Medication Management in Pediatric Chronic Illness: Should Patient Anxiety be Considered?

Claire J. Hoogendoorn

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MEDICATION MANAGEMENT IN PEDIATRIC CHRONIC ILLNESS: SHOULD PATIENT ANXIETY BE CONSIDERED?

by

Claire Jeanette Hoogendoorn

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, the City University of New York

2016
MEDICATION MANAGEMENT IN PEDIATRIC CHRONIC ILLNESS: SHOULD PATIENT ANXIETY BE CONSIDERED?

by

CLAIRE JEANETTE HOOGENDOORN

This manuscript has been read and accepted for the Graduate Faculty in Psychology to satisfy the dissertation requirement for the degree of Doctor of Philosophy.

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Abstract

Medication Management in Pediatric Chronic Illness: Should Patient Anxiety be Considered?

By

Claire J. Hoogendoorn

Advisor: Laura C. Reigada, Ph.D.

Introduction: There is growing support that psychological symptoms can impact various aspects of disease, well-being, and medical treatment for those with a chronic illness like Crohn’s disease (CD). Yet, almost no studies have examined whether psychological symptoms can influence management or efficacy of patient medication regimens. The aims of this project were to examine whether anxiety predicted pediatric patients’ level of medication management, medication prescription changes, and corticosteroid prescription and duration.

Method: A total of 105 pediatric patients ages 8-18 (M=14.5, SD=2.3) completed a validated anxiety questionnaire during a GI office visit (baseline). Prescribed IBD medications were recorded for the subsequent year, including changes (i.e., additions, discontinuations, switches) and corticosteroid prescription duration. Disease activity scores were generated at baseline and 12 months. Logistic and Poisson regressions were used to ascertain the predictive value of anxiety for medication treatment level and frequency of prescription changes. A Pearson correlation was conducted to examine the relationship between anxiety and prospective duration of systemic corticosteroid prescription.

Results: Anxiety symptoms did not predict a higher level of medication treatment, but did show a trend in predicting a greater frequency of total medication changes over the 12-month study period (p=.07). More specifically, patient-reported anxiety symptoms were significantly
predictive of medication switches within the same drug class \( (p<.01) \), with significance remaining after accounting for age and disease characteristics \( (p<.05) \). Additionally, anxiety predicted the likelihood of future corticosteroid prescription, and showed a trending association with future systemic corticosteroid prescription duration.

**Discussion:** This study is among the first to explore whether psychological symptoms predict multiple aspects of medication management for a chronic illness sample. Findings suggest that physicians should assess for psychological distress, be aware of overlapping physical symptoms associated with CD and anxiety, and treat symptoms holistically. Further empirical investigations are warranted to examine the interplay between emotional symptoms and medication management.

**Keywords:** Anxiety, Chronic Illness, Pediatrics, Medication Management
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CHAPTER 1: INTRODUCTION

1. Overview

There is growing evidence that psychological symptoms can affect various aspects of disease and well-being for individuals with a chronic illness. Anxiety in particular has gained attention, given its high rate of occurrence among chronically ill patients (Pao & Bosk, 2011) and its negative effects on disease and functional outcomes (Bernstein et al., 2013; Bregnballe, Thastum, & Schiøtz, 2007; Chavira et al., 2008; Havermans, Colpaert, & Dupont, 2008; Katon, Richardson, Lozano, & McCauley, 2004; McCauley et al., 2007). Anxiety has also been found to be associated with medical treatment outcomes such as increased medical care utilization (Huang et al., 2015; Reigada et al., in press; ten Brinke, et al., 2001; Xu, et al., 2008) and higher health care costs (Bernal et al., 2000; Simon, Ormel, VonKorff, & Barlow, 1995).

Yet, almost no studies have examined whether patients’ psychological symptoms are associated with physician management of their medications. Prescription medication treatment as an outcome is important, especially because pharmacological advances have contributed to an increased emphasis on medications for the management of chronic illness. Accordingly, pharmaceutical expenditures are increasing faster than spending on other types of health care services for those with chronic illness, largely due to an increased number of prescribed medications per patient (Dubois et al., 2000; Mousnad, Shafie & Ibrahim, 2014). Given the increased reliance on medications in medical settings, it is important to examine psychosocial factors that may influence prescription behaviors.

There are several plausible ways through which patient anxiety could affect a physician’s prescribing behaviors as well as the efficacy of the prescribed medications for those with a chronic illness. Specifically, cognitive (e.g. reduced well-being) and somatic correlates of
anxiety could contribute to physicians prescribing a more aggressive medication regimen and/or making more prescription changes, while physiological correlates of anxiety (e.g., hypothalamic-pituitary-adrenal [HPA] and brain-gut-microbiome dysregulation) could affect the ability of medications, in particular corticosteroids, to influence their target cells.

Not only would such knowledge potentially help to improve care for patients with a chronic illness and comorbid anxiety, but addressing this question also has theoretical importance for understanding the relationship between psychological and physical wellbeing. It is possible that differences in medication management associated with anxiety could mediate the relationship between anxiety and disease outcomes observed in various chronic illness samples. While such a role has been established for medication adherence (DiMatteo, Lepper, & Croghan, 2000), the literature assessing the relationship between psychological symptoms and additional components of medication management of chronic illness is quite limited.

2. Inflammatory Bowel Disease and Crohn’s Disease

i. Why Examine Anxiety and Medication Management in IBD?

Psychological distress is more common among individuals with IBD when compared to the general population (Addolorato, Capristo, Stefanini, & Gasbarrini, 1997; Kilroy, Nolan, & Sarma, 2011). The high prevalence of heightened psychological distress in patients with IBD suggests that investigating this relationship could increase our understanding of mental and physical health. Of interest is that both IBD (Bonaz, 2013; Bonaz & Bernstein, 2013; Straub et al., 1998; Straub et al., 2002; Taylor, & Keely, 2007; Ananthakrishnan et al., 2010) and psychological disorders (Charmandari, Tsigos, & Chrousos, 2005; Foster & Neufeld, 2013; Jaremka et al., 2013; Lydiard, 2001; Mantella et al., 2008; Mawdsley & Rampton, 2005; McBurnett et al., 1991; Wingenfeld, Schulz, Damkroeger, Rose, & Driessen, 2009) are
associated with dysregulation of two brain-body pathways—i.e., the HPA and brain-gut-microbiota axes. These physiological pathways provide a common ground through which to view IBD and the presence of anxiety. Further, these brain-body pathways that regulate immune responses are acted upon by medications that suppress immune function, like those prescribed for IBD.

ii. What is IBD?

IBD encompasses a cluster of chronic inflammatory diseases of the gastrointestinal (GI) tract. The two most common types of IBD are Crohn’s disease (CD) and ulcerative colitis (UC). CD and UC have similar signs and symptoms, including chronic remitting and relapsing inflammation in the GI tract, abdominal cramping and pain, diarrhea, vomiting, and poor nutrient absorption (Hanauer, 2006; Rayhorn, 2001; Singh et al., 2011; Schwarz & Blanchard, 1990). These two diseases are differentiated by their distinct underlying pathophysiology. For example, CD can impact any part of the GI tract, and most commonly affects the ileum (small bowel) and the ascending colon, while UC only affects the large colon (Lichtenstein, Hanauer, & Sandborn, 2009). Additionally, in CD, lesions occur in patches and inflammation can be transmural, extending through the intestinal wall from mucosa to serosa. In contrast, UC involves shallower and more uniform tissue damage (Marks, et. al., 2006). Further, the development of granulomas (a small cluster of immune cells that surround foreign substances in the GI tract) and fistulas (an abnormal perforation in the digestive tract) are also particular to CD.

The etiologies of CD and UC are not fully known. A generally accepted hypothesis is that genetic, immunological and environmental factors influence the GI tract’s normal response to foreign and self-antigens, which contributes to a chronic inflammatory response (Geremia, Biancheri, Allan, Corazza, & Di Sabatino, 2013; Sartor, 2006; Sauer & Kugathasan, 2010).
Dysbiosis, or an imbalance between helpful and harmful gut bacteria, also plays a role in maintaining inflammation (Tamboli, Neut, Desreumaux & Colombel, 2004). As there is no cure, treatment of disease is aimed at controlling inflammation with medication and increasing patients’ quality of life.

iii. Anxiety and CD

Several studies highlight the importance of distinguishing between CD and UC when studying the impact of anxiety in IBD (Andrews, Barczak, & Allan, 1987; Mikocka-Walus et al., 2007a; North & Alpers, 1994). For example, Andrews, Barczak and Allan (1987) found that while the prevalence of psychiatric illness was similar between adults diagnosed with CD (33%) and UC (34%), there was only a relationship between psychiatric illness and disease activity for those with CD. Disease activity refers to the presence and severity of disease symptoms, such as diarrhea and extra-intestinal symptoms, assessed with validated measures. The idea that the relationship between psychological distress and disease activity may be specific to IBD type is further supported by review articles conducted by North and Alpers (1994) and Mikocka-Walus and colleagues (2007a), showing that relationships between anxiety and disease activity were more consistent in those diagnosed with CD, compared to UC. Due to these potential differences between the types of IBD, we will only investigate the relationship between anxiety and medications in patients diagnosed with CD.

iv. Review of Medication Management of CD

The objective of medication management in CD is to maintain disease remission, while minimizing drug toxicity (Lichtenstein, et al., 2009; Singh & Dubinsky, 2015). Medication treatments are broadly characterized as either inducing or maintaining remission, and the type of treatment depends on the severity of illness, CD phenotype, and location of GI tract involvement.
(e.g., colon, ileum). While many aspects of disease have to be considered and there are many different approaches to therapy, treatment typically includes a combination of medications from five drug classes: antibiotics, aminosalicylates, immunomodulators, biologics, and corticosteroids.

Induction of remission can be accomplished using antibiotics, aminosalicylates, biologics and corticosteroids. However, local and systemic corticosteroids are usually preferred, given that they are more effective than antibiotics and aminosalicylates (Benchimol, Seow, Steinhart & Griffiths, 2008) and are less aggressive than biologics (Kozuch & Hanauer 2008; Sands, 2000). Once remission has been achieved, patients follow a maintenance medication regimen to sustain remission. Milder cases of IBD are typically managed with antibiotics and aminosalicylates, which provide localized control over dysbiosis and intestinal inflammation (Katz, 2007; Markowitz, 2008). Moderate to severe disease is contained using more potent or aggressive systemic medications that include immunomodulators (Nielsen et al., 2001) and biologics (Barrie & Regueiro, 2007). The more aggressive suppression of the body’s immune system by systemic medications is associated with more serious side effects and adverse events including life-threatening infections, pancreatitis and lymphoma (Farrell et. al., 2000; Sandborn et al., 2005; Su & Lichtenstein, 2004). Table 1 presents a simple summary of the five medication classes.

The location of GI tract involvement can influence the type of medication that is prescribed, as several medications have a targeted delivery within the GI tract. While CD can affect the GI tract anywhere from mouth to anus, the most common sites of disease include the ileum and colon that can be targeted using specific medication coatings (Sauer, & Kugathasan, 2010). Luminal medications that only affect a particular GI location (e.g., colon, small intestine) include aminosalicylates (e.g., sulfasalazine, mesalamine), budesonide, and antibiotics. Systemic
corticosteroids and medications belonging to the immunomodulator (e.g., mercaptopurine, azathioprine) or biologic (e.g., infliximab, adalimumab) classes are believed to affect the entire GI tract.

There are three CD phenotypes, including inflammatory, stricturing/stenotic (narrowing of the GI tract) and fistulizing/penetrating disease (development of an abnormal perforation in the digestive tract). The majority of children develop the inflammatory phenotype, but this can progress to the other two phenotypes over time (Sauer & Kugathasan, 2010). The stricturing and fistulizing phenotypes typically require surgical intervention, but may also require a combination of antibiotic, systemic corticosteroid, immunosuppressive and biologic treatments (Lichtenstein, et al., 2009).

The duration of the illness can also influence patients’ medication management. Patients with recent diagnoses are more likely to have active disease and to receive drugs intended to induce remission, whereas recently diagnosed patients in remission are likely to receive milder first-line maintenance medication treatments (Lin, Blonski, & Lichtenstein, 2010; Rogler, 2013). This is because treatment recommendations typically involve a step-up approach (Devlin & Panaccione, 2010; Lichtenstein, et al., 2009; Lin, et al., 2010; Rogler, 2013). This means that the physician first prescribes less potent medications, such as locally-acting aminosalicylate or antibiotic drugs, and if these medications don’t adequately induce and/or maintain remission, medications can be stepped up to include more potent systemic immunomodulators and biologics (Lin, et al, 2010; Lichtenstein, et al., 2009; Rogler, 2013). Many studies also support a top-down approach for pediatric patients who are likely to have severe disease progression. This regimen involves starting with biologics, which have shown to be successful in inducing remission in adults (Akobeng & Zachos, 2004) and children (Hyams et al., 2007). However, given the
increased chance of developing lymphoma (Mackey, Green, Liang, Dinndorf, & Avigan, 2007) and the lack of long-term studies in pediatric patients, biologics are typically only recommended after trying immunomodulators (Sauer & Kugathasan, 2010).

In summary, the accurate assessment of disease activity, CD phenotype, and extent of GI tract involvement are central to determining medication treatment. Additionally, it is important to reduce drug toxicity, which is related to the type, dosage and duration of the prescribed medication (Cunliffe & Scott, 2002). Optimal medication regimens can be difficult to determine, as patients vary considerably in how they respond to a particular drug—what works well for one patient may not work well for another. For these reasons, physicians determine the medication regimen based not only on objective markers, but also on subjective indicators of disease activity and patient reports of medication effectiveness (Robinson, 1998).

v. **Why Pediatric CD?**

Psychological influences on medication management and efficacy may have a larger impact on pediatric patients’ well-being and quality of life compared to adults diagnosed with CD, given that life-long medication management would be of a longer duration for pediatric patients. Prevalence rates of CD are on the rise, with 3.5 per 100,000 youth developing CD in North America, making up 25% to 30% of all patients with CD (Baldassano & Piccoli, 1999). Children and adolescents with CD are at a higher risk for developing anxiety symptoms compared to healthy youth (Engström, 1992; Loftus et al., 2011; Mackner, & Crandall, 2007), which may become elevated when disease is active (Graff, Walker, & Bernstein, 2009; Pao, & Bosk, 2011). Research has established that the presence of chronic stress in childhood is associated with worsened health outcomes and well-being across the lifespan (Shonkoff, et al., 2012). Furthermore, medications like corticosteroids can also slow the physical development of
pediatric patients (Benchimol, Seow, Steinhart, & Griffiths, 2008; Sauer & Kugathasan, 2010), who already often experience growth delays and a reduced final adult height due to their illness (Hildebrand, Karlberg & Kristiansson, 1994; Kanof, Lake & Bayless, 1988; Markowitz et al., 1993; Kirschner, 1990). Further, studying pediatric samples may provide a clearer picture of the relationship between anxiety and subsequent corticosteroid use, as pediatric patients are more likely to be corticosteroid-naïve (i.e., they have not been prescribed corticosteroids before).
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3. Anxiety as a Predictor of Medication Level and Prescription Changes

i. Importance

The relationship between patient anxiety and physicians’ prescription behaviors is an important area of research, as patients’ communication and emotional state can influence physicians’ perceptions and treatment decisions (Street, Gordon, & Haidet, 2007). Physicians consider patient feedback regarding medication efficacy and negative side effects when making prescription changes (Pithadia & Jain, 2011), and the feedback patients provide can be influenced by various factors including psychological distress. This could negatively affect medication management, potentially contributing to increased prescription changes and the prescription of more aggressive medications (Barratt, Kalantzis, Polymeros, & Forbes, 2005; Walker, Gelfand, Gelfand, Creed, & Katon, 1996). When these changes are influenced by factors other than disease, it exhausts available treatment options and unnecessarily puts patients’ health at risk (Sandborn et al., 2005; Su & Lichtenstein, 2004; Singh & Dubinsky, 2015).

ii. Potential Pathways Through Which Anxiety Could Predict Medication Level and Prescription Changes

a. Overview

Anxiety may predict patients’ medication management for a variety of reasons. It is possible that aspects of medication treatment (e.g., number of different medications, route of administration including injection, medication side effects) could increase patients’ level of anxiety (Graff, Walker & Bernstein, 2009). In addition, more aggressive medications can be considered a marker of more severe disease (Ananthakrishnan et al., 2013; Walker et al., 1996), and disease activity itself can contribute to heightened anxiety (Graff, Walker, & Bernstein, 2009; Mikocka-Walus et al., 2007a). In this way, it is possible to observe a relationship between
anxiety and level of medication treatment that mirrors the relationship between anxiety and disease activity. However, these potential associations assume that anxiety is the consequence of disease and medication factors, while anxiety could also contribute to medication outcomes.

It is possible that anxiety independently contributes to medication outcomes by influencing physician perceptions and resulting treatment decisions. Anxiety is associated with physical symptoms that have no known organic origin (Hughes, Lourea-Waddell, & Kendall, 2008), functional GI disorders like irritable bowel syndrome (Blanchard, Scharff, Schwarz, Suls, & Barlow, 1990), and cognitive factors such as reduced well-being and negative illness perceptions (Ondersma et al., 1997). As patients often do not voluntarily report emotional symptoms, these somatic and cognitive aspects of anxiety may be attributed to disease processes and medication treatments (Kroenke, Jackson, & Chamberlin, 1997). These pathways will be discussed in more detail.

b. Somatic Symptoms

It is well established that there are physical symptoms of anxiety, such as headaches, dizziness, stomach pain and nausea (Hughes, et al., 2008). These physical symptoms are positively associated with the number of comorbid anxiety disorders and severity of anxiety symptoms for patients in various clinical and primary care settings (Campo et al., 2004; Crandall, Timothy, Halterman & Mackner, 2007; Ginsburg, Riddle & Davies, 2006; Hofflich, Hughes & Kendall, 2006; Katon, Lin, & Kroenke, 2007; Kroenke et al., 1994; Roy-Byrne et al, 2008). When patients diagnosed with a chronic illness communicate these physical symptoms, they are more readily attributed to disease, as opposed to psychological functioning, by both the patient and treating physician (Söllner et al., 2001; Meyer, Klemme, & Herrmann, 2000; Kroenke, Jackson, & Chamberlin, 1997). This misinterpretation may result in gastroenterologists
recommending medication changes or more aggressive medications that could have secondary adverse health effects that would otherwise have been avoided.

For patients with IBD, somatic symptoms related to anxiety can be especially challenging to identify, as they often involve GI symptoms that are consistent with IBD. Walker and colleagues (1996) asked 40 adults diagnosed with IBD to report their physical symptoms, which included both GI (e.g., constipation, anorectal pain) and non-GI (e.g., chest pain) symptoms. Next, the research team compared the reported somatic symptoms of 14 participants (out of the 40) who had a psychiatric diagnosis (i.e., major depression, dysthymic disorder, panic disorder, generalized anxiety disorder, or agoraphobia) with the 26 patients who did not. They found that those with a psychiatric diagnosis reported approximately twice as many GI (and non-GI) symptoms than those without a psychiatric diagnosis, even though disease activity was similar between the two groups. Such anxiety-related somatic symptoms could be misconstrued by the patient or physician as being indicative of more severe disease, which could lead to the prescription of more potent medications (Walker et al., 1996).

Several somatic symptoms of anxiety also overlap with common IBD medication side effects. These overlapping symptoms include headaches, dizziness, stomach pain, loose stools, and nausea (Diefenbach & Breuer 2006; Hughes, et al., 2008; Walker et al., 1996). It is possible that physicians more readily interpret the presence of these symptoms as a sign that medication is causing side effects, especially non-GI symptoms such as headaches, rather than that they may be related to anxiety. Such misclassification could contribute to additional medication changes.

c. Co-occurrence of Irritable Bowel Syndrome

Many anxious patients report individual somatic symptoms, but patients can also experience a constellation of somatic symptoms, referred to as functional disorders. One
functional disorder that is common in medically healthy individuals as well as patients with IBD is irritable bowel syndrome (IBS). IBS involves abdominal pain or discomfort (e.g., cramping, bloating) and changes in bowel habits (e.g., diarrhea, constipation) in the absence of infection, disease-related inflammation, or damage to the GI tract (Mertz, 2003).

IBS is highly associated with the presence of a psychological disorder, especially anxiety and depression, with 54% to 94% of individuals with IBS also meeting criteria for a psychiatric comorbidity (Irwin, et al., 1996; Lydiard, Fossey, Marsh, & Ballenger, 1993; Whitehead, Palsson, & Jones, 2002). IBS symptoms are also highly associated with psychological disorders in patients with IBD (Simrén et al., 2002; Walker, Gelfand, Gelfand, & Katon, 1995). Roughly 42% to 62% of adult patients with CD in remission report experiencing IBS-like symptoms (Barratt, Kalantzis, Polymeros, & Forbes, 2005; Minderhoud et al., 2004; Simrén et al., 2002). Barratt and colleagues (2005) found that many IBS symptoms overlap closely with symptoms of CD (more so than UC), and the authors pointed out that misclassification of these overlapping symptoms could contribute to over-treatment with potent medications.

d. Well-being, Illness Perception, and Worry

Research shows that those with a medical illness and comorbid anxiety tend to report reduced well-being, more negative illness perceptions and increased worry (Edgar & Skinner, 2003; Connelly et al., 1989; Sherbourne, Wells, Meredith, Jackson, & Camp, 1996), which could influence physician perceptions and treatment decisions. For example, a study that examined a sample of 208 primary care patients showed that the group with the lowest health perception scores reported more health-related worry, pain, anxiety and depression, and were prescribed more medications, when accounting for measures of physical health (Connelly et al., 1989). Further, decreased well-being could make a patient appear sicker because well-being plays a role
in assessing disease activity (Harvey & Bradshaw, 1980; Best, Becktel, Singleton, & Kern, 1976). Ondersma and colleagues (1997) found that subjective well-being of adolescents with IBD was inversely related to psychological symptoms, though these symptoms were not associated with objective markers of inflammation.

Anxiety-related worries for patients with a chronic illness are often specific to their illness and medication regimen. For example, Drossman and colleagues (1991) showed that greater psychological distress and lowered well-being were associated with patient concerns about their IBD, even after controlling for disease activity. Such illness-focused concerns may influence a physician’s prescribing behaviors when a patient expresses worries surrounding their medication management. In one study, IBD medication side-effects were among the most common illness-related worries reported by adolescents with IBD (Reigada et al., 2011). Hypothetically, worries surrounding illness and medication treatments could increase the chance that patients attribute anxiety-related physical symptoms to medication side effects, and could contribute to prescription changes.

e. Health Care Seeking Behaviors

In general, adults and children with anxiety disorders have higher rates of health care use than non-anxious individuals (Bernal et al., 2000; Deacon, Lickel, & Abramowitz, 2008; Gurmankin Levy et al., 2007; Ramsawh et al., 2010), and this includes those with a medical condition (Huang, et al., 2015; Reigada, et al., in press; ten Brinke, et al., 2001). For example, in adult samples, anxiety has been associated with increased outpatient visits (Huang et al., 2015), as well as emergency visits and hospitalizations (ten Brinke, et al., 2001). These patterns are similar for children and adolescents, where anxiety was associated with increased health care costs (Bernal et al., 2000) and more frequent emergency room visits (Gill et al., 2003; Reigada et
al., 2011; Reigada et al., in press). Hospitalization itself can be a risk for increased medication changes for adult and elderly patients (Beers, Dang, Hasegawa, & Tamai, 1989; Omori, Potyk, & Kroenke, 1991; Parkin, Henney, Quirk, & Crooks, 1976). Increased physician contact could influence treating physicians’ perceptions of whether patients’ disease is well managed, which again could lead to the prescription of more potent medications and/or an increased number of prescription changes.

iii. Studies Examining Anxiety as a Predictor of Medication Outcomes

To our knowledge, only two studies have examined psychological symptoms as potentially contributing to the types of medications adult patients with IBD were prescribed (Ananthakrishnan et al., 2013; Goodhand et al., 2012a), with no studies having investigated this issue in a pediatric IBD sample. Ananthakrishnan and colleagues (2013) conducted a retrospective review of medical records of 5405 patients with CD and 5429 patients with UC at multiple institutions. Their aim was to examine whether anxiety and depression predicted disease-specific endpoints such as IBD-related surgeries and hospitalizations when accounting for disease activity. Medication treatments were assessed as part of their measure of disease activity, and they found that the presence of depression or generalized anxiety predicted the use of more aggressive medication treatments including corticosteroids, immunomodulators and biologics in patients with CD, and corticosteroids in UC. Their main hypothesis was also supported, with results demonstrating that a diagnosis of depression or anxiety was independently associated with an increased risk for subsequent surgery in CD. In addition, Goodhand and colleagues (2012a) conducted a retrospective chart review of 29 patients (14 with UC and 15 with CD) and reviewed the number of corticosteroid courses and disease relapses the year before and after patients were started on an antidepressant medication for comorbid
depression. Results showed a drop in the number of corticosteroid courses and number of relapses for adults with IBD a year after patients were prescribed antidepressants along with their usual medication regimen, in relation to the year before and also in comparison to a control group. Interpretation of these findings is limited by the fact that disease activity was not controlled for, and individuals met criteria for comorbid anxiety and depression preventing the researchers from assessing the impact of anxiety alone. Yet, the associations between psychological symptoms and prescription outcomes observed in these extant studies, suggest that this topic is worthy of further investigation.

Studies showing a relationship between psychological symptoms and an increased frequency of prescribed nonpsychiatric medications are limited to community samples, in which the presence of a chronic illness is not assessed or taken into account. One study by Simpson, Kazmierczak, Power and Sharp (1994) compared 100 patients diagnosed with panic disorder to a group of 100 controls matched on age and gender. Results revealed that those with panic disorder had been prescribed a significantly greater number of non-psychiatric medications over the 10-year period prior to their panic disorder diagnosis than those in the control group. Specifically, 36% of the panic disorder group had been prescribed 20 or more different non-psychiatric medications over the past 10 years, compared to 11% of the control group. However, the authors did not include information about the types of non-psychiatric medications that were prescribed, and findings are limited to those with a diagnosis of panic disorder, rather than anxiety generally. A second and more recent cross-sectional study found that internalizing symptoms of youth in a residential treatment facility was associated with a greater risk for being on a non-psychiatric medication (Nelson et al., 2013). In this study, medications were specified and included asthma medications such as albuterol, allergy medication (i.e., loratidine), and pain medication (i.e.,
ibuprofen). While these two studies provide preliminary support that patient anxiety symptoms may be related to increased prescription changes, both were based on community samples that included individuals with and without physical health issues. It is therefore unclear whether the more frequent prescription of non-psychiatric medications reflected an increased presence of physical illness or was related to the anxiety and mood symptoms themselves.

iv. Conclusion

Jointly, the individual relationships between anxiety, heightened somatic symptoms, reduced well-being, increased worry, and increased healthcare seeking behaviors support investigation of the potential relationship between patient anxiety, level of medication management, and prescriptive changes. If anxiety independently contributes to the level of aggressiveness of patients’ medication regimens and the frequency of medication changes, then there could be important implications for disease outcomes for patients with IBD and comorbid anxiety (e.g., occurrence of adverse events, need for surgery, treatment costs, quality of life).

4. Corticosteroid Prescription and Efficacy

a. Importance

Local and systemic corticosteroids are the only medications that are prescribed solely for short term to induce remission in pediatric and adult CD, and are not recommended for maintaining remission or long-term use (Benchimol, Seow, Steinhart & Griffiths, 2008; Seow, Benchimol, Griffiths, Otley, & Steinhart, 2008). Corticosteroids reduce inflammation by binding to various immune cells throughout the body, and affecting gene expression that results in downregulation of pro-inflammatory activity and upregulation of anti-inflammatory responses (Rhen & Cidlowski, 2005). Corticosteroids are not recommended for maintenance treatment due to their negative side effects. These include elevated blood pressure, high blood sugar,
atherosclerosis (hardening of the arteries; Nashel, 1986), ulcers and gastrointestinal bleeding (Messer, Reitman, Sacks, Smith, & Chalmers, 1983), cataracts or glaucoma (Renfro & Snow, 1992), osteoporosis (Van Staa, Leufkens, & Cooper, 2002) avascular necrosis (bone death; Fisher & Bickel, 1971), increased risk for severe infection and mortality (Lichtenstein et al., 2006), and additional anxiety and depression (Neutel, 2000). While local corticosteroid treatments are associated with lower side-effect profiles (Plevy, 2002), avoidance of corticosteroid treatments is preferred, especially for pediatric patients whose physical growth can be stunted (Sauer & Kugathasan, 2010). If anxiety contributes to increased corticosteroid prescriptions, this would place anxious patients at increased risk for worse health outcomes.

Corticosteroids are prescribed when inflammation is present, and so their prescription can be considered a proxy for the increased presence of disease-related inflammation. Studies show that corticosteroids are prescribed to approximately 35% to 52% of patients within the first few years of diagnosis (Targownik, Nugent, Singh, & Bernstein, 2014), and are prescribed 39%-42% of the time that patients with IBD experience a relapse (Goodhand et al., 2012a). Anxiety is often found to be associated with disease activity (Reigada et al., 2015a; Graff, Walker, & Bernstein, 2009; Mikocka-Walus et al., 2007a), though the literature remains mixed on whether anxiety independently contributes to the occurrence of disease-related inflammation and relapses in IBD (Bernstein, Walker, & Graff, 2006; Bernstein et al., 2010; Levenstein et al., 2000; Mikocka-Walus et al., 2007a). The type of stress that is measured (i.e., stressful events, perceived stress, acute vs. chronic stress) also contributes to the mixed findings (Bernstein, Walker & Graff, 2006; Bitton, et al., 2008; Levenstein et al., 2000). If patient self-reported anxiety predicts increased prescription of corticosteroid treatment, this could provide additional evidence that anxiety symptoms contribute to disease-related inflammation.
Of the five medication classes prescribed to pediatric patients with CD, drugs belonging to the corticosteroid class have a unique relationship with anxiety. Specifically, corticosteroid medications are modeled after the human stress hormone cortisol and the animal stress hormone cortisone to mimic their anti-inflammatory effects in the body (Hench, 1938). Because of this, cortisol and corticosteroid medications bind to the same HPA axis and immune cell receptors (Miller, Cohen & Ritchey, 2002; Swartz & Dluhy, 1978); thus, corticosteroids can influence psychological symptoms. While some studies have demonstrated a link between corticosteroid medication use and the presence of elevated psychological symptoms, this research framed the psychological symptoms as a side-effect of corticosteroid medications (Brown & Chandler, 2001; Korte, 2001; Nahon et al., 2012; Neutel, 2000; Dubovsky, Arvikar, Stern, & Axelrod, 2012). However, relationship between these variables could be bidirectional, meaning that anxiety symptoms could also affect the efficacy of corticosteroid medication. Rates of corticosteroid resistance are already high in IBD at 20% (Munkholm, Langholz, Davidsen, & Binder, 1994), and contribute to disease outcomes, including the need for surgery (Farrell & Kelleher, 2003). Thus, it is important to understand contributors to individual variations in drug response; anxiety may be one modifiable factor that could contribute to this variation.

b. Potential Pathways Through Which Anxiety May Predict Corticosteroid Prescription and Duration

i. Overview

There are several reasons why anxiety may predict whether a patient receives a corticosteroid medication or not. Besides indirect pathways (e.g., somatization, medication nonadherence), anxiety may affect disease relapse and medication efficacy through its influences on the brain-gut-microbiome and HPA axes. In healthy individuals these two pathways are
balanced, but they are dysregulated in the presence of a chronic psychological or physical illness (Grenham, Clarke, Cryan, & Dinan, 2011; Eskandari & Sternberg, 2002). Given the overlapping pathways, the body may respond to physical and psychological stressors similarly (Black, 2002). This further suggests that the presence of both chronic physical and psychological illness could be associated with increased dysregulation of these systems than the presence of a physical or psychological illness alone.

Both brain-body pathways play important roles in immune function. The brain-gut-microbiome pathway coordinates mood, hunger, motility, and inflammatory responses between the brain and the enteric nervous system of the GI tract (Mulak & Bonaz, 2004), while the HPA axis is considered a key biological system in coordinating systemic inflammatory responses (Sapolsky, Romero & Munch, 2000). Medications that modulate immune response, like those prescribed to patients with CD and other chronic illnesses, interact with the GI environment and HPA function, while dysregulation of the GI environment and HPA axis can influence medication metabolism and efficacy. We will discuss in further detail how these brain-body pathways contribute to associations between anxiety and increased disease relapse, as well as anxiety and increased corticosteroid resistance.

ii. Brain-gut-microbiota Axis

Emerging evidence suggests that anxiety influences the composition of gut microbes, leading to lower levels of commensal (i.e., helpful) bacteria and higher levels of pathogenic (i.e., hurtful) bacteria (Rhee, Pothoulakis & Mayer, 2009). These changes in the composition of gut microbes, termed dysbiosis, would be expected to add to the dysbiosis already associated with CD. Heightened dysbiosis is associated with GI inflammation and an increased chance for relapse (Wyatt, Vogelsang, Hübl, Waldhoer, & Lochs, 1993). Enteric microbiota composition is
also involved in medication metabolism (Kang, et al., 2013; Ilett, Tee, Reeves, & Minchin, 1990; Li, He & Jia, 2015; Swanson, 2015; Wilson & Nicholson, 2009), and thus could influence medication efficacy.

Several studies examining the relationship between anxiety and GI microbiota in humans indicate that stress can reduce beneficial bacteria like lactobacilli and bifidobacteria, and can increase the presence of pathogenic bacteria such as E. coli (Collins, 2001; Holderman, Good & Moore, 1976; Knowles et al., 2008; Lutgendorff, Akkermans, & Soderholm, 2008). For instance, exam stress was found to increase the presence of harmful bacteria in the stool of college students (Knowles et al., 2008), and stress from confinement training promoted the growth of harmful fecal bacteria in astronauts (Holderman, Good & Moore, 1976). The majority of studies examining the underlying mechanisms of these effects involve animals, and show that stress can affect the GI microbiota via direct and indirect pathways.

These direct and indirect pathways are driven by release of anxiety-related signaling molecules in the GI tract, which are made possible by brain-gut communication. For example, immune cells within the mucosa of the GI tract (e.g., enterochromaffin and mast cells) communicate with the brain via the vagus nerve and release stress-related signaling molecules in the GI tract including serotonin, corticotropin-releasing factor, and norepinephrine. These signaling molecules associated with anxiety can communicate with pathogens directly, as well influence bacteria indirectly by altering the GI environment. Norepinephrine, for example, can bind directly to pathogenic bacteria and increase their virulence (i.e., host-pathogen communication; Rhee, Pothoulakis & Mayer, 2009), while serotonin and corticotropin-releasing factor contribute to altered motility, fluid secretion, heightened intestinal permeability and GI inflammation (Baganz & Blakely, 2012; Bailey et al., 2010; Bailey & Coe, 1999; Khan & Ghia,
Greater motility and fluid secretion can increase the shedding of commensal bacteria, while intestinal permeability promotes inflammation and the growth of harmful bacteria. Specifically, mucosal changes and increased GI permeability allow pathogenic bacteria to cross the intestinal lining and enter the body. When this occurs, the GI tract can become inflamed, which in turn promotes the further growth of pathogenic bacteria in the GI tract (Craven et al., 2012). Through these pathways, stress can increase dysbiosis and inflammation, and thus increase the chance for disease relapse in CD (Wyatt, Vogelsang, Hübl, Waldhoer, & Lochs, 1993).

If anxiety does contribute to increased dysbiosis in patients with CD, this could increase the occurrence of active disease (requiring more local or systemic corticosteroid prescriptions) and could also contribute to medication metabolism and reduced efficacy generally. For example, increased dysbiosis has been associated with reduced response to antibiotic treatments for patients with clostridium difficile infections (Bakken et al., 2011). However, it is difficult to make specific predictions about effects on other types of medication, since we have limited insight into what the human microbiome looks like in health or disease (Dethlefsen, Eckburg, Bik, & Relman, 2006), and the role of these bacteria in drug pharmacokinetics is still developing (Li, He & Jia, 2015; Swanson, 2015). Because of this, we will focus on corticosteroid efficacy in particular, as its association with the second brain-body pathway, the HPA axis.

iii. HPA axis and Immune Cell Desensitization

When examining the interaction between anxiety and the medications used to treat CD, systemic corticosteroids stand out in that their effects on the body mimic those of the stress-hormone cortisol (Kirwan, Balint, & Szebenyi, 1999). Typically, acute surges of cortisol

2010; Kiank, Taché, Larauche, 2010; Santos et al., 1999; Tannock & Savage, 1974; Velin et al., 2004). Greater motility and fluid secretion can increase the shedding of commensal bacteria,
associated with short-term stress terminate the body’s systemic inflammatory response (De Bosscher, Vanden Berghe, & Haegeman, 2000; Sapolsky, Romero & Munch, 2000). There are many studies demonstrating the effects of chronic anxiety on the function of cortisol, which show that prolonged elevations of cortisol associated with chronic stress lead to a reduced response from target cells, increasing inflammation (for reviews see: Black, 2002; Charmandari, Tsigos, & Chrousos, 2005). In other words, glucocorticoids can begin to have a weaker effect on terminating the inflammatory response when levels are chronically high. Theoretically, this change associated with anxiety could also influence the ability of exogenous corticosteroid medications, which bind to the same receptor sites (Kirwan, Balint, & Szebenyi, 1999; Swartz & Dluhy, 1978), to quiet the inflammatory response in those with a chronic illness.

This homeostatic phenomenon is termed glucocorticoid receptor desensitization, which plays a significant role in resistance toward either cortisol (i.e., glucocorticoid resistance; Miller, Cohen & Ritchey, 2002) or corticosteroid medications (i.e., corticosteroid resistance; Munkholm, Langholz, Davidsen & Binder, 1994). While glucocorticoid receptor desensitization is not synonymous with glucocorticoid or corticosteroid resistance, receptor desensitization does play a significant role in resistance to a signaling molecule (for more, see Chikanza, Kozaci & Chernajovsky, 2003). It appears that the main difference between the terms ‘glucocorticoid resistance’ and ‘corticosteroid resistance’ is based on whether it develops in response to naturally occurring glucocorticoids or administration of exogenous corticosteroid medications, while both bind to the same glucocorticoid receptors. If this is the case, then it could be possible that chronic anxiety is associated with higher resistance to exogenous glucocorticoid molecules, like corticosteroid medications.
Homeostatic change in response to chronically elevated cortisol is the main mechanism believed to underlie the effects of chronic anxiety on increased inflammation in healthy individuals (Cohen et al., 2012). Specifically, Cohen and colleagues (2012) reported that chronic distress in healthy adults led to a decreased ability to terminate an inflammatory response once initiated, and that this decreased immune control was due to glucocorticoid resistance. CD is associated with dysregulation of the HPA axis itself (Straub et al., 1998; Straub et al., 2002), and studies have also shown that immune cells of patients with CD are significantly less sensitive to the effects of exogenous glucocorticoids than immune cells of healthy controls (Franchimont et al., 1999). This is consistent with studies showing high corticosteroid resistance in patients with CD (Munkholm, Langholz, Davidsen & Binder, 1994). Taken together with the literature on chronic stress, these findings suggest that individuals with IBD and co-occurring anxiety may be at an increased risk for corticosteroid desensitization. While medical professionals are comfortable with the idea that corticosteroid treatment has the potential to elevate anxiety symptoms (e.g., Brown & Chandler, 2001; Korte, 2001; Nahon et al., 2012; Neutel, 2000; Dubovsky, Arvikar, Stern, & Axelrod, 2012), no studies have examined whether anxiety influences corticosteroid efficacy in clinical or chronic illness samples, though it is equally theoretically plausible.

c. Studies Examining Anxiety as a Predictor of Corticosteroid Prescription

As mentioned previously, there is limited support for the idea that that anxiety may contribute to the prescription of corticosteroid medications, or their efficacy, in those with a chronic illness. Only one previous study showed psychological symptoms predicted corticosteroid use in adults with CD (Ananthakrishnan et al., 2013), with a second study showing a decrease in corticosteroid courses after patients were prescribed antidepressants alongside their
medication regimen (Goodhand et al., 2012a). A good number of studies show associations between corticosteroid use and psychological symptoms (Dubovsky, Arvikar, Stern, & Axelrod, 2012; Korte, 2001; Nahon et al., 2012; Neutel, 2000), including measures of corticosteroid duration (Kullowatz, Kanniess, Dahme, Magnussen, & Ritz, 2007). However, no studies could be located that investigate whether psychological symptoms can predict a person’s prospective corticosteroid duration or sensitivity in chronic illness samples.

d. Conclusion

The potential impact of psychological symptoms on the need for, and response to, corticosteroid prescriptions is a critical area of study. Not only does corticosteroid prescription offer an indirect measure of inflammation and/or disease relapse, recent studies find that chronic stress and CD are independently associated with insensitivity to glucocorticoids (Cohen et al., 2012; Franchimont et al., 1999). This suggests that patients with IBD and comorbid anxiety could be at a heightened risk for insensitivity to corticosteroids. Reduced corticosteroid effectiveness may increase the number of days that patients with IBD are prescribed a systemic steroid and could harm the patient’s health by increasing the chance of time-dependent negative side effects (Sands, 2000), and increase the need for surgery (Farrell & Kelleher, 2003). Expanding our understanding of the adverse consequences of anxiety on corticosteroid prescription and efficacy could improve treatment outcomes for pediatric patients with CD and comorbid anxiety, as well as for patients diagnosed with other medical illnesses.

5. Project Aims and Hypotheses

The aims of this project are threefold: 1) to examine the cross-sectional association between anxiety symptoms and level of medication treatment for pediatric patients with Crohn’s disease; 2) to test whether anxiety symptoms predict medication prescription changes over a 12-
month period; and 3) to investigate whether anxiety predicts future prescription of corticosteroids and duration.

We hypothesize that anxiety scores will predict the prescription of a more aggressive maintenance medication regimen, taking into account age, illness duration and disease activity. Physicians may prescribe more potent medication treatments to patients with elevated anxiety, since they could interpret somatic symptoms, reduced well-being and healthcare seeking behaviors associated with anxiety as indicating more severe, or less controlled, disease. We also hypothesize that anxiety symptoms will predict a higher frequency of prescription changes to patients’ ongoing medication management, again taking age, illness duration and disease activity into account. Further, increased anxiety symptoms will predict the prescription of a corticosteroid medication over the following 12-month period. Related to this last aim, an exploratory hypothesis is that higher anxiety will be associated with a longer duration of systemic corticosteroid treatment over 12 months.
CHAPTER II: METHODOLOGY

1. Recruitment

Children diagnosed with IBD were asked to complete the Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1997) while checking in at their gastroenterologists’ medical office as part of standard care. A total of 237 anxiety questionnaires were collected between January 2008 and August 2012.

This study is an extension of a funded chart-review project examining the relationship between anxiety and disease activity (Reigada et al., 2015a), and GI health care utilization (Reigada et al., in press) in pediatric patients with IBD. For this larger project, inclusion criteria included having a diagnosis of IBD (either CD or UC) confirmed by endoscopic or radiographic findings, being between the ages of 6 and 18, and having completed the SCARED between January 2008 and August 2010. This project did not have exclusion criteria.

The Institutional Review Boards of Brooklyn College of the City University of New York and Icahn School of Medicine at Mount Sinai granted approval of the study procedures, including an amendment submitted for this study to collect medication information and extend the inclusion criteria date by 2 years to August 2012. A waiver of informed consent was requested for the chart review project, as a consent form would put confidentiality of participants at a greater risk. Specifically, contacting participants would require collection of additional personal information, and consent forms would be the only identifier linking participants to the study once data were de-identified.

Participants were excluded from this study if they returned an incomplete questionnaire \(n = 38\), did not have a diagnosis of CD \(n = 39\), if they did not receive ongoing IBD care for at least 12 months after completing the anxiety questionnaire \(n = 52\), or their primary IBD care
was provided by another medical practice ($n = 3$). After the exclusion criteria were applied, a total of 105 children and adolescents diagnosed with CD remained in the study.

2. **Study Procedures**

Study procedures are illustrated in figure 1. Completion of the anxiety questionnaire was considered baseline, and prescribed IBD medications were recorded for the subsequent year, including changes (i.e., additions, discontinuations, switches) and corticosteroid prescription duration. Disease activity scores were generated at baseline and 12 months. An electronic data collection form was used to record patients’ baseline medication regimen, as well as track prescription changes documented at each physician encounter (e.g., GI doctor visit, phone calls) over a 12-month period following each patient’s baseline date (see appendix A).

Additionally, a pediatric gastroenterologist blinded to patient anxiety scores completed a measure of disease activity for patients at baseline and at 12 months. In order to assess potential subjectivity in establishing disease activity, a second gastroenterologist completed the same measure for a randomly selected 50% of the sample ($n = 53$). Interrater agreement on measures of disease activity was satisfactory ($ICC = 0.76$).
3. Measures

a. Demographic and Disease Characteristics

Baseline demographic and disease information collected from medical records included gender, race, current age, and age of IBD onset. Illness duration was calculated by subtracting age of IBD onset from the patient’s current age.

b. Anxiety Questionnaire

Pediatric anxiety symptoms were assessed using the Screen for Child Anxiety Related Disorders (SCARED). The SCARED is a validated (Birmaher et al., 1997; Birmaher et al., 1999) and commonly used self-report questionnaire that assesses child and adolescent (ages 8 to 18) anxiety symptoms over the preceding two weeks. The SCARED has been used in several medical settings to screen for the presence of anxiety in pediatric patients with a chronic illness.
(Bernstein, Stockwell, Gallagher, Rosenthal, & Soren, 2013; Esenyel, Unal, & Vural, 2014; Mano et al., 2012) including IBD (Reigada et al., 2013). Additionally, while the measure is validated for ages 8 to 18, previously published studies have used this measure for youth below the age of 8 (Reigada et al., 2015; Roy et al., 2008). The questionnaire measures symptoms specific to general anxiety disorder, separation anxiety disorder, panic disorder, social anxiety, and school phobia, and also provides a total anxiety score (see appendix B). The 41-items of the questionnaire are rated on a 3-point scale (0 = not true or hardly ever true; 2 = very true or often true) for a total score ranging from 0 to 82 (higher scores indicating more distress). In physically healthy children with a clinical disorder, the internal consistency is excellent (α = .93), with a score of 25 providing a good cutoff point for discriminating between anxiety and other psychiatric disorders (Birmaher et al., 1999). In pediatric IBD samples, a score of 20 has used to identify those at risk for an anxiety disorder diagnosis (Reigada et al., 2013). Internal item consistency in this sample was excellent (α = .93).

c. Disease Activity

Gastroenterologists generated a disease activity score for each patient at baseline and 12-months using the Harvey Bradshaw Index (HBI; Harvey & Bradshaw, 1980). The HBI score is based on five items that assess patient wellbeing, abdominal pain, frequency of diarrhea, symptoms of an abdominal mass, and extraintestinal symptoms (see appendix C). Total HBI sum scores were coded into inactive (score of < 5) and active (score of ≥ 5) to describe disease activity for the sample (Colombel et al., 2007), and variable was kept continuous when included in statistical models. The HBI is commonly used in retrospective pediatric research to assess disease activity from medical records (Felipez et al., 2012; Willot, Noble, & Deslandres, 2011; Min et al., 2013; Weiss et al., 2009). The HBI is a simplified version of the validated benchmark
Crohn’s Disease Activity Index (CDAI; Best, Becktel, Singleton, & Kern, 1976; Best, 2006; Harvey & Bradshaw, 1980), and total HBI scores consistently correlate with CDAI scores (Best, 2006; Harvey & Bradshaw, 1980; Vermeire, Schreiber, Sandborn, Dubois, & Rutgeerts, 2010). However, the reliability and validity of the HBI tends to be low (Best, 2006; Jørgensen et al., 2005), and internal consistency was low with this sample ($\alpha = .61$).

**d. Medication Treatment Level**

The coding of the medication treatment level at baseline for each patient was established based on standard step-up treatment recommendations for the management of CD (Devlin, & Panaccione, 2010; Rogler, 2013; Lichtenstein, et al., 2009). Rogler’s (2013) categorization was selected as it represents the common classification of treatment levels, and separates acute (i.e., corticosteroids) from maintenance treatments. Treatment levels were coded on a scale from 1 to 5, with 5 representing the most aggressive medication regimen (See Table 2). A level 1 medication regimen involved the prescription of an antibiotic and/or aminosalicylate treatment, and no further medications. Level 2 and 3 treatments included the prescription of a local or systemic corticosteroid, respectively, and regimens could still include level 1 antibiotics and/or aminosalicylates. Level 4 treatments included the prescription of an immunomodulator, and level 5 treatments involved the prescription of a biologic. As indicated, coding was based on the most aggressive medication class prescribed, regardless of whether milder medications may also have been prescribed at the same time.
To capture maintenance medication prescription changes, the addition, discontinuation or switch of antibiotic, aminosalicylate, immunomodulator and biologic medications were tallied for each patient. A *medication addition* was defined as the prescription of an IBD medication that was not previously prescribed. A *medication discontinuation* was defined as discontinuing the prescription of an IBD medication. When a medication addition and discontinuation occurred during the same encounter and within the same drug class, the change was coded as a *medication switch* (e.g., substituting one antibiotic for another). Medication non-compliance was not assessed, and outcome variables reflect only prescriptive changes.

**f. Corticosteroid Prescription and Duration**

All participants were coded as either having received a local or systemic corticosteroid, or not, during the 12-month period. Because a large percentage of patients prescribed a corticosteroid initiated their course before completion of the anxiety questionnaire, patients were also coded as either initiating a corticosteroid course before or after their baseline date. Patients who were prescribed a corticosteroid course both before as well as after their baseline date (e.g., they were prescribed more than one course) were included in the latter group.
For each patient who was prescribed a systemic corticosteroid \( n = 16 \), the number of days that the corticosteroid was prescribed during the study time frame was calculated based on the date the medication was prescribed and discontinued. The start date was considered to be the date that the corticosteroid was prescribed, or patients’ baseline date when treatment was initiated outside the 12-month study period. The discontinuation date was considered to be the date that the corticosteroid was discontinued, or the end of the 12-month time frame, whichever came first. When a specific discontinuation date was not indicated in the medical record notes, the discontinuation date was estimated to be the date of the next physician encounter at which the corticosteroid was no longer prescribed.

4. **Statistical Analyses**

The distributions of all study variables were inspected for normality by visual inspection and examination of skew and kurtosis values (appendix D). Normality was defined as a skew and kurtosis z-score between -2 and 2 (Cramer, 1997; Bulmer, 1979). Report of anxiety symptoms, illness duration, disease activity and frequency of maintenance medication changes (total, addition, discontinuation, and switch) were all positively skewed. Both square root and logarithmic transformations were considered for anxiety, illness duration and disease activity, as these two transformation methods are recommended for positively skewed data (Howell, 2007; Tabachnick, & Fidell, 2007). Square root transformations led to skewness values closest to zero for anxiety and disease activity scores, while logarithmic transformation led to a lower skewness value for illness duration (see appendix E). Transformed variables were used for all analyses, unless otherwise specified. Dependent count variables related to the frequency of medication changes were not transformed, as an assumption of Poisson analyses is that outcome variables follow a positively skewed Poisson distribution.
We examined relations among the predictor variables (i.e., anxiety, illness duration, disease activity) using Pearson’s correlations and analysis of variance, to assess whether there might be multicollinearity problems in the analysis. Continuous variables included anxiety, illness duration, disease activity, and age. Categorical variables included gender and race. Child’s age was highly correlated with illness duration \((r = 0.269, p < 0.010)\). Gender and race were not related to predictors, though sum of total anxiety showed a trending relationship with age \((r = -0.188, p = 0.055)\) and disease activity \((r = 0.185, p = 0.059)\). Given the overlapping variance between anxiety and disease activity and the exploratory nature of this project, relationships were modelled twice to examine the predictive value of anxiety alone, as well as when accounting for disease characteristics and age.

An ordinal logistic regression was performed to ascertain the contributions of anxiety to the likelihood that patients received a higher level of medication treatment (aim 1). A second multivariate ordinal logistic regression was conducted that included illness duration, disease activity, and age. In our dataset, 3 of the 5 levels of treatment (Rogler, 2013) commonly occurred: level 1 antibiotic and aminosalicylate treatment \((n = 19)\), level 4 immunomodulator treatment \((n = 51)\), and level 5 biologic treatment \((n = 28)\). Thus, these three groups were coded as the three levels of the ordinal outcome variable. Seven patients were not included in the analysis because their medication level was based on acute corticosteroid treatment that had a small sample size (3 patients received level 2 treatment; and 2 patients, level 3 treatment) or they were not on any medication (2 patients). This analysis is adequately powered (.80) to detect a medium size effect (that is, a noncentrality parameter of 12 or higher).

Poisson regression was used to model anxiety as a predictor of increased prescriptive changes over 12 months (aim 2). Poisson regression was selected, as our outcome measures were
skewed count data. The main outcome variable was the total number of prescription changes; in addition, the specific types of medication changes were also modeled (i.e., the addition and discontinuation of a medication, and medication switches within the same drug class). Prescription outcomes were modeled as functions of anxiety, as well as (i) illness duration, (ii) disease activity, (iii) age and (iii) anxiety. These analyses are adequately powered (.80) for a medium effect size, given 1 to 3 predictors.

A binary logistic regression was performed to ascertain the effects of anxiety on the likelihood that patients received a corticosteroid medication \((n = 40; \text{both luminal and systemic})\) over the subsequent 12-month period (aim 3, part 1). A second two-step binary logistic regression was conducted testing the effects of anxiety (step 2) on the likelihood of receiving corticosteroid treatment, controlling for illness duration, disease activity and age (step 1). These analyses were repeated to predict prescription of corticosteroid courses that were initiated after baseline \((n = 19)\), to better ascertain the predictive value of anxiety. These analyses are adequately powered (.80) for a small to medium effect size (a noncentrality parameter of 8 or more).

A Pearson correlation was conducted to examine the potential relationship between anxiety and duration of systemic corticosteroid treatment (aim 3, part 2). Of the 40 individuals treated with a corticosteroid, only 16 patients were prescribed a systemic corticosteroid (e.g., prednisone). Given the small sample size, untransformed anxiety scores were used. A power analysis indicated that the effect size of the relationship would need to be large \((r \geq .65)\) in order to detect it.

An alpha of .05 was considered significant. IBM SPSS statistical software version 22 (IBM Corp., 2013) was used for all analyses.
CHAPTER III: RESULTS

1. Sample Characteristics

Demographics and illness characteristics are presented in Table 3. The majority of pediatric patients were White (85.7%), with approximately equal gender distribution (52.4% male). Age ranged from 8 to 18, with age at diagnosis ranging between one and 17 years old. Illness duration ranged from 0 months to 12.5 years, with over half of the sample having been diagnosed with CD for ≥ 1 year, and 26.7% diagnosed 6 months or less, when they completed the anxiety questionnaire. Most of the sample had inactive disease at baseline (n = 92; 87.6%) and at 12-months (n = 89; 84.8%).

Patient-reported anxiety scores ranged from 0 to 52, with a median total of 13.0. Twenty-one patients (20%) had a total SCARED above 25, indicating the potential presence of an anxiety disorder. An additional 11 patients (10%) reported anxiety symptoms that were in the ‘at-risk’ range (a SCARED score of 20 to 24.9), indicative of elevated distress.

<table>
<thead>
<tr>
<th>Table 3. Sample Characteristics (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
</tr>
<tr>
<td>Illness duration, years</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>White</td>
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<tr>
<td>Black</td>
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<tr>
<td>Asian</td>
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<tr>
<td>Other</td>
</tr>
</tbody>
</table>
2. Does Anxiety Predict the Level of Medication Treatment?

At baseline, a total of 1.9% \((n = 2)\) of patients were prescribed no medications, 18.1% \((n = 19)\) were prescribed only antibiotics or aminosalicylates (level 1), and 4.8% \((n = 5)\) were prescribed a corticosteroid as their most aggressive medication (levels 2 and 3). Most patients were prescribed either an immunomodulator (level 4; 48.6%; \(n = 51\)) or biologic (level 5; 26.7%; \(n = 28\)) as their highest level of medication treatment.

The ordinal logistic regression model showed that anxiety did not significantly predict the likelihood of receiving a higher level of medication management, \(\chi^2(1) = 0.032, p = .858\). However, the multivariate ordinal logistic regression model that included illness duration, disease activity, age and anxiety did significantly predict medication level, \(\chi^2(4) = 12.87, p < .05\). Illness duration was the only significant predictor in the model \((p = .001)\), with each one-unit increase in illness duration leading to a 2.24 unit increase in the ordered log-odds of being prescribed a higher level medication regimen. Anxiety, age and disease activity were not associated with an increased likelihood of receiving a higher medication treatment. Table 4 shows descriptive sample characteristics for those prescribed antibiotics/ aminosalicylates, immunomodulators, and biologics.
3. Does Anxiety Predict Medication Prescription Changes?

The total number of medication changes made to a patient’s maintenance medication regimen ranged between 0 and 11 for the 12-month period, with a median of two prescription changes. The addition of a medication was the most common medication change \((n = 56)\), with a median of one medication addition (range 0-5). About half of the patients \((n = 51; \ 48.6\%)\) had one to four medications discontinued, and 27.6% of patients \((n = 29)\) had one to three switches in medication in the same drug class.

The Poisson model that included anxiety as the only predictor showed a trend in predicting greater total number of medication prescription changes over the prospective 12 months, \(\chi^2 (1) = 3.35, p = .067\). Examination of individual types of medication changes

<table>
<thead>
<tr>
<th></th>
<th>Level 1 (n = 19)</th>
<th>Level 4 (n = 51)</th>
<th>Level 5 (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child anxiety, median (range)</td>
<td>11.0 (1-52)</td>
<td>14.0 (0-40)</td>
<td>11.5 (0-50)</td>
</tr>
<tr>
<td>Illness duration years, median (range)</td>
<td>0.5 (0-6)</td>
<td>2.1 (0-12)</td>
<td>2.7 (0-13)</td>
</tr>
<tr>
<td>Disease activity, median (range)</td>
<td>2.0 (0-9)</td>
<td>1.0 (0-8)</td>
<td>0.0 (0-8)</td>
</tr>
<tr>
<td>Child age in years, mean (SD)</td>
<td>14.8 (2.2)</td>
<td>14.6 (2.4)</td>
<td>14.5 (2.3)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>7 (37%)</td>
<td>25 (49%)</td>
<td>13 (46.4%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>16 (84%)</td>
<td>43 (84%)</td>
<td>24 (86%)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (5%)</td>
<td>4 (8%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (11%)</td>
<td>4 (8%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

SD = Standard deviation; Level 1 = Antibiotics/Aminosalicylates; Level 4 = Immunomodulators; Level 5 = Biologics

Table shows raw (untransformed) scores, though statistical analysis and significance presented in text is based on adjusted (transformed) scores.
showed that child anxiety predicted medication switches within the same drug class ($\beta = .32, p < .01$), but not the addition or discontinuation of a medication.

The Poisson model including anxiety, illness characteristics and age significantly predicted the total number of prescription changes, $\chi^2 (4) = 20.37, p < .01$. In this model, child anxiety no longer showed a trend in predicting total prescription changes, though anxiety remained a significant predictor of medication switches when taking illness duration, disease activity and age into account. Table 5 illustrates contributions of each predictor to total medication changes, as well as individual types of medication changes.

Of note, shorter illness duration and higher disease activity were found to be independent predictors of more frequent maintenance medication prescription changes. Illness duration particularly predicted the addition of a medication, while disease activity predicted medication switches within the same drug class.

To better interpret the relationship between anxiety, disease activity and switches between medications, the 38 times that medications were switched for the 29 patients were categorized by medication class. This analysis revealed that switches within the antibiotic medication class were the most common (71%), followed by switches in the immunomodulator class (13%). Only 8% of switches involved biologics, and 8% involved aminosalicylates.
A total of 40 pediatric patients (38.1%) were prescribed either a local or systemic corticosteroid during the 12-month period. Of these 40 patients, 21 (52.5%) initiated their corticosteroid course before they completed the anxiety questionnaire, and 19 (47.5%) were prescribed a corticosteroid course after completing the anxiety questionnaire. Table 6 shows descriptive characteristics for those not prescribed and prescribed (at baseline vs after baseline), corticosteroid medications over the 12-month period.

**TABLE 5. Prescriptive Changes as a Function of Patient Anxiety, Illness Duration, Disease Activity, and Age (N=105)**

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Total Changes RCE (SE)</th>
<th>Addition RCE (SE)</th>
<th>Discontinuation RCE (SE)</th>
<th>Switch RCE (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Anxiety</td>
<td>.04 (.04)</td>
<td>.03 (.07)</td>
<td>.03 (.07)</td>
<td>.25 (.11)*</td>
</tr>
<tr>
<td>Illness Duration</td>
<td>-.45 (.23)*</td>
<td>-.83 (.37)*</td>
<td>-.36 (.36)</td>
<td>.11 (.49)</td>
</tr>
<tr>
<td>Disease Activity</td>
<td>.21 (.07)**</td>
<td>.20 (.11)</td>
<td>.13 (.12)</td>
<td>.36 (.17)*</td>
</tr>
<tr>
<td>Child Age</td>
<td>-.04 (.03)</td>
<td>-.07 (.05)</td>
<td>-.02 (.05)</td>
<td>-.02 (.07)</td>
</tr>
</tbody>
</table>

*p<.05, **p<.01
RCE = regression coefficient estimates
SE = standard error

4. Does Anxiety Predict Corticosteroid Prescription?

A total of 40 pediatric patients (38.1%) were prescribed either a local or systemic corticosteroid during the 12-month period. Of these 40 patients, 21 (52.5%) initiated their corticosteroid course before they completed the anxiety questionnaire, and 19 (47.5%) were prescribed a corticosteroid course after completing the anxiety questionnaire. Table 6 shows descriptive characteristics for those not prescribed and prescribed (at baseline vs after baseline), corticosteroid medications over the 12-month period.
Anxiety was significantly associated with corticosteroid prescription in the analysis of all 40 patients prescribed a corticosteroid treatment during the 12-month study period, $\chi^2(1) = 7.89, p < .01$. This model explained 9.8% (Nagelkerke $R^2$) of the variance in corticosteroid prescription, correctly classified 61.0% of cases, and showed that each one-unit increase in anxiety score increased the likelihood of corticosteroid prescription by 46.0% ($\text{Exp}(\beta) = 1.46$). Anxiety remained significantly associated when illness duration, disease activity and age were included in the model, $\chi^2(4) = 12.28, p < .05$. This model explained 15.0% (Nagelkerke $R^2$) of the variance, correctly classified 65.7% of cases, and the likelihood of corticosteroid prescription increased by 42.5% ($\text{Exp}(\beta) = 1.43$) with each one-unit increase in

### TABLE 6. Descriptive Analysis of Patients Not Prescribed, and Prescribed (At Baseline vs After), a Corticosteroid Medication ($N = 105$).

<table>
<thead>
<tr>
<th>Sample Characteristics</th>
<th>No corticosteroid prescription ($n = 65$)</th>
<th>Corticosteroid prescription at baseline ($n = 21$)</th>
<th>Corticosteroid prescription after baseline ($n = 19$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety†, median (range)</td>
<td>11.0 (0-52)</td>
<td>16.0 (1-35)</td>
<td>19.0 (4-40)</td>
</tr>
<tr>
<td>Illness Duration†, median (range)</td>
<td>2.0 (0-13)</td>
<td>0.5 (0-5)</td>
<td>2.9 (0-11)</td>
</tr>
<tr>
<td>Disease Activity†, median (range)</td>
<td>1.0 (0-11)</td>
<td>1.0 (0-11)</td>
<td>3.0 (0-8)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>14.7 (2.3)</td>
<td>14.5 (2.4)</td>
<td>13.9 (2.6)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>31 (48.0%)</td>
<td>9 (42.9%)</td>
<td>10 (52.6%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>57 (87.7%)</td>
<td>17 (81.0%)</td>
<td>16 (84.2%)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (9.2%)</td>
<td>2 (9.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3.1%)</td>
<td>2 (9.5%)</td>
<td>2 (10.5%)</td>
</tr>
</tbody>
</table>

SD = Standard deviation
†Table shows raw (untransformed) scores, though statistical analysis and significance presented in text is based on adjusted (transformed) scores.
anxiety score. Decreased illness duration, lower age, and increased disease activity were not individually associated with increased likelihood of corticosteroid treatment.

To establish whether anxiety predicted the prescription of future corticosteroid courses, the two models were run a second time predicting only courses that were prescribed after completion of the anxiety questionnaire ($n = 19$). **Anxiety continued to significantly predict future corticosteroid treatment**, $\chi^2(1) = 7.38, p < .01$, and explained 11.1% (Nagelkerke $R^2$) of the variance in corticosteroid prescription, correctly classifying 80.0% of cases. Each one-unit increase in anxiety score increased the likelihood of corticosteroid prescription by 60.4% ($\text{Exp}(\beta) = 1.60$). The two-step model that included illness duration, disease activity and age at step one, and anxiety at step two was significant at both steps. Specifically, illness duration, disease activity and age collectively significantly predicted future corticosteroid prescription, $\chi^2(1) = 10.28, p < .05$, with disease activity being the only significant individual predictor ($p = .013; \text{Exp}(\beta) = 2.01$). When adding anxiety at step two, the predictability of the model increased, $\chi^2(4) = 13.61, p < .01$, with disease activity ($p = .053; \text{Exp}(\beta) = 1.74$) and anxiety ($p = .079; \text{Exp}(\beta) = 1.42$) both showing a trend as individual predictors. Overall, this model explained 19.9% (Nagelkerke $R^2$) of the variance in corticosteroid prescription, and correctly classified 81.9% of cases.

5. **Does Anxiety Predict Systemic Corticosteroid Duration?**

Mean duration of corticosteroid prescription for the 16 pediatric patients was 124.9 ($SD = 57.0$) days, and ranged between 41 and 241 days. All 16 patients were prescribed a single course of systemic corticosteroids, meaning that the number of days of corticosteroid treatment were consecutive. **The Pearson correlation between anxiety and number of days that patients received systemic corticosteroid treatment was not significant**, $r (16) = .101, p = .710$. 
Because visual inspection of the association showed a possible positive trend between the two variables, as well as a potential bivariate outlier (Figure 2), Mahalanobis distances were calculated to test for the presence of a bivariate outlier. While the highest Mahalanobis distance value (MD = 7.3, \( p = .026 \)) did not surpass the \( p < .001 \) cutoff of 13.8, exclusion of this patient had a noticeable impact on results. **Correlation that excluded this patient showed a trend between anxiety and systemic corticosteroid duration of a medium to large effect size, \( r (15) = .429, p = .111 \)** (Figure 3).
Figure 3. Anxiety and Systemic Corticosteroid Prescription Duration ($n = 15$)

To get a better sense of the potential predictive value of anxiety in determining future corticosteroid prescription duration, descriptive and t-test analyses were used to examine the mean number of days that pediatric patients with and without elevated distress were prescribed systemic corticosteroids. Six patients with an anxiety score above 20, indicating elevated distress, were prescribed systemic corticosteroids for a mean duration of 142.2 ($SD = 57.0$) days. When including the outlier, the remaining 10 patients without elevated levels of distress were prescribed a systemic corticosteroid for a mean duration of 114.5 ($SD = 57.3$) days, $t(14) = -0.94$, $p = .365$. When excluding the outlier, the remaining nine patients without distress were prescribed a systemic corticosteroid for a mean duration of 100.8 ($SD = 39.7$) days, $t(13) = -1.67$, $p = .119$. 
CHAPTER IV: DISCUSSION

1. Summary of Findings

This study set out to examine whether patient-reported anxiety symptoms predicted pediatric patients’ level of medication treatment and frequency of prescription changes, as well as the prescription and duration of corticosteroid treatments. Contrary to our hypothesis, anxiety symptoms did not predict a more aggressive level of medication treatment at baseline. Anxiety did show a trend in predicting the total number of prescription changes made to patients’ maintenance medications over a 12-month period, and significantly predicted prescription changes that involved switching between medications belonging to the same drug class. When we controlled for disease characteristics and age, anxiety continued to independently predict prescription changes involving medication switches, but not the total frequency of prescription changes. Among our sample, higher baseline anxiety significantly predicted which patients were prescribed a local or systemic corticosteroid medication over the subsequent year. There was some evidence of a relation between anxiety scores and subsequent duration of systemic corticosteroid use that should be investigated in a larger sample (as well as the relationship between anxiety and corticosteroid efficacy). Overall, results provide preliminary evidence that anxiety may contribute to specific aspects of medication management, particularly to medication switches and the prescription of acute corticosteroid treatment.

2. Anxiety: Not a Predictor of the Level of Medication Treatment

The finding that greater anxiety did not predict the prescription of more aggressive medications when accounting for age and disease activity was contrary to our hypothesis. These results differ from prior research with adult patients with CD and a comorbid psychiatric diagnosis (anxiety and depression) who were found to have an increased chance of
immunomodulator or biologic medication prescription (Ananthakrishnan et al., 2013). This difference may be due to the fact that we examined anxiety symptoms rather than the presence of psychiatric diagnoses, or could reflect a difference between pediatric and adult CD patients. Specifically, physician-patient interactions become more complex for pediatric patients in that they involve a third party, namely the parent(s) (Croom, et al., 2011; Gabe, Olumide, & Bury, 2004). Research shows that physician-parent interactions dominate this triadic relationship in pediatric care, leading to the parent being the main source of ‘patient’ feedback (Gabe, Olumide, & Bury, 2004; Tates & Meeuwesen, 2001). Therefore, parental perceptions of their child’s anxiety, or parents’ own anxiety, may play a larger role than child-reported anxiety when considering medication treatment outcomes.

While anxiety did not predict patients’ level of medication management, illness duration was a predictor. Patients with shorter illness duration were more commonly prescribed milder medications belonging to the aminosalicylate and antibiotics classes, while a longer illness duration predicted the prescription of more aggressive medications that included immunomodulators and biologics. Physicians tended to follow the traditional ‘step-up’ treatment approach (Lin, et al., 2010; Rogler, 2013), which involves prescribing milder locally-acting medications first (depending on severity of disease) and moving toward more aggressive medications, depending on a patient’s response and illness progression.

It is possible that patient anxiety has varying influences on medication management that varies by clinic and its specific treatment approach. For example, physicians at some clinics may be more aware of patients’ emotional well-being (due to use of psychological screeners, or increased communication; Nobile, & Drotar, 2003). Though untested, it is possible that awareness of psychological distress alone could decrease its potential effects on medication
outcomes. Specifically, physicians may be able take into consideration that reported physical symptoms and reduced well-being are related to emotional distress, rather than disease processes or medication treatments. Given these uncertainties, and limited number of studies that have examined the potential predictive value of psychological symptoms on patients’ overall medication management, it is recommended that further investigations be conducted to examine these relationships.

3. Anxiety: A Predictor of Medication Prescription Changes

Pediatric patients experiencing more anxiety symptoms had more prescription changes that involved switching one medication for another within the same drug class, including after disease characteristics and age were taken into account. While no studies could be located that have examined whether psychological symptoms predict the frequency of prescription changes in chronic illness samples, our findings match studies showing that anxiety is related to the prescription of non-psychiatric medications in community samples (Nelson et al., 2013; Simpson, Kazmierczak, Power & Sharp, 1994).

There are several reasons why anxiety may predict prescription changes involving a switch in medications. One possibility is that cognitive and somatic correlates of anxiety influence physician assessments, which then lead them to try different but similar medications. For example, a patient’s anxiety-related somatic symptoms could be interpreted as medication side effects. In support of this, side effects of antibiotics like metronidazole and ciprofloxacin include headaches, diarrhea and stomach pain (Andersson, 1980; Iannini, 2007), which overlap with anxiety-related somatic symptoms (Hughes, et al., 2008). Given our findings, treating anxiety using psychotherapy or anti-anxiety medications may be a safe and cost-effective option to improve treatment outcomes.
Another possible explanation for the relationship between anxiety and medication switches is that the presence of anxiety may be associated with more severe dysregulation of the brain-gut-microbiome axis, leading to reduced medication efficacy. Anxiety can worsen GI dysbiosis (Rhee, Pothoulakis & Mayer, 2009), and dysbiosis can impact medication metabolism (Bakken et al., 2011). It is possible that anxiety independently predicted medication switches by decreasing drug efficacy via this pathway, though current empirical support for this pathway is quite limited. If dysbiosis mediates this relationship, then treating anxiety with anti-depressant medications that influence serotonin signaling would be especially helpful, as these types of medications have shown to reduce brain-gut dysregulation (Guseva et al., 2014).

It is also possible that heightened distress is a consequence of more severe disease. While anxiety continued to significantly predict medication switches when accounting for disease activity, our measure of disease activity collected at two time-points likely did not fully capture the patients’ severity of illness. Further, our measure of disease activity does not differentiate between IBD-related GI symptoms versus functional GI symptoms (e.g., anxiety-related and IBS) (Barratt, Kalantzis, Polymeros, & Forbes, 2005). It is also possible that a third variable, such as genetic factors, contribute to more severe disease as well as increased anxiety. These factors contributed to difficulties in establishing the directionality of the relationships between disease activity, anxiety and medication treatment.

If these prescription changes are made in response to non-disease factors, then this could negatively affect the patient’s health and well-being. An increased number of medication prescription changes means that the body is processing a higher number of medications within a specific period of time. This can increase stress on the liver and kidneys that are involved in drug metabolism (Benet, Kroetz, Sheiner, Hardman, & Limbird, 1996), and can also heighten the
chance for experiencing medication interactions and negative side-effects due to limited liver enzyme availability (Remmer, 1970). Such effects can contribute to lowered patient well-being and worse health outcomes.

Prescription changes are also costly. Switching medications is particularly costly for insurance companies and private payers, as it requires the discontinuation of one medication and the introduction of an additional medication, leading to a double cost. As mentioned previously, Kappelman and colleagues (2008) reported that medication management accounts for the largest percentage of costs (35%) associated with CD treatment in the United States, and medications continue to constitute larger percentages of the costs of treating a chronic illness (Dubois et al., 2000; Mousnad, Shafie & Ibrahim, 2014).

These initial findings are the first to show a relationship between psychological symptoms and prescription changes made to patients’ medication regimen in a chronic illness sample, and supports further investigation in IBD and other chronic illnesses. Findings portray a consistent picture of anxiety symptoms having a modest yet noteworthy association with medication management. While the influence of anxiety on prescription changes was not substantial enough to alter patients’ overall level of medication treatment, anxiety does influence changes within a drug class. This could mean that the influence of patient anxiety on medication management is small. Yet, this effect of anxiety on medication switches could still reduce the well-being and increase treatment costs.

4. Anxiety: A Predictor of Corticosteroid Prescription

Results showed that higher baseline anxiety was generally associated with corticosteroid prescription during the 12-month period, and this was particularly the case when considering patients who initiated a corticosteroid course after completing the anxiety questionnaire. The
finding that anxiety was predictive of future corticosteroid prescriptions supports the idea that anxiety contributes to disease-related inflammation and the course of disease. While results have been mixed when investigating these potential relationships in IBD (Mikocka-Walus, et al., 2007a), it is possible that medication prescriptions themselves contribute to mixed findings. Specifically, when anxiety is associated with more aggressive medications and more severe disease (e.g., Ananthakrishnan et al., 2013), the potent systemic suppression of immune function could lower measures of disease activity more so than milder locally-acting medications. This could then alter the observed relationship between anxiety and measures of disease-related inflammation. Studies showing mixed findings for the relationship between anxiety and disease-related inflammation in IBD typically do not account for medication prescriptions (Banovic, et al., 2010; Bitton et al., 2008; Faust et al., 2012; Mawdsley et al., 2006; Ondersma et al., 1997) or do not examine associations between anxiety and medications (Goodhand et al., 2012b; Porcelli, Leoci & Guerra, 1996). The relationship between stress and inflammation is more consistent among healthy samples and animal models of disease (Black, 2002; Hänsel, Hong, Cámara, & Von Kaenel, 2010; Mawdsley & Rampton, 2005; Salim, Chugh, & Asghar, 2012), where medications are not a factor.

As self-reported symptoms of anxiety predicted increased corticosteroid prescription, an indicator of increased inflammation, findings support the idea that youth’s perceptions of stress are important when considering the risk for heightened inflammation. This is in line with the literature supporting that the perception of stress, rather than stressful life events, is associated with an increased chance for disease relapse in patients with IBD (Bernstein et al., 2010; Cámara et al., 2011; Levenstein, 2008). However, the observed association could also reflect that anxiety is a side effect of corticosteroid prescription. A literature review on psychiatric side effects of
corticosteroid medications by Warrington and Bostwick (2006) concluded that changes in mood were common in both children and adults, which included anxiety, hyperactivity, depression and insomnia. Regardless of the directionality, the finding that patient-reported anxiety symptoms predicted increased prescription of corticosteroid treatment suggests that anxious patients are at an increased risk of developing worse health outcomes, related to increased inflammation and risk for disease relapse and/or exposure to a medication with many toxic side effects.

5. Anxiety: A Possible Predictor of Systemic Corticosteroid Prescription Duration

To our knowledge, we are the first to investigate whether anxiety predicts subsequent duration of a corticosteroid prescription in the chronic illness literature, and our results suggest that further investigation may be warranted. On average, those who were at increased risk of distress were prescribed corticosteroids for an additional 14 to 41 consecutive days over the 12-month period, compared to those reporting lower levels of anxiety. This added duration in corticosteroid prescription for patients with distress may suggest that these patients are experiencing corticosteroid resistance, defined as a lack of response to corticosteroid treatment after 30 days, or corticosteroid dependence, defined as recurrence of symptoms when treatment is tapered or discontinued (Sands, 2000; Tung et al., 2006). However, given the small sample size and weak trend, these differences may represent a type 1 error; it is possible that distress is not associated with the duration of systemic corticosteroid prescription.

This is an important topic, as studies show that up to 1 out of 2 pediatric and adult patients with IBD show corticosteroid resistance or dependence (Munkholm, Langholz, Davidsen, & Binder, 1994; Tung et al., 2006), and the medical community is currently unable to account for this level of variation in patient response (Chikanza, Kozaci, & Chernajovsky, 2003; Franchimont, & Chrousos, 2007). If anxiety and corticosteroid resistance are indeed related, they
have potential implications for other disorders that rely on corticosteroid treatments, such as asthma, lupus, and rheumatoid arthritis (Chatham & Kimberly, 2001; Rachelefsky, 2003; van Everdingen, Jacobs, van Reesema, & Bijlsma, 2002). These illnesses are also associated with a high prevalence of anxiety and depression (Ainiala, Loukkola, Peltola, Korpela, & Hietaharju, 2001; Gettings, 2010; Katon et al., 2007), and have the same issue of large variability in response to corticosteroid treatments (Barnes, 2013; Chikanza, 2002; Szefler, et al., 2002).

Additionally, further integration of neuro- and medical science may benefit patients with chronic inflammation and comorbid distress. Since the stress hormone cortisol and exogenous corticosteroid treatments bind to the same glucocorticoid receptors, it is surprising that the study of glucocorticoid resistance in these two fields has not been united. While neuroscientists have used exogenous glucocorticoids as part of the Dexamethasone Suppression Test for many years to better understand the function of cortisol (Carroll, 1982), researchers should explore the implications of altered endogenous glucocorticoid levels on medication efficacy in the medical setting.

6. Limitations

Several features of this study may limit the generalizability of findings. For one, we can only infer the causality of anxiety on medication treatment outcomes, as data collected over the 12-month study time frame are correlational. Interested researchers could confirm and explore these causal relationships in future studies. Additionally, participants were all recruited from the same GI practice and the treating physicians may follow similar medication management practices. Researchers should examine the relationship between anxiety and medication management across different GI practices with differing medication management and communication styles. Furthermore, given the small sample of patients receiving systemic
corticosteroids, this study lacked power to detect a relationship between anxiety and prospective systemic corticosteroid duration of medium effect size. A study with a larger sample would allow researchers to draw firmer conclusions about the association between anxiety and systemic corticosteroid duration.

The present study does not take into account several important aspects of medication treatment, including adherence, changes in prescribed dosages, and medication management of comorbid mental and physical illnesses. This precludes us from examining the full impact that anxiety may have on medication management and prescription changes. Because we were unable to track medication management or other therapeutic treatment (i.e., psychotherapy) of a comorbid mental illness, and anxiety was measured at a single point in time, we could not differentiate between anxious patients who received or did not receive treatment for their anxiety. However, research suggests that anxiety among pediatric patients largely remains untreated (Evertsz et al., 2012). Tracking psychotropic medications would have allowed for better insight into how treating anxiety may affect medication management of CD; research shows preliminary evidence that the prescription of serotonin reuptake inhibitors can influence medication management for CD (Goodhand et al., 2012b).

Lastly, biomarkers and labs were not consistently available when estimating disease activity from medical charts. Consistent use of objective measures such as serum or stool inflammatory markers would allow for a clearer differentiation between measures of anxiety and disease activity. Furthermore, we did not account for disease phenotype (e.g., inflammatory, stricturing/stenotic, fistulizing/penetrating disease) or location (e.g., ileal, ileocolonic, colonic, luminal, perianal), though these aspects of disease can influence treatment recommendations (Lichtenstein, et al., 2009).
7. **Recommendations for Physicians**

The finding that anxiety is associated with various aspects of medication management, suggests that physicians may need to take steps in addressing the presence of psychological distress in their patients. Identifying and treating emotional distress in youth with IBD may improve disease outcomes and reduce unwarranted medication costs. Recommendations include assessing for psychological distress, increasing communication about psychosocial issues, identifying anxiety- versus disease-related physical symptoms, and treating psychological symptoms.

i. **Assessing for Psychological Distress**

Utilizing screeners may be one effective mechanism for identifying distressed youth. Besides the SCARED, there are many validated measures of psychological distress, such as the commonly used Hospital Anxiety and Depression scale (HADS; Zigmond & Snaith, 1983), Patient Health Questionnaire (PHQ; Kroenke, Spitzer, & Williams, 2001), and Patient Reported Outcomes Measurement Information System (PROMIS, 2012), which can be completed and scored in a brief amount of time. If a screener is not yet implemented, asking patients, including pediatric patients, directly about feelings of depression and anxiety may be another effective way to identify those experiencing distress (Kroenke, Jackson, & Chamberlin, 1997).

Educating physicians on the stigma and somatization of anxiety and depression may also help them identify psychological distress in patients. Physicians often have difficulty with such identification, with accuracy estimates often falling below 50% (Cull et al, 1995; Fallowfield et al, 2001; Passik et al., 1998; Söllner et al., 2001; Kroenke, Jackson, & Chamberlin, 1997). Additionally, the assumption that physical causes underlie all reports of physical symptoms contributes to difficulties in identifying psychological distress in patients with chronic illnesses.
However, research supports that there are several patient factors that predict the potential presence of anxiety or depressive symptoms. For example, the number of patient reported somatic symptoms is a powerful indicator, as well as physician perceptions that the patient is difficult (Kroenke, 2003). In fact, adult patients in primary care were two to three times more likely to have an anxiety or mood disorder when the physician rated their visit as difficult (Jackson and Kroenke, 1999; Hahn et al., 1996; Hahn 2001; Kroenke, 2003). By improving physician training on discussing and identifying psychosocial issues and psychological distress, patient outcomes can be improved and physician frustration reduced.

ii. Increasing Communication around Psychosocial Issues

A main barrier to discussing psychosocial issues for chronic illness patients during office visits is the competing doctor-patient expectation about who should initiate discussion on the subject (i.e., patient or physician). Previous research suggests that physicians often do not ask about the presence of psychosocial issues, including in pediatric settings (Cheng, DeWitt, Savageau, & O'Connor, 1999; Detmar, Aaronson, Wever, Muller, & Schornagel, 2000), and under-estimate patients’ willingness to discuss such issues (Detmar et al, 2000; Kroenke, Jackson, & Chamberlin, 1997). While most patients are comfortable talking about their emotional and psychosocial functioning, 25% of cancer patients reported they were only willing to discuss such issues if the physician brought it up first (Detmar et al., 2000).

Physicians may require additional training on topics related to the presence of psychosocial issues and their relation to medication management and patient well-being (Söllner et al., 2001; Zachariae et al., 2003). One way to help physicians raise psychosocial issues is to
enhance their quality of communication generally (Kroenke, Jackson, & Chamberlin, 1997). A lack of training in good communication skills can lead to distancing and avoidance when emotionally difficult communications occur (Baile et al, 1997). Good communication skills promote patient disclosure and medication adherence (Levetown, 2008), and studies support that effective doctor-patient communication is associated with enhanced discussion of psychosocial concerns (Nobile, & Drotar, 2003).

iii. Accounting for Psychological Factors when Assessing Disease Activity

When treating patients, it is important for gastroenterologists to differentiate between disease activity and comorbid IBS symptoms. The overlap between the two is so tricky that Barratt and colleagues (2005) found that the gold-standard activity index, the CDAI (Best, Becktel, Singleton, & Kern, 1976), did not distinguish between patients with disease versus IBS symptoms, and overestimated disease activity for those with mostly IBS symptomology. It is important that improvements are made to classify patient symptoms with high precision, so that patients are protected from potentially unnecessary and hazardous treatments (Barratt, Kalantzis, Polymeros, & Forbes, 2005). Barratt and colleagues (2005) argue that assessing for discriminant features between IBS and IBD would be most helpful, which they found included bloating and excess gas, fatigue, constant high pain (versus intermittent pain), and infrequent passage of stool.

iv. Treating Comorbid Psychological Distress

Anxiety is a clearly defined psychiatric condition with efficacious treatments available including integrative psychotherapy approaches for pediatric patients diagnosed with IBD (Reigada et al., 2015b). Besides improvements in psychological symptoms (Reigada et al.,
2015b), one study showed that psychological treatment reduced hospital days and sick-leave days for patients with CD (Deter et al., 2007).

Prescription of antidepressant medications may also help patients with IBD experiencing psychological distress. In fact, some researchers have suggested that certain antidepressant medications may not only be helpful as an auxiliary to standard medications used to treat CD, but may also be effective as a first-line treatment to maintain remission in both anxious and non-anxious patients with mild CD activity (Brustolim, et al., 2006; Guseva, et al., 2014).

Serotonin has a myriad of effects throughout the body, including a crucial role in maintaining gut homeostasis (Guseva, et al., 2014) and regulating HPA axis function (Dinan, 1996). By helping regulate these dysregulated brain-body systems associated with anxiety, depression, and chronic inflammation, antidepressant medications are unique in that they can target all associated issues simultaneously. Serotonin signaling has long been implicated in anxiety and depression (Naughton, Mulrooney, & Leonard, 2000). Serotonergic modulation of the immune system has also been implicated in IBD and IBS, with a handful of studies showing that intestinal enterochromaffin cells (which produce serotonin in the GI tract) and GI serotonin production are altered in patients with IBD and IBS (Belai, Boulos, Robson, & Burnstock, 1997; Coates et al., 2004; Guseva et al., 2014). Lastly, antidepressant medications have been found to be effective for reducing unexplained physical symptoms (Jackson, Santoro, Tomkins, Balden, & Kroenke, 1999).

Research supports that specific types of anti-depressants may be better than others in reducing GI inflammation, and this depends in part on the type of serotonin receptors that these agents affect. For example, serotonin receptor 5-HT7R appears to be critically involved in acute and chronic GI inflammation (Guseva et al., 2014). The antidepressant bupropion shows
especially promising effects for treatment of IBD, in that it lowered the production of tumor necrosis factor-alpha in mice (Brustolim, et al., 2006) and case reports have reported reduced disease activity in adult patients (Kane, Altschuler & Kast, 2003; Kast, & Altschuler, 2001). The antidepressants paroxetine (Eirund, 1998) and phenelzine (Kast, 1998) have also shown promise as anti-inflammatory agents for the treatment of IBD.

While most gastroenterologists are comfortable with the idea of prescribing antidepressant medications as a supplement to standard medication treatment for CD, many do not routinely prescribe them and are skeptical that they could potentially serve as primary therapeutic agents (Mikocka-Walus et al., 2007b). Further testing is warranted, however, as antidepressants have a high safety profile (Peretti, Judge, & Hindmarch, 2000). It appears that by regulating, rather than suppressing immune function, the chance for adverse side effects (such as infection) is reduced. However, antidepressants do have the potential to interact with corticosteroid medications (corticosteroids reduce serotonin; Pretorius, 2004), and when prescribed for adolescent patients, the added risk for suicidality should also be taken into consideration (Bridge et al., 2007).

v. Summary

In summary, it is important that gastroenterologists take the potential presence of psychological distress into account when assessing disease activity and selecting medication treatments for patients with CD. The presence of psychological symptoms can be assessed using validated screeners, by asking patients directly about psychological distress, and by improving doctor-patient communication generally. Once psychological distress is identified, it is also important that physicians separate anxiety- versus disease-related physical symptoms, so that both can be optimally treated. The addition of psychological treatments or antidepressant
medications, especially buproprion, may benefit patients with CD. Treatment of CD with antidepressant medications with anti-inflammatory properties would also provide the added benefit of addressing anxiety-related symptoms, disease-related symptoms, and IBS-related symptoms simultaneously. However, further controlled clinical trials are needed to establish the potential anti-inflammatory effects of antidepressant medications in humans.

8. Future Research Directions

This study is among the first to explore whether psychological symptoms predict multiple aspects of medication management for a chronic illness sample. Given our findings, further empirical investigations are warranted to examine the complex interplay between emotional symptoms and medication management. Capturing a more complete snapshot of medication management, including medication adherence, prescription changes pertaining to medication dosages, psychotropic medication use, and medication treatment for comorbid physical illnesses would strengthen future research. Further, large, multi-institutional, longitudinal studies assessing multiple chronic illness samples would elucidate psychosocial contributions to medication management beyond biological need. Depressive symptoms may be particularly important to assess due to their high comorbidity with anxiety (Axelson & Birmaher, 2001), relationship with worsened IBD disease course (Mittermaier et al., 2004), medication non-adherence (Murphy, Wilson, Durako, Muenz, & Belzer, 2001; Kennard et al., 2004), and increased healthcare-seeking behaviors (Richardson, Russo, Lozano, McCauley, & Katon, 2008; Kennard et al., 2004).

If relationships between anxiety and future medication management are consistently observed in IBD and other chronic illness samples, then the pathways proposed to underlie the observed relationships should also be examined. Several measures can be collected to assist in
examining the proposed cognitive, emotional, behavioral and physiological pathways. In particular, future studies should examine whether diurnal cortisol patterns of anxious and non-anxious IBD patients differ; this could help establish whether dysregulation of the HPA axis operates differently for patients with IBD and comorbid anxiety. Increased HPA axis dyregulation associated with IBD and co-occurring anxiety could be associated with more severe systemic and intestinal inflammation, which would require more medications to control and could influence medication efficacy. In addition, measures of bacterial composition as well as norepinephrine, serotonin, and corticotropin-releasing factor levels in the cerebrospinal fluid and the GI tract could help scientists better establish the bidirectional relationships between brain and body, and investigate how anxiety may be related to IBD disease activity and medication treatment. Cognitive-behavioral measures could include patient-reported somatic symptoms and well-being, as well as measures of medical care use. Researchers could compare biological, psychological and behavioral predictors of medication regimen aggressiveness and prescribed medication changes related to dosages, duration, and frequency.

It is also crucial for future studies to investigate the role of psychological interventions, including the addition of psychotherapy or psychotropic medications. Previous work has shown that psychotherapy can improve psychological and treatment outcomes in IBD patients (Deter et al., 2007; Reigada et al., 2015b), and the health and cost benefits of treating anxiety should continue to be examined in pediatric IBD. Additionally, initial findings suggest that antidepressant medications may be beneficial in addition to a patients’ typical medication regimen, and may even be effective as a primary treatment for GI inflammation. Future studies should explore whether identification and treatment of anxiety decreases disease inflammation and relapses, medical costs, and prescription changes (including corticosteroid prescriptions) for
patients with IBD and other chronic illnesses. Lastly, inclusion of diagnostic interviews would allow researchers to assess whether emotional distress or specific psychological disorders are associated with medication management of pediatric patients.

9. Conclusion

Overall, results suggest that anxiety has predictive value for the management of medications in a pediatric chronic illness sample. These findings support the idea that a brief anxiety questionnaire completed in a medical waiting room is useful for identifying youth who may require more frequent medication changes, and who are at an increased risk of being prescribed corticosteroid treatments. Additionally, results support the value of implementing psychological screeners at pediatric GI clinics and underscore the importance of further research attention targeting the role of anxiety in disease processes and treatment.

A growing body of literature points toward shared physiological responses associated with chronic physical and psychological illnesses. Future studies should attempt to establish the causal relationships between anxiety and disease activity, and the role of physiological dysregulation associated with both these variables. While elevated distress may be a result of more severe disease or a third unaccounted variable (e.g., variations in genetic predisposition), the presence of anxiety could also have additive independent effects on physiological dysregulation and health outcomes when left untreated.

Our findings provide preliminary evidence that there may be a utility in assessing anxiety symptoms when managing medications for patients with IBD (Goodhand et al., 2012a; Walker et al., 1996). Physicians should assess for psychological distress, be aware of overlapping physical symptoms associated with IBD, IBS and anxiety, and treat symptoms holistically. These recommendations are consistent with an interdisciplinary understanding that both physical and
emotional symptoms should be accounted for when treating a physical illness (Katon, Lin & Kroenke, 2007; Sperry, 2006).
APPENDICES

**Appendix A.** Visual of the electronic form used to collect medication information at each documented encounter over 12 months. Illustrated here are the additions (mercaptopurine), discontinuations (budesonide), and switches between medications belonging to the same medication class (Metronidazole to Ciprofloxacin).

<table>
<thead>
<tr>
<th>ID</th>
<th>Date_SCARED</th>
<th>Physician Visit</th>
<th>Physician Visit</th>
<th>Physician Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6/25/09</td>
<td>7/28/09</td>
<td>9/1/09</td>
<td>10/15/09</td>
</tr>
</tbody>
</table>

**GC Local**
- Budesonide

**GC Systemic**
- Antibiotic: Metronidazole, Ciprofloxacin
- Aminosalicylate
- Immunomodulator: Mercaptopurine
- Biologic
Appendix B. The Screen for Child Anxiety Related Emotional Disorders

Directions: Below is list of statements that describe how people feel. Read each statement carefully and decide if it is “Not True” or Hardly Ever True” or “Somewhat True or Sometimes True” or “Very True or Often True” for you. Then for each statement, check the box that corresponds to the response that seems to describe you now or within the past 2 weeks. Please respond to statements as well as you can, even if some do not seem to concern you.

<table>
<thead>
<tr>
<th>Statement</th>
<th>0 Not True or Hardly Ever True</th>
<th>1 Somewhat True or Sometimes True</th>
<th>2 Very True or Often True</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. When I feel frightened, it is hard to breathe.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. I get headaches when I am at school.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. I don’t like to be with people I don’t know well.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. I get scared if I sleep away from home.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. I worry about other people liking me.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. When I get frightened, I feel like passing out.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. I am nervous.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. I follow my mother or father wherever they go.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. People tell me that I look nervous.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. I feel nervous with people I don’t know well.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. I get stomachaches at school.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. When I get frightened, I feel like I am going crazy.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. I worry about sleeping alone.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. I worry about being as good as other kids.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. When I get frightened, I feel like things are not real.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. I have nightmares about something bad happening to my parents.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. I worry about going to school.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. When I get frightened, my heart beats fast.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. I get shaky.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 Not True or Hardly Ever True</td>
<td>1 Somewhat True or Sometimes True</td>
<td>2 Very True or Often True</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------</td>
<td>----------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>20</td>
<td>I have nightmares about something bad happening to me.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>I worry about things working out for me.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>When I get frightened, I sweat a lot.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>I am a worrier.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>I get frightened for no reason at all.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>I am afraid to be alone in the house.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>It is hard for me to talk with people I don’t know well.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>When I get frightened, I feel like I am choking.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>People tell me that I worry too much.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>I don’t like to be away from my family.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>I am afraid of having anxiety (or panic) attacks.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>I worry that something bad might happen to my parents.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>I feel shy with people I don’t know well.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>I worry about what is going to happen in the future.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>When I get frightened, I feel like throwing up.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>I worry about how well I do things.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>I am scared to go to school.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>I worry about things that have already happened.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>When I get frightened, I feel dizzy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>I feel nervous when I am with other children or adults and I have to do something while they watch me (for example: read aloud, speak, play a game, play a sport).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>I feel nervous when I am going to parties, dances, or any place where there will be people that I don’t know well.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>I am shy.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Harvey-Bradshaw Index (HBI) —
A simple index of Crohn’s disease activity

<table>
<thead>
<tr>
<th>Patient name: ____________________________</th>
<th>Date of HBI calculation: ____________________________</th>
</tr>
</thead>
</table>

*Please check one box per number (except for #5)*

1. General well-being
   *(yesterday)*
   - Very well = 0
   - Slightly below par = 1
   - Poor = 2
   - Very poor = 3
   - Terrible = 4

2. Abdominal pain
   *(yesterday)*
   - None = 0
   - Mild = 1
   - Moderate = 2
   - Severe = 3

3. Number of liquid or soft stools per day *(yesterday)* = ______________

4. Abdominal mass
   - None = 0
   - Dubious = 1
   - Definite = 2
   - Definite and tender = 3

5. Complications
   *(check any that apply; score one per item except for first box)*
   - None
   - Arthralgia
   - Uveitis
   - Erythema nodosum
   - Aphthous ulcers
   - *Pyoderma gangrenosum*
   - Anal fissure
   - New fistula
   - Abscess

**Harvey-Bradshaw Index score =**
*(please add scores of questions 1 through 5)*

---

**Appendix D. Skewness and Kurtosis Values for Study Variables**

<table>
<thead>
<tr>
<th>Study Variable</th>
<th>Skewness (Std. Error)</th>
<th>Skewness Z-score</th>
<th>Kurtosis (Std. Error)</th>
<th>Kurtosis Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Anxiety</td>
<td>.855 (.236)</td>
<td>3.623*</td>
<td>.617 (.467)</td>
<td>1.321</td>
</tr>
<tr>
<td>Illness Duration</td>
<td>1.47 (.236)</td>
<td>6.229*</td>
<td>1.44 (.467)</td>
<td>3.084*</td>
</tr>
<tr>
<td>Disease Activity</td>
<td>1.47 (.236)</td>
<td>6.229*</td>
<td>2.07 (.467)</td>
<td>4.433*</td>
</tr>
<tr>
<td>Age</td>
<td>-.377 (.236)</td>
<td>-1.597</td>
<td>-695 (.467)</td>
<td>-1.488</td>
</tr>
<tr>
<td>Total Medication Changes</td>
<td>1.46 (.236)</td>
<td>6.186*</td>
<td>3.05 (.467)</td>
<td>6.531*</td>
</tr>
<tr>
<td>Addition</td>
<td>1.22 (.236)</td>
<td>5.169*</td>
<td>1.70 (.467)</td>
<td>3.640*</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>1.17 (.236)</td>
<td>4.958*</td>
<td>.683 (.467)</td>
<td>1.463</td>
</tr>
<tr>
<td>Switch</td>
<td>2.01 (.236)</td>
<td>8.517*</td>
<td>4.011 (.467)</td>
<td>8.587*</td>
</tr>
</tbody>
</table>

* Z-score is <-2 or >2
APPENDIX E

Appendix 5. Comparison of square root and logarithmic transformation of skewed independent and covariate variables

<table>
<thead>
<tr>
<th>Square Root Transformation</th>
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<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Skewness</td>
<td>Skewness Std. Error</td>
<td>Skewness Z-score</td>
<td>Kurtosis</td>
<td>Kurtosis Std. Error</td>
<td>Kurtosis Z-score</td>
</tr>
<tr>
<td>Patient Anxiety</td>
<td>-0.188</td>
<td>0.236</td>
<td>-0.797</td>
<td>-0.406</td>
<td>0.467</td>
<td>-0.869</td>
</tr>
<tr>
<td>Illness Duration</td>
<td>0.555</td>
<td>0.236</td>
<td>2.352*</td>
<td>-0.471</td>
<td>0.467</td>
<td>-1.009</td>
</tr>
<tr>
<td>Disease Activity</td>
<td>0.308</td>
<td>0.236</td>
<td>1.305</td>
<td>-1.14</td>
<td>0.467</td>
<td>-2.441*</td>
</tr>
<tr>
<td>* Z-score is &lt;-2 or &gt;2</td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Logarithmic Transformation</th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Skewness</td>
<td>Skewness Std. Error</td>
<td>Skewness Z-score</td>
<td>Kurtosis</td>
<td>Kurtosis Std. Error</td>
<td>Kurtosis Z-score</td>
</tr>
<tr>
<td>Patient Anxiety</td>
<td>-0.863</td>
<td>0.236</td>
<td>-3.657*</td>
<td>0.133</td>
<td>0.467</td>
<td>0.285</td>
</tr>
<tr>
<td>Illness Duration</td>
<td>0.362</td>
<td>0.236</td>
<td>1.534</td>
<td>-0.923</td>
<td>0.467</td>
<td>-1.976</td>
</tr>
<tr>
<td>Disease Activity</td>
<td>-0.318</td>
<td>0.236</td>
<td>-1.347</td>
<td>-1.23</td>
<td>0.467</td>
<td>-2.634*</td>
</tr>
<tr>
<td>* Z-score is &lt;-2 or &gt;2</td>
<td></td>
<td></td>
<td></td>
<td></td>
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