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REVIEW

Treatment of psychological co-morbidities in common gastrointestinal and hepatologic disorders

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Abstract

Anxiety and depressive disorders frequently coexist with gastrointestinal and hepatologic conditions. Despite their high prevalence, approach to treating these co-morbidities is not always straightforward. This paper aims to review the current literature into etiology of psychological co-morbidities and their treatment in three conditions commonly encountered at gastroenterology outpatient clinics, namely inflammatory bowel disease (IBD), irritable bowel syndrome (IBS) and chronic hepatitis C (HepC). The paper demonstrates that although psychotherapy (and cognitive-behavioural therapy in particular) has been established as an effective treatment in IBS, more studies are needed in HepC and IBD. Antidepressants have been recognized as an effective treatment for psychological and somatic symptoms in IBS and for depression in HepC, but good quality studies in IBD are lacking despite the promising preliminary findings from animal models and case studies. Further studies in this area are needed.

Key words: Inflammatory bowel disease; Irritable bowel syndrome; Hepatitis C; Psychological co-morbidities; Antidepressants; Psychotherapy

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INTRODUCTION

Anxiety, depression and poor quality of life are highly prevalent in the chronically ill[1-3]. They can also interact with each other. For example, psychological status is known to independently impact on health-related quality of life[4]. Moreover, there is a positive relationship between the presence of anxiety and depression[5]. All these associations are common among people suffering from chronic gastrointestinal and hepatologic disorders. Indeed, there is evidence that anxiety and depressive disorders frequently coexist with gastrointestinal[6,7] and hepatologic[8,9] conditions. In the case of gastrointestinal diseases this may perhaps be explained by the fact that the gut, while responding to environmental and physiological factors, also directly cooperates with the brain through the so-called brain-gut axis[10]. In the case of hepatologic disorders the etiology seems much more complex and this will be explained in more detail below.

Although psychological co-morbidities are highly prevalent in gastrointestinal and hepatologic disorders, the approach to treating these co-morbidities is not always straightforward. This paper aims to review the current literature into etiology of psychological co-morbidities and their treatment in three conditions commonly encountered at gastroenterology outpatient clinics, namely inflammatory

bowel disease (IBD), irritable bowel syndrome (IBS) and chronic hepatitis C (HepC). These three conditions were selected from among many gastrointestinal and hepatologic disorders due to their commonness but also due to their etiological differences and thus possible different origins of psychological difficulties. For example, IBD is 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. IBS is 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, while HepC is a chronic and potentially life threatening hepatologic disorder with a significant psychological burden, present mainly in those sufferers aware of their diagnosis.

IBD

Epidemiology

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. The prevalence of IBD ranges from 37 cases to 246 cases per 100 000 persons for UC and from 26 cases to 199 cases per 100 000 persons for CD depending on the region of the world[11]. The disease's prevalence is not equally distributed among races, with the Jewish and Caucasian populations at highest risk[12]. Both sexes have been observed to be equally affected by IBD, however, UC is slightly more common in men, and CD in women[13].

Presentation, etiology and psychological co-morbidities

IBD is characterised by an inappropriate immune response that causes characteristic inflammatory lesions in the gut wall. Both CD and ulcerative colitis involve inflammation of the bowel wall and both have a relapsing course. CD 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 anemia. 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 anemia being less common than in CD[14].

The etiology of IBD is unknown. Nonetheless, genetic, immune and environmental factors have all been implicated in its causation[15]. Studies also report that stressful life events exacerbate the disease[16]. More specifically, it has been conceptualized that psychological stress may be linked to the exacerbation of IBD, and UC in particular, by inducing systemic and mucosal pro-inflammatory responses[17]. IBD is at present an incurable condition and its course is unpredictable. As the disease is usually diagnosed in young adults, sufferers must often cope with their disease for many years. Their quality of life and psychosocial wellbeing may be profoundly impaired as a consequence of systemic symptoms, surgery, medication side effects and prevalent fatigue. Both CD and UC have a significant impact on patients' self-image, social relationships and sexual functioning[15,18]. Moreover, IBD is often associated with IBS[19]. According to researchers, up to 60% of IBD patients in remission, concurrently suffer symptoms of IBS[20]. Therefore, for these patients, quality of life and psychosocial well-being remain impaired regardless of whether IBD is active or quiescent. Furthermore, in population-based studies, more than 50% of IBS patients have reported psychiatric symptoms[21]. Thus, anxiety and depression in patients with IBD may be partly explained by co-existent IBS. In view of the above findings, it is not surprising that the rate of anxiety and depression in patients with IBD is around 30% during remission[22] and as much as 70% during relapse[23]. However, the etiology of these psychological co-morbidities in IBD is associated with a number of controversies, as reported by the present author elsewhere[24].

Standard treatment

Common treatment options for IBD include aminosalicylates (e.g. sulfasalazine, mesalazine), glucocorticoids (e.g. prednisolone), immunomodulators (e.g. azathioprine 6MP, methotrexate), and antibiotics (e.g. metronidazole, ciprofloxacin). Less common treatments for severe disease include cyclosporine and monoclonal antibodies (e.g. infliximab)[25,26]. 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 wk of treatment whereas corticosteroids are used when a rapid 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[25]. However, all listed treatment options are associated with some side effects and, importantly for the purpose of this paper, some of these side effects may be of psychological nature (e.g. mood changes, mania, depression and psychoses induced by corticosteroids)[27].

Treatment of psychological co-morbidities

Psychotherapy including supportive-expressive, interpersonal and psychodynamic modalities as a treatment for psychological problems in patients with IBD has been examined in a small number of studies[28-31] and by-and-large proved ineffective for treating psychological co-morbidities.

The few studies that examined cognitive-behavioural therapy showed more encouraging results. Schwarz and Blanchard (1991), in a randomised controlled trial with 29 participants, found cognitive behavioral therap (CBT) to be an ineffective way to treat psychological problems in a mixed IBD group of CD and UC patients[32]. However, others[33], 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[34] 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. The same group of researchers subsequently conducted a randomized controlled trial with 41 adolescents with subsyndromal depression and showed reduction in depression and anxiety at 3 mo in the experimental but not the control group[35]. Moreover, 15.4% of the CBT group *vs* 25% of the comparison group had moderate/severe disease activity at 2 wk post treatment, with a drop from 28.6% and 29.4% at baseline, respectively. However, this group difference was not statistically significant. Further, in the most recent randomised controlled trial, Diaz Sibaja *et al*[36] showed CBT to be an effective treatment for anxiety and depression in IBD, the effect of which was maintained at 12 mo follow-up. However, this study did not measure the impact of CBT on the course of the disease. Moreover, small studies into hypnotherapy have indicated its significant potential in improving the course of the disease[37,38].

A review evaluating evidence arising from these studies concluded that psychotherapy has little impact generally on the course of disease in IBD, although it may be beneficial for patients with anxiety and depression[39]. A more recent paper reviewing psychological co-morbidity and treatment in IBD suggested that, based on initial evidence, CBT has a potential to treat anxiety and depression in IBD effectively[40]. There is however only limited evidence on the impact of CBT on the course of the disease and this should be further explored. Larger studies measuring both psychological status and disease activity are clearly needed in this area as CBT seems to be a promising pathway for psychological treatment in patients with IBD. Larger controlled studies into the influence of hypnosis on clinical outcomes could also be of interest as preliminary findings are encouraging and hypnosis has also been found effective in IBS[41].

With respect to pharmacological treatment of depression and anxiety in patients with IBD, to date, there has been little formal research on the use of antidepressants in IBD, with most published data being uncontrolled and anecdotal. In the systematic review co-authored by the present author, it was observed that even though antidepressants seem to improve both mental and somatic status of IBD patients, the low quality of available studies makes it impossible to make a definitive statement on their efficacy[42]. In the review, 12 relevant publications were identified, all presenting non-randomised studies. In 10 papers, paroxetine, bupropion and phenelzine were found effective for treating both psychological and somatic symptoms in patients with IBD. In the subsequent qualitative interview study we showed that gastroenterologists commonly treat IBD patients with antidepressants for pain, anxiety and/or depression, and insomnia[43]. Gastroenterologists reported that tricyclic antidepressants (i.e. amitriptyline, dothiepin, prothiaden, doxepin, imipramine, nortriptyline) were successful in reducing pain, gut irritability, and urgency of defecation. However, only a few doctors had experience of treating IBD patients with newer antidepressants. The most recent update to the systematic review on the role of antidepressants in IBD[44] found a positive impact of antidepressants (i.e. desipramine and fluoxetine) on inflammation in IBD. However, the evidence came mostly from animal trials. Good quality human data are lacking and randomized controlled trials are warranted. They are especially needed as antidepressants may offer a yet relatively unexplored contribution to the management of IBD.

IBS

Epidemiology

Functional disorders account for up to 50% of referrals to gastroenterologists in outpatient clinics[45,46], with IBS alone accounting for 20% of gastroenterology output practice[47]. The prevalence of IBS has been estimated at 17 per 100[48], making it one of the most common disorders in gastroenterological practice[49].

Presentation, etiology and psychological co-morbidities

IBS is a chronic relapsing condition in which there is abdominal pain or discomfort associated with altered bowel habits (constipation and/or diarrhoea)[50]. Other common symptoms include flatus and bloating. IBS is classified as a functional gastrointestinal disorder (FGID), meaning that it presents with non-structural symptoms and is identified only by symptoms[51]. In line with other FGIDs, the etiology of IBS is controversial. IBS is considered to be a disorder in which sensory and motor[50] and inflammatory[52] changes can play a role. It is conceptualized that the symptoms of IBS can be the result of altered motility, impacted on by such factors as psychological difficulties, food, infections and hormones. 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[46]. 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[53]. However, FGID is perhaps best understood as a product

of interaction between psychological factors and altered gut physiology *via* the brain-gut axis[10]. Because of this, the biopsychosocial model has been found useful in effectively understanding FGIDs and their treatment[54-55]. Interestingly, in population-based studies, more than 50% of IBS patients have reported psychiatric symptoms[21]. These findings lend support to the notion that the patient's psyche plays an important role in the etiology and course of IBS.

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)[56] and that psychological factors are likely to be involved in this process[20]. 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 evidence on the existence of pathological abnormalities in the gut in patients with IBS[57].

Standard treatment and treatment of psychological co-morbidities

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[58]. Conventional pharmacological treatment includes bulking agents, antidiarrhoeals, antispasmodics, prokinetics, serotoninergic agents and antidepressants[58,59]. Non-drug treatments such as probiotics and peppermint have also been found effective in IBS[60].

As IBS has been considered a partly psychological disorder, it is not surprising that psychological (psychotherapy) and psychiatric treatments (antidepressants) for IBS have been the subject of many studies, as evidenced by systematic reviews and meta analysis[59,61,62]. In the most recent high quality meta analysis including 32 randomised controlled trials, tricyclics and SSRIs have been found equally effective for symptoms of IBS, with no serious adverse events[61].

In the same study the researchers observed that while antidepressants are effective in the treatment of IBS, there are few high-quality studies on the use of psychological therapies in IBS. Nevertheless, they showed that a range of different psychological therapies were able to significantly reduce physical symptoms in patients with IBS, with studies on CBT providing greatest evidence[61]. Another important observation has been made by researchers working on the role of hypnosis in treating IBS[41,62]. In a systematic review comprising 14 trials (eight without and six with a control group), Tan *et al*[41] observed that hypnosis improves both the cardinal symptoms of IBS and non-colonic symptoms in the majority of patients. Wilson *et al*[62] reported on 18 trials of which four were randomized, two controlled and 12 uncontrolled and showed that hypnotherapy was effective in the management of IBS. However, these authors also recommended better quality trials. Although pharmacological treatment with antidepressants has been found effective in IBS, some researchers claim the superiority of psychological treatments over antidepressants in terms of long-term reduction in health care costs[63]. However, there is a scarcity of studies comparing antidepressants to psychotherapy and such studies could shed some light on which treatment modality is more effective in patients with IBS.

HEPC

Epidemiology

Hepatitis C is a chronic disorder which carries a mortality risk, being a major cause of cirrhosis, end-stage liver disease and liver cancer[64]. The current typical modes of acquisition for acute hepatitis C in Western countries are intravenous drug use and sexual intercourse[65]. 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[66]. For HepC, 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 behaviors[67]. In a recent population-based survey, the prevalence of chronic HepC in Australia was estimated at about 2 per 100[68], with the 20-24 years age group having the highest HepC prevalence of around 5% (95% CI: 3.3%-8.1%) with a male to female ratio of 1.8:1.0.

Presentation, etiology and psychological co-morbidities

HepC is a viral infection. Typically, within 2 wk 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 HepC. In 15% of patients, HCV RNA in serum becomes undetectable and these patients either do not develop the disease or develop it later[14]. The majority of patients experience no clinical symptoms[69] but up to 25% of patients may develop jaundice, and 10%-20% report non-specific symptoms such as fatigue, nausea and vomiting[14]. In some studies, up to 90% of patients had documented psychiatric and/or substance abuse diagnoses[70]. Particular research on military veterans, showed that approximately 50% of patients with HepC have been diagnosed with depression, 40% with anxiety, 30% with post-traumatic stress disorder and 20% with psychosis[70,71]. In another study with patients awaiting treatment with interferon α, depression was diagnosed in only 28% of patients and anxiety in 24%[8]. A recent Canadian population-based study showed that, in 1995, 22% of all HepC population had some mental health condition and this rate increased to 32% by 2000 and 35% by 2005, with depression being most prevalent[9]. The discrepancies

in the prevalence of anxiety and depression in patients with HepC may depend on many factors such as age differences of participants or concurrent treatment with interferon α. 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[72] in patients with HepC. This is because patients' scores on psychological measures appear to vary depending on whether they are aware or unaware (many patients may spend years with occult infection) of their HepC positivity[73,74]. 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 HepC have been classified as substance and alcohol users, addiction and other high risk behaviors are likely to be confounding factors contributing to the level of psychological problems in HepC[70,73]. 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 HepC[75], as the disease is stereotypically associated with alcoholism, drug addiction and the human immunodeficiency virus. Moreover, according to some researchers, HepC itself may contribute to the psychological morbidity through pathophysiological events resulting from infection[76], which may impact on cognitive functioning[77].

Standard treatment

Until this decade, the disease had a very low success rate from antiviral monotherapy with standard interferon α, with only about 6% to 13% of patients achieving virological clearance when treated for 24 and 48 wk, respectively[78]. A major improvement in therapy has resulted from a combination therapy comprising interferon α and ribavirin, which has given a response rate of 35% during a 24-wk therapy and 43% during a 48-wk therapy[79]. This response rate has further increased after the recent development of pegylated forms of interferon α, which in combination with ribavirin produces a 56% response rate after a 48-wk therapy[80].

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[81]. According to Manns and colleagues (2001), in the case of both treatment modalities, about 35% of patients suffer from irritability and 40% from insomnia.

Treatment of psychological co-morbidities

There is some general agreement, based on clinical practice, on how to treat depression and other psychiatric conditions in HepC[82]. These researchers found most psychotropic medications (antidepressants, mood stabilizers, antipsychotics, and neuroleptics) to be safe to use in the management of patients with HepC and psychiatric illness, and for the management of interferon-induced neuropsychiatric adverse effects. In their recent systematic review, Sockalingam *et al*[83] evaluated 9 trials on antidepressants in HepC and found SSRI antidepressants safe and efficacious in treatment of depression after interferon therapy.

In contrast to IBS, but consistent with a limited number of relevant high quality studies in IBD, psychotherapy has not been widely studied in HepC and no randomized controlled trials or systematic reviews are available. Only two studies that used psychotherapy have been found[84,85]. Lang *et al*[84] conducted a small retrospective survey of 29 HepC patients treated with interferon and suffering depression who were about to discontinue the treatment. Twenty three of these patients were provided with a psychiatric care comprising antidepressants and psychotherapy which improved their treatment compliance. However, the study was not randomized and it applied supportive psychotherapy together with pharmacological treatment using antidepressants. It is, therefore, hard to estimate whether the positive result was achieved due to the effectiveness of antidepressants or psychotherapy or the combination of the two. Skibinski[85] in their non-randomized controlled study showed that short-term group cognitive-behavioural therapy does not improve quality of life whilst individual therapy does. However, groups were not directly compared as the researchers used Spearman correlation as their only type of analysis and correlated a particular group with symptoms. As HepC patients commonly suffer from mental disorders and as antidepressants may not be as effective as psychotherapy in preventing long-term relapses of these problems, studies into efficacy of psychotherapy are needed. Randomised controlled trials are clearly warranted.

CONCLUSION

Psychological co-morbidities are highly prevalent in patients with chronic gastrointestinal and hepatologic disorders. Although psychotherapy (and CBT in particular) has been established as an effective treatment in IBS, more studies are needed in HepC and IBD. Antidepressants have been recognized as an effective treatment for psychological and somatic symptoms in IBS and for depression in HepC, but the good quality studies in IBD are lacking despite the promising preliminary findings from animal models and case studies. Further studies in this area are needed.

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