathogen. I think clearly bacterial flora have an important role play in triggering IBD. In its susceptibility. So I haven't figured psychological factors in there (laughs).

Participant 8

October 2005

Age: 50
Sex: ▮▮▮
Undergraduate studies where: ▮▮▮▮▮▮▮▮
Postgraduate studies where: RAH
How many years in gastroenterology: 19 ▮▮▮▮▮▮
Were you born in Australia: No
Do you speak other languages: ▮▮▮▮▮
In high school did you graduate in sciences or humanities: Sciences
Patients per week: 1
Work: RAH

What is your experience of treating inflammatory bowel disease patients?

I've been treating IBD patients since 1985 so it's 20 years.

- How comfortable do you feel with treating IBD patients?

Yes.

2. How many patients with IBD have you treated?

This week   1

This month   2

This year   10

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

Yes. In patients with CD with depression.

If yes:

3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?

Most patients I treat for depression have Crohn's disease. I haven't noticed any difference.

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?

Doxepine for difficulties with sleep and anxiety.

3c. What was the result of this treatment?

Mood disorder improved but the disease was not affected.

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?

Not on the bowel but on the patient's overall functioning yes.

If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?

NA

4. What is your opinion of the use of antidepressants in IBD in general?

I think if they have severe IBD, they become depressed. So I think it's a secondary effect of IBD. It can affect patients' life and treatment. Early intervention is important. But I also think they don't treat IBD.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

I think they can improve the treatment. They improve the compliance with looking after nutrition and …to what extent?

Yes.

If they become depressed they have difficulty with multi variables: nutrition, diet, they become socially isolated.

6. What is your opinion of the use of antidepressants in general?

In general? They are useful drugs, particularly for people with organic depression. They work for them fabulouesly. They are also good for pain management and IBS.

7. Have you ever suggested using other psychological treatment in IBD patients? Psychotherapy, relaxation?

If the patient was depressed I suggest them to go and see a psychiatrist. Yes, I have suggested psychotherapy. Not just because they have got IBD but if they're having trouble

with coping. I think that psychological support is important and should be a part of a mangement. They can receive psychotherapy from their GP, not necessary from the psychiatrist. For example young people with sexual, psychosexual problems, problems with body image.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

I would like to speak to them about it. I would find whether a trial is a risk to them. Would it be an alternative to the standard treatment?

No.

Adjunct?

Yes.

9. Would you like to add any comments?

No. Psychological factors are important in IBD. The psychology of patients is very important. Patients living with chronic diseases should get support.

10. Would you like to receive a copy of results of this study?

Yes, that could be interesting.

11. What is the cause of IBD in your opinion?

I think there are genetic factors, some undiagnosed environmental factors and immune reaction.

Participant 9

24 October 2005

Age: 45
Sex: █████
Undergraduate studies where: ████ ████████████
Postgraduate studies where: ███████████████████
How many years in gastroenterology: 17
Were you born in Australia: Yes
Do you speak other languages: ████████
In high school did you graduate in sciences or humanities: sciences
Patients per week: 6
Work: RAH

1. What is your experience of treating inflammatory bowel disease patients?

Guess, I have been treating patients with IBD for 20 years. I would see 6 new patients with IBD per week.

2. How many patients with IBD have you treated?

This week   6

This month   20

This year   200

Do you feel comfortable with treating these patients?

Yes.

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

Yes.

What were the reasons?

Depressive symptoms. In some cases anxiety related symptoms. Depression usually a reactive depression, not a true organic depression. Sometimes I've tried patients using antidepressants, low dose amitriptyline for some abdominal symptoms rather than particularly for depression per se. I also use them to reduce abdominal pain and gut irritablity in some patients.

If yes:

3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?

I don't seem to have to use antidepressants much in UC. If anything it would be more common to use in patients with CD. I can't , I guess I must have but I can't think of any particular one that I've treated with UC.

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?

Most commonly SSRIs.

Which one?

Sepramil, Zoloft. Can't think of other names. They'd all be known to you. As well as low dose amitriptyline. Very occasionally the patients take doxepine, if they're on it, I don't change it.

Have you ever use mirtazapine or bupropion?

What's the… name?

Mirtazapine? Advil, I think? (I was wrong, it's called avanza)

I don't use it myself. But I have some patients who take them.

And bupropion?

No.
Ok.

3c. What was the result of this treatment?

Usually helpful.

But mainly for depression?
Yes.

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?

No.

If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?
NA

4. What is your opinion of the use of antidepressants in IBD in general?

Useful adjunct treatment. I don't use it to treat IBD but I use it managing the patient as a whole and their general well-being.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

I don't see much about SSRIs. I think low dose amitriptyline can certainly reduce some gut irritability, some of the gut sensitivity. They can also improve sleep patterns in many patients because they seem better rest, they feel better.

6. What is your opinion of the use of antidepressants in general?

Really good if necessary. I think they are generally overprescribed. But I guess if the medication is safe that does not matter. If the medication has significant side effects or adverse-effects that's the problem. But I think some new antidepressants have relatively few side effects and very few adverse effects so a lot of people seem to get on them and do not seem to be ready to come off them.

Yes, I heard there is a problem of permanent use of them. What do you think of long-term side effects?

Well, I don't know. I am not aware of any long term side effects. I guess there must be some but I don't know them.

7. Have you ever suggested using other psychological treatment in IBD patients?

On a couple of occassions I have suggested relaxation therapy and hypnotherapy but have had very limited success.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

I think that would be fine.

9. Would you like to add any comments?

Would you, I suppose a trial of antidepressants if they had evidence of depression or I don't know if I would support patients giving drugs if they have no signs of mood disturbance.

I think nobody would really approve it. It must be some psychological issue.

So, if there is some way that you can measure depression and mood problem, then I think that's good.

10. Would you like to receive a copy of results of this study?
Yes

11. What is in your opinion the cause of IBD?
If I knew that I would win Nobel Prize but… I belive it's an infection. Nobody knows.

Participant 10

9th November 2005

Age: 59
Sex: ███
Undergraduate studies where: ███████████
Postgraduate studies where: █████████████████████
How many years in gastroenterology: 29
Were you born in Australia: Yes
Do you speak other languages: No
In high school did you graduate in sciences or humanities: Sciences
Patients per week: 10
Work in: QEH

1. What is your experience of treating inflammatory bowel disease patients?
Oh, I treat them every day.
For how many years?
Nearly 30.

- How comfortable do you feel with treating IBD patients?

I feel pretty comfortable. I mean, I think anyone that treats IBD patients is going to come across difficult patients, figuring out what the best thing to do is. I think I'm probably as experienced as anyone.

2. How many patients with IBD have you treated?

This week   5-10

This month   40

This year   200

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

That would be uncommon but I do use antidepressants. Yes. Generally speaking I would say that people with IBD are not often seriously depressed. They may be mildly depressed. It's not been my experience that IBD has a high incidence of depresssion associated with it. So I reckon I would say per 100 patients with IBD maybe 5 will be on antidepressants. That's not very many, really. It's not an association that I'm very consious of, but it does come up every now and again.

Do you use for example antidepressants for pain?

Some of them I give antidepressants for pain. It's basically the tricyclics. I mean that's the only group of antidepressants, I think, that are actually useful in some people for pain. I

320

mean I tend to be a tricyclic user when I use antidepressants. Maybe that's because I'm older, I suppose. I guess if I'm thinking of using the SSRIs, I might get some advice from a psychiatrist. I tend not to you on my own back, I suppose. I am happy to use the tricyclics off my own back without necessarily getting a second opinion.

If yes:

3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?

No, I don't think so. As I say, in those diseases it's not a very common association and I wouldn't like to say that you have it more often with UC or CD. I think it's just an uncommon thing with both. I don't have any impression of that.

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?
Well, I use tricyclics. That's what I use. I either use amitriptyline or I tend to use imipramine but I don't know why I use them. I know a lot of other people use amitriptyline as well as it seems to become the classic. I actually use imitpramine and I'm not sure whether I have a good explanation for doing that. But it's just a sort of long term thing. I think it just seems to provide slightly better effects?. Sometimes you try to achieve different things. Sometimes you are actually trying to help their sleeping pattern, sometimes you're trying to help their pain, sometimes you are trying to help their depression. You know, you try to do different things. Typically sleeping is sometimes an issue and with tricyclics you get some benefit from that. But not with SSRIs. They don't help you sleep, I don't think much.

Ok. But do you have any experience with SSRIs for example do you remember patients taking them?

I'm sure there is a small number people on them but as I said I don't think it's a sort of a common thing.

3c. What was the result of this treatment?

That's a bit hard, you have to remember the individual patients. The one that I remember well is someone taking 250mg of amitriptyline. Ok, so it's a high dose and it certainly helped him to sleep. I didn't actually prescribe that much amitriptyline. I think he eventually saw a psychiatrist who actually put the dose up to that. I think it certainly has a beneficial effect on his sleeping patterns. And whether it has a beneficial effect on his pain I guess I'm not clear but he actually takes amiscontinal, one of those narcotic analgesics on a regular basis. So, I'm not sure whether it's reduced that dose, I don't think it has, but it actually keeps him feeling reasonable and helps him sleep.

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?

I don't have any impression on that. I mean I treat with them other problems. I don't necessary feel that antidepressants are going to be helpful for IBD.

If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?
NA

4. What is your opinion of the use of antidepressants in IBD in general?

I don't use antidepressants because they might be helpful for IBD. I use antidepressants because they might be helpful because people are depressed or are sleeping poorly or have a lot of pain. I mean that's all I use them for. I don't use them for IBD.

5. But do you see any role? Depression, pain and…?

Sleeping problems. I don't think there have been many studies that looked at whether antidepressants have the role in terms of, you know, reducing bowel inflammation. I can't think about the study which has addressed that. I certainly don't have any strong feelings about that. I don't think antidepressants do help IBD but maybe someone can persuade me to the contrary but that's my impression.

6. What is your opinion of the use of antidepressants in general?

Well, as I said I'm a user of a tricyclic group. Because I feel confident using them. I think it's just a sort of group you see. I see people who can't sleep very well and are sort of anxious and that's why I use the tricyclic group. Other people see people who have different sorts of, depression, I suppose. And might be able to use SSRIs. But I tend not to use SSRI myself. I tend not to be the prescriber. I leave it to the local doctor maybe sometimes or I leave it to the psychiatrist. I feel happy with the tricyclics but not necessarily totally happy about using SSRI.

You generally probably don't use them too often.

No, I use tricyclics sometimes but I have almost never, I try to remember the last time with SSRI. The person with SSRI would see the psychiatrist. I know that the psychiatrists tend to use SSRIs and they don't tend to use tricyclics but I am actually a tricyclic user because they treat problems I most commonly see in people, they can't sleep or have a lot of pain or that sort of stuff.

7. Have you ever suggested using other psychological treatment in IBD patients?

I would probably use some tranquilizers every now and again, minor tranquilisers, but not because I think they have an official effect on IBD, but because you know people are anxious etc.

Anything apart from pharmacological therapy?

No. The things to think about, you know acupuncture, I have never used that. Hypnotherapy, I've never seen a study that used hypnotherapy and IBD. So I never use that.

Psychotherapy?

No, not in a professional way, not via psychologist. I think I think that psychological factors have something to do with IBD, I wouldn't like to say that it's non-psychological. Because I think there are some people who have their relapses when they get stressed or anxious. So my feeling is probably that anxiety is at least part of why people get relapses of IBD. Probably not why they get the IBD but certainly why they get relapses now and again. It's always hard to assess these things and do studies which actually show people get relapses when they're stressed. My anecdotal impression is it's a factor.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

I'm not intrinsically against it. I'd like to see some preliminary data whether it actually is useful, I suppose. I can't think about any preliminary data that actually does that but there might be out there.

9. Would you like to add any comments?

No. I think I've probably said enough.

10. Would you like to receive a copy of results of this study?

If theres an executive summary or an abstract that would be good.

11. What is the cause of IBD?

I probably believe that most inflammatory bowel disease is some sort of immunological disorder where people in some way lose tolerance to their own bacteria. I think that's the most important aspect of it. Now, the question is why does that happen? Why is CD more common than it used to be, and well I don't know the answer to that, because there is all sorts of possibilities like using antibiotics in young children, everything from sort of breast feeding to dietary changes. But I'm not sure that diet is very important but things like 20-30 years ago breastfeeding became unpopular. Maybe that's a factor. Maybe antibiotics in youn children is a factor. Whether chronic psychological problems, or chronic anxiety or whatever is a factor. I guess I'm less clear. We know that genetic factors are relevant. But maybe that's not all that important. But maybe we just don't know the genes but I think genetic factors is a part of it. I guess nobody knows. I think you have to separate when you are thinking about the psychology you have to separate out things that actually cause the disease in the first place and things that cause relapses of the disease. I think, relapses is related to a psychological factor, or would be important, at least in some people.

Participant 11

11th November 2005

Age: 55
Sex: ███
Undergraduate studies where: ████
Postgraduate studies where: ██████
How many years in gastroenterology: 25
Were you born in Australia: No
Do you speak other languages: No
In high school did you graduate in sciences or humanities: Sciences
Patients per week: 2
Work: QEH

What is your experience of treating inflammatory bowel disease patients?

I treat small number of patients. I don't know exactly how many. I have a handful in my clinic and a handful in a private practice.

How many years have you been doing this?

Well, in clinical practice since about 1985 but I finished my training in 1981.

- How comfortable do you feel with treating IBD patients?

Reasonably. I think the more difficult patients I would probably hand on to people with more experience. But the average patient I feel reasonably comfortable with.

2. How many patients with IBD have you treated?

This week   2

This month   2? I don't keep count.

This year   no idea

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

Not consciously. I would say probably not, actually. It's not something that I think about, particularly.

If yes:

3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?
NA

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?
NA

3c. What was the result of this treatment?
NA
3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?
NA
If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this? You just didn't meet a patient who..

Needed antidepressants? I wouldn't think of treating IBD per se with antidepressants

We are talking of pain, or depression, or other…

And I don't get involved in treating depression, so I see my role as detecting depression, I don't prescribe antidepressants for depression, that's somebody else's [role].

4. What is your opinion of the use of antidepressants in IBD in general?

It's not something I've thought about, particularly as a problem.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

Actually, IBD per se I have no idea. I'm sorry this is not an issue I've ever…
That's ok.

6. What is your opinion of the use of antidepressants in general?

Obviously they have a role in treating depression. They have a role in treating pain problems. They have a role in treating functional gut disorders. For example in diarhoea predominant irritable bowel they may be helpful. I guess if you think about things like chest pain, but that's really a pain disorder. I have tried to use them in patients with globus without success, globus syndrome. So it may be the sort of areas that I would consider using them.

What type of antidepressants do you use?

I would only prescribe tricyclic antidepressants. I've never prescribed an SSRI because if I don't feel comfortable with them. I don't think the data they work on pain disorder or functional diarhhoea. They are very limited to say the least. I don't know of any good literature on those things. And I don't treat depression. Disorders that I use antidepressants for, the literature really is based upon tricyclics.

7. Have you ever suggested using other psychological treatment in IBD patients?

No.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

It depends on the evidence on which a trial is based. If there is a reasonable hypothesis proposed and the trial was properly conducted then I wouldn't have any hesitation that patients are involved in such a trial.

9. Would you like to add any comments?
No.

10. Would you like to receive a copy of results of this study?
Yes.

11. In your opinion what is the cause of IBD?

I think it's a mixture. Current thinking would suggest it's an interaction between the host and the environment so there is a host make-up either presumably genetically based in some way that makes them predisposed to react to a stimulus in a certain way. And then there is a exposure to a stimulus which leads to IBD in susceptible people. An immune based inflammatory response which (*not clear*) susceptibility and exposure to an environmental trigger, in a broader sense. But of course the manifestation of the disease are influenced by other things as they are in any disease. So how the patient responds to the disease, how much the disease affects them in terms of their quality of life, etc, etc, etc. will be influenced by other aspects, usually by the patients or the patient's environment in terms of their social circumstances. So obviously a person who is depressed, a person who is anxious, a person who is less well able to cope will probably suffer greater detriment in terms of impact on quality of life than the person who is comfortable, has capabilities that allow them to cope with life stressors, has a supportive environment, etc. But I think that is independent on disease activity, I mean that's just their coping mechanisms.

Participant 12

16th November 2005

Age: about 50
Sex: ▮▮▮▮
Undergraduate studies where: ▮▮▮▮▮▮▮▮
Postgraduate studies where: ▮▮▮▮▮▮▮
How many years in gastroenterology: 26
Were you born in Australia: No
Do you speak other languages: Yes, ▮▮▮▮▮▮
In high school did you graduate in sciences or humanities: Sciences
Patients per week: 10
Work: QEH

1. What is your experience of treating inflammatory bowel disease patients?

20 years.

- Do you feel comfortable with treating IBD patients?

Yes.

2. How many patients with IBD have you treated?

This week   10 and new cases: 3, 10, 50

This month   40

This year   150

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

Yes.

What were the reasons?

Irritable bowel.

And apart from IBS, in IBD?

No, only IBS.

But have you ever used antidepressants in IBD?

Not lately.
Have you ever met a patient that you treated with them for pain?

With IBS, not with IBD.

If yes:

3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?
NA
3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?
NA
3c. What was the result of this treatment?
NA
3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?
NA
If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?

No need. With IBD if inflammation treated the psychological well-being improves.

4. What is your opinion of the use of antidepressants in IBD in general?

If there is clear indication they may have a role but not the primary.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

They may have a role but not to primary manage. Small proportion of patients with psychological disorders, depression may benefit.

6. What is your opinion of the use of antidepressants in general?

In properly indicated patients.

7. Have you ever suggested using other psychological treatment in IBD patients?

No.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

I would be happy for that.

9. Would you like to add any comments?

No.

10. Would you like to receive a copy of results of this study?

Yes.

11. What is the cause of IBD?

Reaction to an infectious agent.

Participant 13

16th November 2005

Age: 53
Sex: ███
Undergraduate studies where: ████████████
Postgraduate studies where: ████████████████
How many years in gastroenterology: 20
Were you born in Australia: Yes
Do you speak other languages: No
In high school did you graduate in sciences or humanities: Sciences
Patients per week: 6
Work: QEH

What is your experience of treating inflammatory bowel disease patients?

It's a fairly extensive experience. I was overseas ████████████████, I treated patients there and have been treating patients ever since then. I see between 2-10 IBD patients per week.

- How comfortable do you feel with treating IBD patients?

Quite comfortable.

2. How many patients with IBD have you treated?

This week   6

This month   20

This year   100

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

Yes.

What were the reasons?

If they had a problem with pain, for post inflammatory irritable bowel syndrome.

If yes:
3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?
No.

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?

330

Amitriptyline.

What was your reason?

Helps for postinflammatory bowel syndrome.

Did you use SSRI?

No.

3c. What was the result of this treatment?

Good. Good effects.

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?

No.

If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?
NA

4. What is your opinion of the use of antidepressants in IBD in general?

I normally use them in patients with IBD in remission but when they still have a lot of abdominal pain.

So do you mainly use them during relapse or during remission?

During remission.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

They control the pain.

6. What is your opinion of the use of antidepressants in general?

Obviously they are useful to treat endogenous depression. In terms of gastroenterology, we only use low doses to treat IBS. And they can be associated with other organic diseases like IBD and cealiac's disease.

7. Have you ever suggested using other psychological treatment in IBD patients?

No. Not in general.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

Yes, I would be agreeable.

9. Would you like to add any comments?

I think the tricyclic antidepressants seem to work better than the newer SSRI.

In IBD?

Yes. To control the pain.

10. Would you like to receive a copy of results of this study?

Yes. Thank you.

11. What is the cause of IBD in your opinion?

The most likely causes are immunological and bacterial.

Participant 14

16th November 2005

Age: 41
Sex: ███
Undergraduate studies where: ████████████
Postgraduate studies where: █████████████████
How many years in gastroenterology: 12
Were you born in Australia: Yes
Do you speak other languages: Yes, ██████
In high school did you graduate in sciences or humanities: Sciences
Patients per week: 5
Work: QEH

1. What is your experience of treating inflammatory bowel disease patients?

I see them every week.
How many years have you done it?
12

- How comfortable do you feel with treating IBD patients?

Comfortable.

2. How many patients with IBD have you treated?

This week   5

This month   12

This year   50

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?
No.
If yes:
3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?
NA
3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?
NA
3c. What was the result of this treatment?
NA
3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?
NA
If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?

333

I didn't see anyone, I haven't diagnose anyone with depression.

What about pain?

I haven't used them specifically for pain in IBD.

4. What is your opinion of the use of antidepressants in IBD in general?

They are useful if patients are depressed. We use them now for IBS, diarrhoea predominant. For some gut diseases with diarrhoea. In the exacerbation of the disease in IBD, I treat the IBD rather than giving them antidepressants. Maybe to treat chronic pain, but again it's more for IBS pains.

What antidepressants would you use in this case?

Pain and diarrhoea – amitriptyline.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

There is no impact on IBD but patients feel better. They help their mental state, help their depression.

6. What is your opinion of the use of antidepressants in general?

I think there is an important role for them.

7. Have you ever suggested using other psychological treatment in IBD patients?

Not specifically.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

It wouldn't bother me provide that there is available reason why they need antidepressants.

9. Would you like to add any comments?

No.

10. Would you like to receive a copy of results of this study?

Yes.

11. What is in your opinion the cause of IBD?
A combination of genetic, environmental and immunological causes.

Participant 15

23rd November 2005

Age: 64
Sex: ▮▮▮
Undergraduate studies where: ▮▮▮▮▮
Postgraduate studies where: ▮▮▮▮▮▮▮
How many years in gastroenterology: 30 years
Were you born in Australia: No
Do you speak other languages: No
In high school did you graduate in sciences or humanities: Sciences
Patients per week: part-time work about 30 regular patients and 6 new per year
Work: QEH

1. What is your experience of treating inflammatory bowel disease patients?

I've been a gastroenterologist for 30 years so I've come in contact with patients over that time in various contexts. They often are regular attendants at clinic because of the chronicity of their illness. So I see new patients but also have long-term contact with them.

- How comfortable do you feel with treating IBD patients?

They are hard work often because their exacerbations make them sick and also they have to be squeezed in as urgent appointments in a busy schedule. So it puts pressure on gastroenterologists. It's a two way process, isn't it? They are anxious when they have this and the doctors often are running busy.

2. How many patients with IBD have you treated?

This week   1

This month

This year   6 new, 30 people in sum

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

Usually with well established IBD only if they are more overtly depressed. Whereas in IBS I have used low dose tricyclics as a night time dose when the depression did not seem to be a dominant feature.

But did you actually use them in patients with IBD for depression?

Yes, but not in the hope of getting improvement when a patient is just anxious about their disease. If I detected depression and at least what one does in a consulting practice, one puts in the letter to the referring GP: I feel this patient may be depressed and would you consider evaluating that further and treating. I think that referring doctors will often take heed of that. Because one often is reluctant to start the medication that isn't in one's own direct field. Because that requires then an ongoing supervision and it would mean bringing

them back more frequently. So if you can see how this system is structured and one is reluctant to change medication if they're already on something or to increase the dose. But one usually does it by suggestion, to the referring doctor. But I feel that if they are overtly depressed, this may have some effect on the course of their disease. But we know it's hard to establish.

If yes:
3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?

No, I don't think my experience is enough to judge that and it would be anecdotal. And I'm not sure that one is more prone to depression than the other which has been the question asked. CD often has a bias towards the younger age of onset and UC is in a broader age.

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?

I've used tricyclics in the past remembering how long I have been in this before the SSRIs were available. So amitriptyline and nortriptyline, these are broad generic names. Then the SSRIs, as I say, I leave that to the GP rather than recommending one brand. And it's less directive than one might be.

3c. What was the result of this treatment?

My anectodal impression is that it's helped the patient and that I think it has done them no the harm at least. It might have improved the exacerbation for which one is usually seeing the patient. But the numbers are small and over a long period of time.

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?

Most of these people that I've been involved with have usually been on treatment only for 6 months, which is a common duration for one episode. My impression is that it has helped to control the exacerbation. But in terms of long term reduction, as maintenance treatment, I don't think I might have opinion about that.

If no:
3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?
NA

4. What is your opinion of the use of antidepressants in IBD in general?

It has a limited and secondary place. I don't think it is primary treatment. And not something that most of my colleagues, when discussed in meetings, seem to favour.

5. To what extent do you think antidepressants can have an impact on the disease? What impact? Theoretically?

Limited. In terms of mechanisms and so on I think we don't have good models to base it on unless it's some immunomodulatory thing of course, as we've discussed. Some people ask, you know, you should have some sort of hypothesis first, but I don't think it works that way. I think we do things and then we look for mechanisms simply because ther e is an impression that this may have psychosomatic overtones or where it reduces (*not clear*) so that the illness 'gets people down', to use lay terms. And therefore the question arises: is there a place for psychotropics? One could even extend this to mild anxiolitic things, you know I'm reluctant to use benzodiazepines, which some of these people are on for anxiety. In the past you used those things more readily and as a result people became habitutaed which is a secondary problem.

6. What is your opinion of the use of antidepressants in general?

I think they have a place in severe depressive states that do not respond to the initial talking therapy which is time consuming. Therefore a shortcut is often used to introduce them early maybe, got some bad press in recent times. Starting too early in young people and the risk of suicide precipitation. Remembering that some people with CD are youngsters, when they present they're in their late adolescence and so on. I think one needs to have a good reason to introduce them when nothing else has worked. I see them as secondary and as I said I would suggest them for overt depression, if I feel the person is significantly depressed.

7. Have you ever suggested using other psychological treatment in IBD patients?

Yes, I occasionally do suggest seeing somebody in the psychological field. Whether it's the loose term of a counsellor, psychologist, clinical psychologist and ocassionally, if I think it's going to be an ongoing management, then a psychiatrist. It may be one that has time to talk to them and does not rely entirely on psychotropics. So I have referred a few patients, often by suggestion to the local doctor.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

If they were willing to participate and my suggestion to them there is a trial going on, I would have no objection to it. Again they have to be aware how much time it consumes and I think quite often people if it's against placebo don't realise that half of them will get an inactive agent. Their understanding of double blinded trial in the public is not very big. Somebody would need to explain that to them. Unless you are evaluating one agent against another, which you've got to often in this field. It's against placebo, isn't it?

9. Would you like to add any comments?

No, I think it's a field I have a broader interest in. Apart from depression as I mentioned to you before, there are things like life events, early childhood development, notions of attachment theory, the notions of pathological attachment and early childhood separation. Some people feel that this may have an effect in IBS, rather than IBD. Some people want to try to separate IBS symptoms from IBD symptoms which is very difficult, and this is a problem. They have discomfort and bloating and various things that appear to be in the setting of IBD being in a relatively good remission on a CDAI index or other we might use. So there is an overlap.

10. Would you like to receive a copy of results of this study?

Yes. Maybe. Thank you. I would be interested to see but you will probably present them as a final summary, won't you? As part of your thesis.

Yes. I will.

11. What is in your opinion a cause of IBD?

It's an immune overreaction to something. I think is the current view, isn't it? All sorts of buzz words come up; loss of 'immune tolerance' and so on, but then there are current hypotheses explaining a sort of agent activator cascade, the problem is, as with all of these things, and I think you need to always remember this, is that when you don't have good explanations for normal mechanisms: what allows the gut to function? Normally, good bacteria and all sorts of food things that go in, We don't understand how that is well tolerated. We are not in a position to give good explanations to abnormal mechanisms. We often try to explain abnormal mechanisms as if we understand normal mechanisms clearly. And we don't, because these are hypotheses that people put up if you think about it, we don't know. We intervene at various stages, try to arrest cytokine activites, but what the initial trigger is, and what keeps it going, we don't know. The same story with IBS. Is it in fact initiated by some sort of infection in most of us? and then it goes on? That's one hypothesis. Does that lead to visceral hypersensitivity? With immunoactivation, why don't we all get IBD, you might ask. Because we all are exposed to these agents, there may be genetic factors which predispose, But when you think about it, genetic factors are not nearly as strong in IBD as in cealiac disease. Where there are pretty good markers and family history is much stronger in caeliac's disease than it is in UC. CD may be a little bit more stronger than UC. So the genetic story is a part of it, obviously, but it doesn't seem to stand out as a clear marker.

Participant 16

23rd November 2005

Age: 38
Sex: ▮▮▮
Undergraduate studies where: ▮▮▮▮▮▮▮
Postgraduate studies where: ▮▮▮▮▮▮
How many years in gastroenterology: 6 years
Were you born in Australia: Yes
Do you speak other languages: No
In high school did you graduate in sciences or humanities: Sciences
Patients per week: 4
Work: QEH

1. What is your experience of treating inflammatory bowel disease patients?

I probably currently have about 80-100 patients with IBD.

How many years in gastroenterology?
6 years as a consultant

- How comfortable do you feel with treating IBD patients?

For most of them reasonably comfortable. For the severe end of the spectrum it can be a difficult problem with a few headaches, but for those I might pass onto someone else. For the majority of patients I am reasonably comfortable

2. How many patients with IBD have you treated?

This week   4

This month   20-25
This year   70-80

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

Yes.

If yes what was the reason?

Well, I suppose sometimes with IBD patients some of the symptoms can be related to IBS and I think certainly some patients will have both and the evidence is reasonably good that antidepressants are one of the better medications for IBS, so to particularly deal with those aspects especially for patients with diarrhoea I suppose, the tricylic antidepressants can be quite helpful to help slow diarrhoea, and I think occassionaly underneath there is a feeling that antidepressants might be helpful for those people where the disease is getting on top of them psychologically as well.

3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?

I don't think I can say I have noticed anything striking.

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?

I'd more often use tricyclic antidepressants, most often Amitripyline, just through familiarility. With the tricyclics I think there is probably a little bit better evidence that they are more helpful for certainly for pain, and as mentioned for constipating effect that can be quite helpful. Occasionally been inclined to use SSRIs for those who have predominantly constipation I might try those drugs first as less likely to be a problem for those with IBD as opposed to IBS. The majority would be amitripline.

Have you ever used SSRI?

I certainly have, for Irritable Bowel. I would not be adverse to using it. I have ceratinly used SSRIs at times.

Do you remember the name of the medications that you use?

Sepramil, citalopram, zoloft.

3c. What was the result of this treatment?

Variable response. In some people tricyclics have intolerable side effects, haven't liked it. But there was a percentage of people where I used it with some success. Again, I can't think of anyone definitely with SSRIs where it's been particularly helpful, but I can think of at least a few people who have had IBD where they have definitely been better, there seems to be a symptomatic improvement, and also probably a psychological improvement for some, on tricyclics.

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?

Symptomatic improvement is due to IBD or IBS symptoms, they are sometimes difficult to distinguish. I can't say I've seen the reduction in their inflammatory markers or improvement macroscopically. I don't think I can say that. But certainly symptomatically.

If no:
3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?
NA
4. What is your opinion of the use of antidepressants in IBD in general?

I think there is a place for them. Obviously not first line and to be used in combination with other immunomodulating treatments, whichever. 5ASA, steroids and so on, they're obviously first line, but again in some patients it's a bit more difficult to control disease. Tricyclics particularly, but I suppose other antidepressants in their place, it's certainly, I've had some success.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

Again, I think it comes back to symptoms, to take some of the edge off symptoms, and whether it's through that direct effect, or whether it's directly a psychological improvement on sense of well-being, I guess in the end it maybe doesn't matter that much. That there is a psychological benefit as well from being on the antidepressants.

6. What is your opinion of the use of antidepressants in general?

I suppose there's a lot of feeling that they are overused. Personally I give people the option, explain to them very clearly why, or how I think it will be beneficial and I make clear the benefits I would expect to get out of it. There's a lot of suggestions in the public, press, I guess from some medical quarters that they are being overused. But I think the difficulty is that they are being used for a lot of indications which aren't just depression, and I think there's validity to that, so I don't think it's an easy question to answer.

7. Have you ever suggested using other psychological treatment in IBD patients?

I have suggested psychological counselling for some people, not many, but a few I've suggested that they could exercise, made those sort of points, can't say that I stress it a lot, but those sorts of things do come up, especially if people are really struggling with their disease.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

You mean placebo-control, that sort of trial?

Yes.

I would say whenever I am using it that it's sort of a therapeutic trial, that's how I tend to put it to people, that it's a trial and explain that it doesn't have to go for a while. If it's placebo-controlled traila that makes it more difficult. Look, I am sure that there are definitely some patients, quite a few patients who are willing, certainly not patients who are desperate who wouldn't want to necessarily take the risk of being on a placebo arm. So if there was some benefit to them, I think a lot of those patients, I think if it's put to people in a right way then there would certainly be some IBD patients who would be willing to, yes.

9. Would you like to add any comments?

No. Not particularly.

10. Would you like to receive a copy of results of this study?

Yes. Thanks.

11. What is the cause of IBD?

Well, the cause of IBD overall in broad terms I guess it's an autoimmune disease which is triggered by some event which is not clear and is perpetuated by perhaps another event

which is not clear. Mainly it seems to be a problem that is t-cell mediated. A lot of putative causes / agents, I don't think we really have enough evidence to really say its an infective agent, rather than being some specific unusual organism, I suspect it's probably an abnormal immune response to a fairly common intestinal flora, rather than a toothpaste or microbacterium, or.. I don't know. We could keep going on, but I don't think we'd get any close to an answer!

Participant 17

Age: 39
Sex: ███
Undergraduate studies where: ████████████████
Postgraduate studies where: ███████████
How many years in gastroenterology: 8 years
Were you born in Australia: No
Do you speak other languages: Yes
In high school did you graduate in sciences or humanities: Sciences
Patients per week: 2
Work: QEH

1. What is your experience of treating inflammatory bowel disease patients?

I think something like 100-150 patients with CD and UC, mainly CD. Since 1997.

- How comfortable do you feel with treating IBD patients?

Comfortable.

2. How many patients with IBD have you treated?

This week   2

This month   2

This year   -

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

Yes. A few patients who were depressed, who we felt could be partly because of the disease. Partly we felt that because of the steroids. But it's only the minority, a very few.

If yes:

3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?

No.

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?

Prothydin, which is a tricyclic.

Have you ever used SSRI?

No.

3c. What was the result of this treatment?

Seemed to improve. Whether it was because of the medication, I'm not sure, or the psychotherapy supports it.

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?

I didn't notice any.

If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?
NA

4. What is your opinion of the use of antidepressants in IBD in general?

I think that we can choose patients who would need it, and I think a subgroup probably will benefit, but it's like in the depression, it's reactive, it's multifactorial, the disease per se, as well as medications (*not clear*). In the subgroup there could be a role.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

I'm not really sure what it will have. I know that stressors is thought to be… I have seen some patients who start with a stressing event. Although I am not convinced in the mind that antidepressants alter the course of illness. I doubt it.

6. What is your opinion of the use of antidepressants in general?

Well in IBS a small dose of amitryptilene, in a RCT, in the only RCT in the world was from our uni back home, showed that amitryptilene in a small dose improves bowel symptoms in IBS.

And in other diseases?

Generally, I think, a large variety of depressive symptoms can be tackled by reasuring patients. What could be overslipped on the psychotherapy, but not necessarily as formal psychotherapy. I would not commonly use them, but usually I would not hesitate in using them either, obviously.

7. Have you ever suggested using other psychological treatment in IBD patients?

I am not sure I would send them to the psychiatrist, but if part of being with the patient would qualify as psychotherapy, then the answer is yes.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

I would have nothing against if a patient wanted to take part in a trial. There is some link with some component of a psychological problem here as well so we need to understand something about that. Whether the particular patient will benefit, I am not sure. But this could improve our knowledge your knowledge.

9. Would you like to add any comments?

One aspect of it I suppose is that it has a major impact on a patient's lifestyle. A patient's earning capacity, working capacity, so I suppose providing the support of the family is one of the things which will help in maintaining mental well-being, it's not really psychotherapy, it's not anything sort of, general support, it's one of the things in this major life event, support in that sense.

10. Would you like to receive a copy of results of this study?

Sure.

11. What is the cause of IBD in your opinion?

There are a lot of theories. My theory is, because back home ███████, now we see it more often. So, the feeling is that now ██████ we're getting cleaner
The theory that I subscribe to is that as a neonate, if a person lives in a clean environment, so not exposed to antigens, and when they grow up, they are exposed to antigens, the immune response is not well tolerant of those antigens. While if as a neonate I lived in a contaminated environment, which is what ██████ was earlier, then I already have my antigens, if later I encounter the antigens, my body would be able to tolerate it. That theory seems to fit, in this fact that back home in I████ now, IBD is getting more common. So, it may be that in a cleaner environment the people are all getting contaminated and there is lack of exposure. There are some studies supporting this. I know it's only one small viewpoint,

It's interesting…
In fact there is an article in Lancet which came that took 100 people with CD and 100 people with no CD and asked whether they were babies in the house with running tap water vs house with no running tap water 50 years ago. Those who had CD had running tap water. And in the houses with no running tap water no CD.
It's better to be dirty!

Participant 18

Age: 33
Sex: █████
Undergraduate studies where: ████████████
Postgraduate studies where: ████████
How many years in gastroenterology: 2
Were you born in Australia: No
Do you speak other languages: Yes
In high school did you graduate in sciences or humanities: Sciences
Patients per week: 3
Work: QEH

What is your experience of treating inflammatory bowel disease patients?

Two years experience so far.

Do you feel comfortable with treating IBD patients?

Yes.

2. How many patients with IBD have you treated?

This week   3

This month   10

This year   30

3. Have you ever used antidepressants or suggested using antidepressants in these patients for any reason?

Once. That's very rare. Long hospitalization. Obviously depressed patient.

If yes:
3a. Did you notice any difference in the effect of antidepressants on the disease between CD and UC patients?

No. It's difficult to say.

3b. If you have treated IBD patients with antidepressants, what kind of antidepressants (brand name, generic name, group) did you order? What were your reasons?

Citalopram.

And what was your reason?
Familiarity.

3c. What was the result of this treatment?

The patient got discharge so I don't recall asking whether it had an effect yet because usually it takes about 3 weeks to work.

3d. Did you notice any influence of the treatment with antidepressants on the course of IBD?

No.

If no:

3e. If you have not treated IBD patients with antidepressants or recommended their use, what would be your reasons for this?
NA

4. What is your opinion of the use of antidepressants in IBD in general?

Only if required. I don't think I use it to treat IBD.

5. To what extent do you think antidepressants can have an impact on the disease? What impact?

I suppose that could be theoretical benefit because stress is a trigger for flares so if you can reduce the response to any stress… However, I have never seen any proof to that. Maybe other doctors.

6. What is your opinion of the use of antidepressants in general?

I think they are useful in reactive depression and major depression. I think they are underused because we, gastroenterologists rarely have time to ask about depression. Two simple questions are not enough in this case. You need the depression scales, scores, which we don't have time to use. We probably underestimate that.

7. Have you ever suggested using other psychological treatment in IBD patients?

No.

8. How would you feel if your IBD patient would like to take part in a trial with antidepressants? What are your reasons?

I have an open mind.

9. Would you like to add any comments?

Not really.

10. Would you like to receive a copy of results of this study?

Why not. Yeah.

11. What is the cause of IBD?

I think it's an abnormal immune response to bowel flora. I think that's the best…

Appendix 16

Features of 12 studies describing the effect of antidepressants on the course of inflammatory bowel disease in order of the quality significance

Study name	Design	Participants	Disease type	Method	Results
Kast and Altschuler 2001 (USA)	Case report	2: Female, 44 y.o., 10 years with CD, CDAI: 202, mesalamine 500mg (2 a day), once a year a relapse treated with steroids, depression treated with fluoxetine (40mg) not effectively Male, 45 y.o., 20 years with CD, CDAI: 275, azathioprine (100mg) and bowel resections, fluoxetine for pain not effective.	CD	Bupropion 150mg (3 times daily) for depression (a female) and for pain and smoking cessation (a male)	Female:19-month remission, bupropion dependant, no other medication, CDAI = 0 Male: CDAI=45, 3-4 diarhoeas daily because of ileal-cecal valve, 50mg azathioprine, still on bupropion. Positive effect of bupropion on IBD activity (CD).
Walker et al. 1996 (USA)	Non-randomised open label study	8, recruited between March and October 1993 in tertiary care medical facility in Seattle, English-speaking, 18 y.o. or older, presented with IBD	Not specified	Tools: NIMH Diagnostic Interview Schedule (psychiatric interview), GI symptom interview and the Briere Child Maltreatment interview (history of childhood abuse and neglect), SF-36, Tridimensional Personality Questionnaire Patients diagnosed with major depression (n=8) have their depression confirmed by the Hamilton Depression Inventory (HAM-D) and started treatment. Treatment: paroxetine (paxil) 20mg, after 1 month two patients had the dosage increased to 40mg. Length: 8 weeks and reinterviewed + SF-36 and HAM-D	Decrease in mean HAM-D (pre-treatment 29.0+-7.8; post-treatment 8.1+-6.1; t=13.6, df=7, p,0.0001) and significant reduction in functional disability on most scales of the SF-36. The SF-36 measures changes in several domains of patient function including physical limitations, occupational role, emotional role, social function, pain, mental health, vitality, and health perception (higher scores associated with increased quality of life) Positive effect of paroxetine on IBD activity (not specified).

Study name	Design	Participants	Disease type	Method	Results
Scott, Letrent, Hager and Burch 1999 (USA)	Case report	1, 42 y.o., black male, depressed with chronic abdominal pain, weight loss, insomnia, anhedonia, with flare of CD, taking 6-mercaptopurine, prednisone and total parenteral nutrition. Treated in the past for depression with sertraline ineffectively and with amitriptyline successfully.	CD	Amitriptyline gel 80 mg/day intramuscularly. Improvement in mood but not in pain. Then, transdermal gel Amitriptyline 150mg applied to the chest at bedtime. Tool: Hamilton Depression Scale	Follow-up 6 weeks. Depression did not respond adequately to transdermal amitriptyline, however, patient stated that his mood improved. Patient's abdominal pain remained unchanged, however, did not experience any adverse events associated with transdermal medication. No effect of amitriptyline on IBD activity (CD).
Eirund 1998 (Germany)	Case report	1, male, 67 y.o., 17 years with UC, 4 relapses per year despite the treatment with sulfasalazine	UC	Treatment with paroxetine (20mg) for panic disorder	Panic disorder cured. No relapse of UC for 10 months. Positive effect of paroxetine on IBD activity (UC).
Kast 1998 (USA)	Case report	1, female, 33 y.o., 18 years with CD, taking azathioprine (75mg), prednisone (60mg) and acetaminophen (3 tablets daily), 3 bowel resections, despite this in relapse	CD	Phenelzine treatment for anxiety-prominent major depressive episode (15mg 3 times daily – 30mg 3 times daily)	Depression cured. After 7 days of treatment bowel movements dropped from 10 to 3-4 per day, after the increase to 30mg 1 bowel movement daily, depression responded, no cramps. Azathioprine and prednisone tapered off. Remission for 2 years until the treatment with phenelzine stopped. After 6 weeks since the stop relapse. Positive effect of phenelzine on IBD activity (CD).
Kane, Altschuler and Kast 2003 (USA)	Case report	4, (2 women, 2 unspecified)	CD	Treatment with bupropion (100mg daily) for smoking cessation (2 women) and depression (2 unspecified)	CDAI<150 within 6 weeks (without a change in standard medication for IBD) Positive effect of bupropion on IBD activity (CD).
Torras Bernaldez et al. 2003 (Spain)	Case report	3 depressed patients, no IBD diagnosed before depression	-	Treatment with Paroxetine for depression	Patients present with chronic diarrhoea, 2 treated with corticosteroid + immunosuppressants, 2 diagnosed with CD, one with unspecified bowel disease. Controversial paroxetine.
Ginsburg et al. 2005 (USA)	Guideline	0	Not specified	NA	All antidepressants recommended in irritable bowel syndrome recommended in IBD.
Kast 2003 (USA)	Review	NA	CD	NA	Bupropion recommended and mirtazapine not recommended.

Study name	Design	Participants	Disease type	Method	Results
Kast and Altschuler 2004 (USA)	Letter	NA	CD	NA	Bupropion recommended.
Kast and Altschuler 2005 (USA)	Review	NA	CD	NA	Bupropion recommended.
Kast 2005	Discussion	NA	CD	NA	Bupropion recommended.

Quality assessment of 12 studies describing the effect of antidepressants on the course of inflammatory bowel disease

	Kast et al. 2001	Walker et al. 1996	Scott et al. 1999	Eirund 1998	Kast 1998	Kane et al. 2003	Torras et al. 2003	Ginsburg et al. 2005	Kast 2003	Kast et al. 2004	Kast et al. 2005	Kast 2005
Length of treatment	2 years	8 weeks	6 weeks	10 months	2 years	No data	No	NA	NA	NA	NA	NA
Follow-up	Yes, regular follow-up for 2 years	Yes, 2 follow-up, all patients completed	Yes, detailed every day monitoring for 6 weeks.	1 follow-up after 10 months	Yes, regular follow-up for 2 years	1 follow-up after 6 weeks	Yes	NA	NA	NA	NA	NA
Clear description of treatment	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Description of participants	Yes	Yes	Yes	Yes	Yes	No	No	NA	NA	NA	NA	NA
Validated instruments	Yes	Yes, but only for depression and quality of life	Yes (depression), No (CD)	No data	No	Yes	No	NA	NA	NA	NA	NA
Limitations	-	Disease type not specified, disease activity index not used.	Lack of CD activity index. Focus only on depression and pain, no information about frequency of stools.	No objective activity index used.	No objective activity index used.	Lack of explanation of patients characteristics, Lack of further follow-up, no length of treatment provided.	Lack of evidence that IBD did not exist before the onset of depression, no details about length of treatment, no description of treatment and participants, no information about instruments.	Guideline paper without research. IBD treated as IBS, which may not be appropriate as they are different conditions.	A review study without the research. Theoretical considerations only.	A letter referring to Kane et al. 2003	A review study without the research. Theoretical considerations only.	A discussion referring to Kast et al. 2001 and Kane et al. 2003

	Kast et al. 2001	Walker et al. 1996	Scott et al. 1999	Eirund 1998	Kast 1998	Kane et al. 2003	Torras et al. 2003	Ginsburg et al. 2005	Kast 2003	Kast et al. 2004	Kast et al. 2005	Kast 2005
Impact of treatment with antidepressants on the IBD activity	Positive effect of bupropion on IBD activity (CD).	Positive effect of paroxetine on IBD activity (not specified).	No effect of amitriptyline on IBD activity (CD).	Positive effect of paroxetine on IBD activity (UC).	Positive effect of phenelzine on IBD activity (CD).	Positive effect of bupropion on IBD activity (CD).	Controversial paroxetine.	All antidepressants recommended in irritable bowel syndrome recommended in IBD.	Bupropion recommended and mirtazapine not recommended.	Bupropion recommended.	Bupropion recommended.	Bupropion recommended.

Legend to tables:

y.o. – years old

CD – Crohn's disease

CDAI – Crohn's Disease Activity Index

IBD – inflammatory bowel disease

HAM-D – Hamilton Depression Inventory

UC – ulcerative colitis

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