Fatigue in Inflammatory Bowel Disease: Developing an understanding of the research need through a narrative review.

Patients with Inflammatory Bowel Disease (IBD) are affected by a number of symptoms, undergo lifelong pharmacological treatments and clinical interventions. (Bennebroek Evertsz' *et al.*, 2012; O'Connor *et al.*, 2013) Fatigue is one of the most experienced symptoms of patients with IBD, and has some of the largest impact on patients' lives.(Czuber-Dochan, Ream and Norton, 2013) IBD related fatigue is only identified in a relatively small proportion of those affected. (Van Langenberg and Gibson, 2014; Williet *et al.*, 2017)

The complex aetiology of IBD fatigue, its subjective nature and the lack of a standardised measure of fatigue add to the challenge of developing suitable and effective management methods. (Simrén *et al.*, 2008; Whitehead, 2009; Czuber-Dochan, Ream and Norton, 2013) IBD usually has an early onset and is a chronic, incurable, condition. It does not typically shorten lifespan, therefore addressing how patients deal with their disease is a principal aspect of care.(Graff, Walker and Bernstein, 2009) IBD is incurable and, owing to the physical and psychological impact of the disease, it significantly reduces patients health related quality of life.(Huppertz-Hauss *et al.*, 2015)

IBD fatigue is one of the top 5 research priorities highlighted by the Nurses European Crohn's and Colitis organisation (N-ECCO) due to its pervasiveness and it's unclear aetiology.(Mowat *et al.*, 2011; Dibley *et al.*, 2017) Fatigue is an extremely common complaint among patients with chronic disease and has been identified as one of the most burdensome symptoms of IBD.(Stjernman *et al.*, 2010; Dibley *et al.*, 2017) Several studies have identified fatigue as one of the leading concerns of IBD patients.(Drossman *et al.*, 1989; Casati and Toner, 2000; de Rooy *et al.*, 2001) Recently, the symptom of fatigue has received greater attention as part of overall health-related quality of life (HRQoL) assessments in patients with chronic disease, including IBD.(Swain, 2000) The subjective nature of fatigue, poor understanding and lack of proven therapies with which to treat, this symptom is often ignored or underestimated by clinicians. (Czuber-Dochan W1, Dibley LB, Terry H, Ream E, 2013; Czuber-Dochan, Norton, Bredin, *et al.*, 2014)

Fatigue related to LTC is defined as an 'extreme and persistent sense of tiredness, weakness or exhaustion'(Dittner, Wessely and Brown, 2004) which can be physical, mental or both and is not easily resolved by sleep or rest.(Arnett and Clark, 2012) Fatigue can be attributed to both physical and mental exertion(Pawlikowska *et al.*, 1994; Van'T Leven *et al.*, 2010) or as the outcome of pathological processes.(Pawlikowska *et al.*, 1994; Van'T Leven *et al.*, 2010) The international classification of diseases code presents fatigue as an assortment of physical, cognitive and emotional symptoms affecting undertaking of daily tasks.(Elizabeth Haney, MD; M.E. Beth Smith, DO; Marian McDonagh, PharmD; Miranda Pappas, MA; Monica Daeges and Ngoc Wasson, MPH; and Heidi D. Nelson, MD, 2015) It is not known whether fatigue in a given disease is a result of being chronically ill or whether it represents a specific symptom of that disease.(Swain, 2000). Fatigue is often attributed to LTC conditions, however it is experienced by most people at some point in life and can usually be allied to excessive physical activity, stress or ill health.(Wu, Wyrwich and McSweeney, 2006) Fatigue is often the first symptom reported in acute physical or mental illness,(Minden, Orav and Reich, 1987; Dittner, Wessely and Brown, 2004; Radbruch *et al.*, 2008) often preceding and following the period of illness.(Vollmer-Conna *et al.*, 2004; Wu, Wyrwich and McSweeney, 2006) In LTC, fatigue can lead to a chronic psychological depletion of energy reserves and result in functional impairment (Romberg-Camps *et al.*, 2010), this type of fatigue which arises from a pathological process or psychological disorder of a longer duration is often referred to as chronic fatigue. IBD fatigue has been reported as multidimensional and complex, impacting individual's activities of daily living and reducing their HRQoL.(Stjernman *et al.*, 2010)

Incidence and prevalence of IBD is increasing globally.(Wilson *et al.*, 2010; Jussila *et al.*, 2012; Molodecky *et al.*, 2012) Historically IBD incidence has varied according to geographical location, with higher incidence in the western world being linked to industrialisation. However emerging data speculates that there is increasing incidence in eastern countries, potentially due to immigration, more westernised diets and lifestyles and better healthcare systems.(Sood *et al.*, 2003; Thia *et al.*, 2008) . In the UK it is estimated that there are 300,000 people affected by IBD. CD and UC affects 5-10 and 10-20 new patients, respectively, per 100,000 people per year. (Topchiev *et al.*, 2017)

The causal relationship between chronic fatigue and diminished HRQoL is not completely understood, though an intricate interaction of several factors, such as pain, malnutrition, phycological distress,

sleep difficulties and ongoing inflammation is reportedly involved.(Graff *et al.*, 2011; Goldenberg *et al.*, 2013)

The prevalence of IBD fatigue is reported as 41-48% for patients in remission and 71-86% in patients with active disease.(Van Langenberg and Gibson, 2010; Czuber-Dochan *et al.*, 2013) This was deduced from three studies where fatigue was measured as a secondary outcome, relating predominantly to level of disease activity, HRQoL or mental health (I.M. *et al.*, 2003; Björnsson *et al.*, 2004; Minderhoud, Samsom and Oldenburg, 2007). Since the publication of these results further studies have reported the prevalence of IBD fatigue, the findings of recent publications suggest that when disease is in remission, fatigue in UC varies from 22-36% , and 27-41% in CD.(Häuser *et al.*, 2005; Romberg-Camps *et al.*, 2010; Graff *et al.*, 2011; Jelsness-Jørgensen *et al.*, 2011) In a population with mixed disease activity, fatigue prevalence was reported as 44-64%.(Lesage *et al.*, 2011; Römkens *et al.*, 2011; Tinsley *et al.*, 2011; Bager *et al.*, 2012) Some studies have compared levels of fatigue in IBD with that reported in other LTC such as PSC (Björnsson *et al.*, 2004) and Multiple Sclerosis (MS) (Bol *et al.*, 2010). Similar levels of fatigue have been reported in these conditions when compared with IBD, one study suggesting the fatigue in MS shows similar characteristics to that observed in UC.(Bol *et al.*, 2010) Despite the reported similarity of fatigue in IBD prevalence to that seen in other health conditions, as a symptom IBD fatigue has only recently begun to receive a similar level of attention in research and clinical practice.

The reported prevalence of IBD fatigue may be confused by severe and complex IBD presentations. There is also the limitation of the use of different fatigue measurement scales and tools, with no clear cut off point to define fatigue that requires an intervention.

A consensus on the standard care for IBD-related fatigue, particularly regarding screening and management, is non-existent.(Kreijne *et al.*, 2016) Currently there are no clinical guidelines on how to measure IBD fatigue in practice. There is no cut-off point for diagnosing IBD fatigue using measures that have been validated in an IBD cohort, at present a diagnosis of IBD fatigue is at the discretion of the clinician. The IBD Fatigue scale (Czuber-Dochan, Norton, Bassett, *et al.*, 2014) and the Functional

Assessment of Chronic Illness Therapy Scale (FACIT-F) (Tinsley *et al.*, 2011) have been validated in an IBD cohort but are still not widely implemented and do not have diagnostic cut off points.

Throughout the reviewed literature to date, different scales measuring types of IBD fatigue have been applied, the Multi-Dimensional Fatigue Inventory scale (MFI) being the most widely used (Smets *et al.*, 1995). Alternately there are differing scales used to measure functioning in IBD patients. Some of these scales are symptom specific such as the Fatigue Impact Scale (FIS) (Fisk *et al.*, 1994) whilst other focus on HRQoL measurements (Ware, John E., 1992). Alternatively there are some studies where the authors developed their own questionnaires (Hershfield, 2005; Tanaka and Kazuma, 2005; Joyce *et al.*, 2008; Topchiev *et al.*, 2017). Only the IBD questionnaire (IBDQ) was developed with an IBD cohort, however it is designed to measure quality of life (QoL) rather than fatigue and encompasses just one question relating to fatigue and one other on energy levels (Irvine, 1999). Czuber-Dochan developed a questionnaire comprising of 41 questions, in collaboration with IBD patients for the assessment of fatigue and QoL.(Czuber-Dochan, Norton, Bassett, *et al.*, 2014)

Several studies report that the domains most strongly associated with fatigue are physical (functional, reduced activity), cognitive (mental, sensory) and emotional (motivational, mood). (Casati and Toner, 2000; Whitehead, 2009; Czuber-Dochan, Ream and Norton, 2013) It is important that we consider fatigue within a biopsychosocial model of care and consider how different physical and psychological factors interact with each other as a cause for IBD fatigue.

There is comprehensible positive association between disease activity and high levels of fatigue. (Jelsness-Jørgensen *et al.*, 2012; Graff *et al.*, 2013; Cohen *et al.*, 2014; Kappelman *et al.*, 2014; Van Langenberg and Gibson, 2014) Throughout the literature there are also other identifiable factors, both modifiable and not, contributing to IBD fatigue. These include such factors as malnutrition, sleep deprivation, muscle depletion and various vitamin and mineral deficiencies that are potentially linked to disease symptomology. Due to the severity of IBD, related psychological distress is also common.(Keeton, Mikocka-Walus and Andrews, 2014) The risk of developing depression or anxiety one year or less before diagnosis with UC suggests symptoms might be a pre-clinical manifestation of IBD. Most anxiety or depression diagnosed subsequent to diagnosis of IBD occurs during the year

after IBD is diagnosed, indicating that these somatic symptoms might be reactive to the diagnosis rather that playing any aetiological role in IBD development.(Kurina *et al.*, 2001)

Available epidemiological data demonstrates a high prevalence of psychological illness in IBD. In one study it was observed that depression was significantly commoner in IBD compared with controls, 27.2% in CD and 12.3% in Controls, with anxiety being common in IBD than controls, 8% in CD and 4.7% in controls.(Walker *et al.*, 2008) These data indicate that depression is the more prevalent psychological co-morbidity when compared to anxiety disorders in these cohorts. These co-morbidities potentially influence both the onset and clinical course of the disease.(Maunder and Levenstein, 2008) There is significant association between baseline anxiety and depression scores, a flare up of symptoms in IBD patients, and disease relapse at 12 and 18 months follow up.(Mittermaier *et al.*, 2004) Similarly, higher depression scores at baseline in a sample of 100 patients treated with infliximab was associated with a lower rate of disease remission.(Persoons *et al.*, 2005) This suggests that improvements in depressive symptoms are not solely related to improvements in the course of IBD.(Szigethy *et al.*, 2009) In a study comparing people with UC to people with other LTC, patients with UC reported significantly more worrying over disease complications, depression and embarrassment.(Lönnfors *et al.*, 2014)(Rubin *et al.*, 2010)

Stress management techniques in CD have been shown to significantly reduce tiredness when compared to the standard of care.(García-Vega and Fernandez-Rodriguez, 2004) Lower psychological well-being has been independently associated with IBD related fatigue(Simrén *et al.*, 2008) and changes in fatigue over time.(Graff *et al.*, 2013) Patients with IBD in remission who had self-directed personality traits were less tired when compared to those who did not show traits of a self-directed personality type.(Banovic *et al.*, 2012) Individuals who were able to adapt their behaviour to fit the situation in accordance with their chosen goals have lower levels of fatigue when compared to those people who are not able to adapt.(Opheim, Fagermoen, Jelsness-Jørgensen, *et al.*, 2014) Quantitative studies considering other LTCs identify a strong interaction between disease related fatigue and depression and emotional stress. (Mohr, Hart and Goldberg, 2003; Armes, Krishnasamy and Higginson, 2004; Fuller-Thomson and Nimigon, 2008)

Social isolation has been linked with depression in IBD, increased levels of social support led to improvements in social functioning and a comparative reduction in depression and fatigue (Mohr, Hart and Goldberg, 2003; Häuser *et al.*, 2005; Tanaka and Kazuma, 2005). In a European, questionnaire based study, 48% of respondents felt that their life was significantly or somewhat affected socially by IBD symptoms, even when in remission.(Lönnfors *et al.*, 2014) 35% of respondents felt like IBD prevented them from pursuing an intimate relationship, with 17% reporting that IBD has caused their relationship to end. The same study reported that 75% of participants reported absenteeism at work with the most common reason being fatigue. Relatives play in important role in the process of acceptance of fatigue, as their acceptance of and support in managing disease related symptoms, such as fatigue, are highly valued by IBD patients. (Beck *et al.*, 2013) one study suggested that lower social support was related to decline in 'vigour' in individuals with UC (Tanaka and Kazuma, 2005), however these findings are not supported by more recent evidence. (Simrén *et al.*, 2008; Opheim, Fagermoen, Bernklev, *et al.*, 2014; Norton *et al.*, 2015)

The management of long-term conditions (LTC) such as IBD, is widely acknowledged as one of the principal challenges facing the 21st century National Health Service (NHS). An estimated 70% of the total health care expenditure in England is associated with 30% of the population who have one or more LTC.(House of Commons Health Committee, 2014) IBD treatment has improved mainly due to prescription medication, however this has brought around a significant increase in healthcare costs.(Marchetti and Liberato, 2014) The cost of care for IBD patients is estimated to be in the range of £631 - £762 per patient per year.(Buchanan *et al.*, 2011) This suggests an overall annual cost to the NHS of up to £470 million, with earlier research estimating the annual average cost of care per patient to be as high as £3,000.(Luces and Bodger, 2006; Molodecky *et al.*, 2012)

Research on the pathogenesis of IBD related fatigue, effective measurement and its impact on IBD patients will allow the discovery of predictors of severe fatigue that requires clinical intervention, also the development of clear treatment pathways and structured support for IBD patients (Kreijne *et al.*, 2016). This has the potential to improve patients HRQoL, experience of healthcare engagement and reduce cost to the NHS by reducing inadequate or inappropriate testing or referrals and targeting effective interventions to the right people at the right time.

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