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Health literacy associated differences of medication use in Crohn's disease

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Boston University

BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**HEALTH LITERACY/ASSOCIATED DIFFERENCES OF MEDICATION USE
IN CROHN)UDISEASE**

by

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M.B., Nanjing Medical University, 2013

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**HEALTH LITERACY-ASSOCIATED DIFFERENCES OF MEDICATION USE
IN CROHN'S DISEASE**

ANZHU YU

ABSTRACT

Purpose: The aim of this study was to explore a difference in medication use (defined by medication selection and medication self-discontinuation) between patients with limited and adequate health literacy. This study also investigated whether the association between medication use and clinical remission of CD was different across the health literacy spectrum.

Methods: A cross-sectional study was conducted by analyzing an existing dataset from the IBD Health Literacy study in the Department of Gastroenterology at Boston Medical Center (BMC). Among 61 patients who were enrolled, 26 had limited health literacy and 35 had adequate health literacy. Medication use was defined by medication selection and medication self-discontinuation. Medication selection was further defined as whether patients with monotherapy were on one of the following medications including 5-ASAs, immunomodulators (including thiopurines and methotrexate), biologics and prednisone; medication self-discontinuation was further defined as whether patients had ever discontinued medications (including thiopurines and biologics) without physician recommendation. Harvey Bradshaw Index score was the assessment of clinical remission of CD. Newest Vital Sign scores were applied to assess health literacy.

Results: The odds ratios for patients who were on 5-ASAs and immune modulators (including thiopurines and methotrexate) monotherapy at the time of visit to

have limited health literacy, compared to patients who were on monotherapy of biologic agent, were 3.75 (95%CI (0.46-38.26), $p = 0.22$) and 1.25 (95%CI (0.13-9.67), $p = 0.83$), respectively. The odds ratio for those who ever self-discontinued any medications to have limited health literacy versus those who did not was 1.62 (95%CI (0.42-6.24), $p = 0.48$). The odds ratio for patients who ever self-discontinued any medications to be in clinical remission against those who did not was 0.46 (95%CI (0.1-1.85), $p = 0.27$). The odds ratio for associations between medication self-discontinuation and clinical remission were 0.6 (95%CI (0.06-4.58), $p = 0.63$) in patients with limited health literacy and 0.5 (95%CI (0.06-4.62), $p = 0.51$) in patients with adequate health literacy.

Conclusion: There were no differences of medication use between limited and adequate health literacy. The association between medication self-discontinuation and clinical remission of CD was indifferent across the health literacy levels. The results of this study provides a foundation for future studies on health literacy associated differences in CD populations and helps promote the effectiveness of treatment for CD by arousing more attention to different health literacy populations.

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
AZA	Azathioprine
BMC	Boston Medical Center
CD	Crohn's Disease
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
GI	Gastrointestinal
HBI	Harvey Bradshaw Index
HIV	Human Immunodeficiency Virus
HL	Health Literacy
IBD	Inflammatory Bowel Disease
MDI	Metered-Dose Inhaler
MPR	Medication Possession Ratio
MTX	Methotrexate
NAAL	National Assessment of Adult Literacy
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NVS	Newest Vital Sign
OR	Odds Ratio
TNF- α	Tumor Necrosis Factor- α

UC.....	Ulcerative Colitis
5-ASAs.....	5- Aminosaliclates
6-MP	6-Mercaptopurine

INTRODUCTION

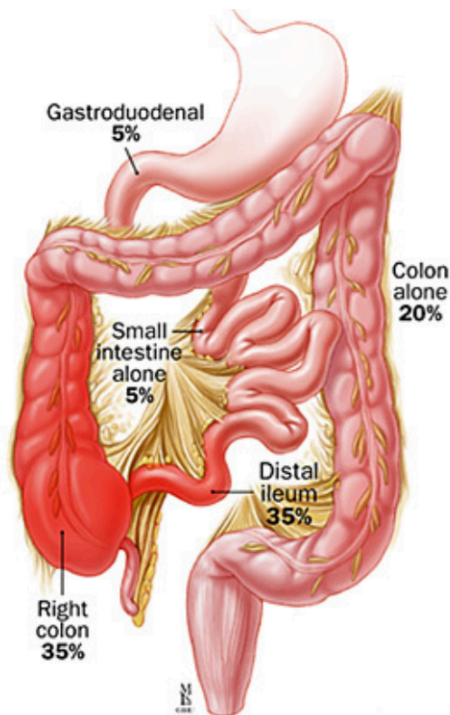
Crohn's disease (CD)

Crohn's disease (CD) is an immune-mediated, chronic inflammatory intestinal condition with extra-intestinal manifestations. It is one of two primary disorders that are collectively termed inflammatory bowel disease (IBD).¹ CD is characterized by relapsing transmural inflammation that can affect any part of the gastrointestinal (GI) tract from the mouth to the anus. The terminal ileum is the most frequently involved segment.¹⁻³ In North America, the incidence rate ranges from 3.1-14.6 cases per 100,000 person-years for CD, with a prevalence of 26-199 cases per 100,000 persons.^{1,4} Epidemiological risk factors associated with CD include age between 15 and 30 years, Jewish descent, urban lifestyle, higher socioeconomic class, and a family history of the disorder.¹ Other risk factors include genetic predispositions³, oral contraceptive use, and pre-existing immunodeficiency disorders such as chronic granulomatous disease and Wiskott-Aldrich syndrome.¹

The inflammatory processes of CD can evolve towards either a fibrostenotic obstructing pattern or a penetrating pattern (or "phenotype") complicated by the formation of fistulas and abscesses. A fibrostenotic obstructing pattern is usually seen in ileocolitis when persistent inflammation has resulted in recurrent scarring of the intestinal wall and subsequently narrowing the intestinal lumen; a penetrating pattern develops when the inflammation affects all layers of the intestinal wall, leading to either a perforation (i.e. –leakage of bowel content into abdominal cavity) or a fistula (i.e. –

connection of one segment of bowel to another or even another organ).⁵ The disease phenotype at clinical presentation will impact prognosis and guide treatment.¹ In addition, clinical manifestations will vary according to the location of the disease (Figure 1).¹

Figure 1. Common locations of Crohn's disease⁶



Patients with ileocolitis more commonly present with chronic right lower quadrant abdominal pain and obstructive symptoms due to narrowing of the terminal ileum as it abuts the ileocecal valve. Less commonly, if the disease is complicated, these patients may develop leukocytosis and fevers that sometimes mimics an acute appendicitis.¹ Patients with more proximal small bowel involvement (jejunoileitis)

characteristically present with diarrhea, malabsorption, and steatorrhea, and are at greatest risk for malnutrition.¹ Patients with Crohn's disease that only involves the colon, Crohn's colitis, typically present with bloody diarrhea, crampy abdominal pain and rectal urgency, sometimes with fecal incontinence. If the perianal region is involved, patients can develop strictures of the anal canal, perianal fistulae and abscesses.¹ In addition to those complications described above, if untreated or refractory, CD can progress to result in bowel perforation, intra-abdominal and pelvic abscesses, partial or complete intestinal obstruction and massive hemorrhage from intestinal ulcerations.¹

Although the gold diagnostic standard for CD is endoscopy with biopsy, CD is a clinical diagnosis that integrates history, symptoms, laboratory findings, radiographic and histopathology features.^{1,2} CD shares a variety of features with many other diseases, in particular ulcerative colitis (UC), the other primary form of IBD.¹ Approximately 15% of IBD does not have the characteristic appearance of either CD and UC; this is termed *indeterminate colitis*.¹ Once a diagnosis of CD is established, phenotypes and disease activity should be assessed, according to Montreal classifications (Table 1), in order to help identify the most appropriate therapeutic regimen.^{2,7}

Montreal Classification for Crohn's Disease	
Age of Onset (A)	[A1] Below 16 years old [A2] Between 17-40 years old [A3] >40 years old
Disease Location (L)	[L1] Ileal [L2] Colonic [L3] Ileocolonic [L4] Isolated upper disease modifier
Disease Behavior (B)	[B1] Non-stricturing, non-penetrating [B2] Stricturing [B3] Penetrating [p] Perianal disease modifier

Table 1. Montreal classification for Crohn's disease

Clinical Remission of CD

Patients with CD typically experience clinical disease remission and relapse throughout their lifetime. Periods of remission can last anywhere from a few days to years, and relapses can occur even with treatment. Factors that can trigger a flare-up include stress, missed medications, recent use of non-steroidal anti-inflammatory drugs (NSAIDs), and smoking.⁸ Clinical remission is defined by the complete absence of CD symptoms. Various scoring systems have been used to quantify the degree of clinical symptoms in patients with Crohn's disease. For example, the Harvey Bradshaw Index (HBI) is a simple index of Crohn's disease activity obtained by evaluating five aspects of disease: general well-being, abdominal pain, number of liquid or soft stools for the day prior to the visit, abdominal mass and complications.^{9,10}

Medications in Current Use

Treatment options for CD have become more complex as new medications have been developed. Major groups of medications indicated for the treatment of CD include: 5-Aminosalicylates (5-ASA), immunomodulators (thiopurine derivatives and methotrexate (MTX)) “biologics” (manufactured antibodies against proteins that cause inflammation, i.e. -infliximab) and corticosteroids (i.e. - prednisone).

Corticosteroids

Corticosteroids are very effective in the short-term treatment of acute flares in patients with moderate to severe CD, but are not recommended as a maintenance therapy.¹¹⁻¹³ Patients who respond well to corticosteroids typically notice a benefit within 1-2 weeks and remain in remission as the steroids are tapered and discontinued.¹¹ Those patients who do not respond to corticosteroid therapy will need a more intense medication, either an immunomodulator, biologic or a combination of the two.¹¹

5- Aminosalicylates (5-ASAs) (Mild Disease)

Aminosalicylates work by inhibiting the cyclooxygenase and 5-lipoxygenase pathways of arachidonic acid metabolism, processes that generate numerous nonspecific inflammatory substances such as thromboxanes, leukotrienes, prostaglandins, free radicals and nitric oxide.¹² While 5-ASA medications can be used first-line to induce

remission in mild (and in some cases moderate) CD, the evidence cannot point to a clear benefit of 5-ASA medications in CD patients who have achieved clinical remission.^{11,12}

Immune modulators: (Moderate Disease)

6-Mercaptopurine (6-MP) and azathioprine (AZA)

6-MP and AZA are thiopurine derivatives which impair purine biosynthesis and inhibit cell proliferation; they may also exhibit direct anti-inflammatory properties.^{11,12} Both agents are used in patients with more moderate CD who are either refractory to or dependent on corticosteroids, as well as those who have recurrent flares of disease requiring repetitive courses of steroids.^{11,12,14} Therapeutic onset of 6-MP and AZA is about 12-17 weeks after initiation.^{14,15} Studies have shown improved rates of clinical remission when thiopurines are used in combination with biologics.^{14,16-18} Side effects of thiopurines include nausea, vomiting, dose-related bone marrow suppression, hepatotoxicity, and infections, etc.¹¹

Methotrexate (MTX)

MTX was first recognized as cancer therapy because it blocked DNA synthesis and induced cell death by inhibiting dihydrofolate reductase, a key enzyme in pyrimidine synthesis.¹¹ Because MTX possessed immune modulating and anti-inflammatory properties, it was then introduced to treat autoimmune diseases such as rheumatoid arthritis and CD.^{11,12} MTX is currently recommended for induction treatment and maintenance therapy in moderate to severe Crohn's disease. Time to therapeutic onset

may be more rapid with MTX than thiopurine derivatives.^{11,12,19} Parental administration (i.e. -intramuscular administration) is important in treating CD, particularly in patients with small bowel diseases whose drug absorption may be impaired.^{11,12}

Biologics: (Moderate to Severe Disease)

Biologics refers to antibodies cultured in laboratories that can bind and block certain proteins, such as tumor necrosis factor- α (TNF- α), which promote inflammation in the intestines as well as other tissues and organs.²⁰ The onset of therapeutic benefit from biologics may range from 6 to 14 weeks after initiation, though many experience a more rapid response.²⁰ Infliximab (Remicade®) is one of the biologics that are intended for both induction and maintenance of remission in patients with moderate to severe CD.

Infliximab (Remicade®)

Infliximab is a chimeric monoclonal IgG1 antibody that binds to and neutralizes tumor necrosis factor- α (TNF- α), one of the principle cytokines that mediate the T_H1 immune response to the inflammation of CD.^{11,12,21} Infliximab is used to treat moderate to severe CD, which includes disease that is steroid-dependent, steroid-refractory, failing to respond to other therapies or has penetrating complications.^{11,22-24} The combination of infliximab and thiopurine has been shown to be more effective than monotherapy for CD. Though similar evidence is not available for the combination of infliximab and MTX given similar properties of the medications, this combination is widely used in clinical

practice.^{11,23,25} Possible side effects of infliximab include fever, anaphylaxis, drug intolerance, respiratory infections and reactivation of tuberculosis.^{11,23}

Goals and Strategy of Therapy

To date, no unique therapeutic target has been identified in CD. Therefore, current medical therapy seeks to dampen the generalized inflammatory response.^{11,12} Specific goals of treatment include controlling acute exacerbations of disease (i.e. –inducing remission), treating complications, preventing disease progression and maintaining remission.¹¹ Although the goals of the treatment vary in each individual patient, the primary objective is to induce and maintain CD remission. The first goal is induction of CD remission, which refers to the control of inflammation and thus symptoms in acute active CD.²⁰ Once CD remission is achieved, the long-term aim of managing CD is to maintain the remission.²⁶ While most medications can be used for both induction and maintenance of CD remission, one clear exception is prednisone, which is only indicated for induction of remission due to various side effects associated with long-term use (i.e.- moon face, buffalo hump, truncal obesity, infections, osteoporosis, hypertension, hyperglycemia, and psychiatric symptoms).^{27,28}

Two therapeutic strategies are currently utilized in the treatment of CD:

Strategy # 1: “Step-up” therapy

Step-up therapy refers to a reactive treatment approach that progressively intensifies as disease severity increases. With this approach, a patient with mild to

moderate disease would start with a milder, but less toxic first-line agent such as a 5-ASA. If the 5-ASA fails, treatment would be gradually escalated to a stronger but greater risk treatment such as an immunomodulator and/or a biologic.²⁹⁻³¹ Such a conventional strategy would potentially avoid medication overuse as well as unnecessary exposure to possible adverse effects.³¹

Strategy #2: “Top-down” therapy

Top-down therapy reverses the conventional step-up therapy by beginning with an early introduction of intensive therapy such as biologics in moderate to severe CD, aiming to reduce complications and improve quality of life.^{29,30,31} Studies have shown that an early introduction of infliximab in top-down therapy had a longer remission period compared to step-up therapy in pediatric patients with moderate to severe CD.^{32,33}

Health Literacy

Health literacy, according to the Centers for Disease Control and Prevention (CDC), refers to “the degree to which a patient can obtain, communicate, process, and understand basic health information and services in order to make appropriate decisions”.^{34,35} Improving health literacy is increasingly critical as the complexity of health-related choices, tasks and decisions rises with the explosion of publically-available health information and technology.³⁶ Results from a pooled analysis of published results on health literacy revealed a 26% (95%CI: 22%-29%) weighted prevalence of limited health literacy among 31,129 subjects from 85 studies between 1963 and 2004.³⁷ In an

early study conducted at two public hospitals in 1995, researchers found that 35.1% of English-speaking patients and 61.7% of Spanish-speaking patients had inadequate or marginal functional health literacy.³⁸ While improving health literacy is necessary, health providers tend to underestimate extent of the problem; this contributes to the challenges patients with limited health literacy experience in trying to understand and utilize health information.³⁹

Limitations in health literacy are especially great among older patients, race/ethnic minorities and undereducated populations.^{36,40-43} Data from the 2003 National Assessment of Adult Literacy (NAAL) found that adults aged ≥ 65 years old had the smallest proportion of persons with proficient health literacy skills and the highest proportion of persons with health literacy skills below the basic level.^{36,43} This NAAL report also found that Caucasian and Asian/Pacific Islander adults had highest average health literacy whereas Hispanic adults had the lowest average health literacy.^{36,43} In addition, the report observed that adults who had not attended or completed high school had a higher percentage of Below Basic health literacy than other educational groups.^{36,43} The observations from the NAAL report were consistent with the results from several other studies, demonstrating that health literacy has been associated with age, race/ethnicity, and education.^{41,42}

Health Literacy in Chronic Diseases

While there are few studies of health literacy in CD, limited health literacy has

been associated with a range of poor health-related outcomes in many other chronic diseases.⁴⁴ In a study of individuals with chronic obstructive pulmonary disease (COPD), researchers found associations between limited health literacy and greater disease severity, worse quality of life, more emergency utilizations.^{45,46} Another study in asthmatics revealed a strong correlation between limited health literacy and poor knowledge of their disease as well as improper use of metered-dose inhaler (MDI), a self-administered device delivering aerosolized asthma medications into the lungs.⁴⁷ An association between limited health literacy and all-cause mortality and cardiovascular death was also found in a prospective cohort study of community-dwelling older adults.⁴⁸ Limited HL is significantly related to worse glycemic control and poorer disease knowledge in type 2 DM.⁴⁹ Other studies have found similar associations in hypertension, diabetes, and HIV/AIDS.⁵⁰⁻⁵² However, our understanding of the role of health literacy in Crohn's disease is largely based on extrapolation from other chronic diseases.

Health literacy in Medication Use

Patients with limited health literacy are more likely to have problems understanding, managing and adhering to medication instructions.⁵³ In Crohn's disease, patient preference is an important factor when initiating a new treatment such as a biologic; most patients want to be involved in this decision.⁵⁴ Participation in a decision pertaining to treatment, a process called "shared-decision making", demands a certain degree of knowledge and health literacy. Although the selection of medications depends highly on disease behavior and severity, biologics are recognized as the most effective

class of drugs across a range of disease severity, and therefore have the potential to be used in moderate, moderate to severe or severe disease). Participation in treatment decisions optimizes the chance that the chosen therapy matches the patient's preference and may improve medication adherence.⁵⁵ Another issue that may be related to health literacy in CD populations is self-discontinuation of medication. CD patients who self-discontinue medications may have done so for a variety of reasons linked to limited health literacy such as lack of knowledge or understanding (remission vs. cure, need for medication refills, concerns about a side effect), as well as increased barriers to care (insurance or financial problems or scheduling conflicts (i.e. – inability to take off work for an infusion)). These self-discontinuations often go unreported at the time.

Study Rationale

The goal of treatment for CD aims to induce and maintain remission. Patients must engage in their care throughout the course of treatment in order to achieve these goals. There is substantial evidence that patients with limited health literacy have poorer health outcomes, as well as difficulties in managing and adhering to medications.

Because most studies on health literacy were conducted in other chronic disease states, knowledge of the role of health literacy in the CD setting is lacking. Understanding how health literacy impacts the treatment of CD would help both physicians and patients promote physician-patient communication and improve the quality of care delivered.

Therefore, the aim of the present study was to generate more knowledge on the impact of health literacy in CD treatment. More specifically, this study examined whether limited

health literacy diminished the effectiveness of treatment, leading to less clinical remission, by biasing patient's preferences on the medication selections and promoting the medication self-discontinuations.

Primary Study Objective

The primary objective was to explore if there was a difference in medication use (i.e., medication selection and patient self-discontinuation) between patients with adequate and limited health literacy (as measured by Newest Vital Sign scores).

Secondary Study Objectives

One secondary objective of this study was to examine if there was a difference in medication use (i.e., medication selection and patient self-discontinuation) between patients who have and who have not achieved clinical remission (as measured by Harvey Bradshaw Index score) at the time of recruitment.

Another objective was to investigate if there was effect modification by health literacy in the association between medication use (i.e., medication selection and patient self-discontinuation) and patient-reported clinical remission (as measured by Harvey Bradshaw Index score).

METHODS

Study Design

This is a secondary analysis of an existing dataset from a cross-sectional IBD Health Literacy study conducted within the Gastroenterology department at Boston Medical Center. The current study was also a cross-sectional study. Therefore, the medications analyzed in this study represented the medications patients were on at the time of recruitment in the parent study, and the clinical remission of CD referred to the condition whether patients were in remission at the same time. Data were collected between Sep. 23, 2014 and Aug. 20, 2015. Both the IBD Health Literacy study and the present study were approved by the Institutional Review Board at the Boston University School of Medicine. The IBD Health Literacy study measured the associations between health literacy and patient-reported outcomes, including subjective health status, and quality of life and depression in the setting of IBD populations.

Study population

Data from ninety-nine subjects from the IBD Health Literacy study were analyzed for this study. Of the data set examined, 38 patients were excluded after initial screening because they were diagnosed with UC or indeterminate colitis. Accordingly, Sixty-one patients were included in this study based on the inclusion/exclusion criteria.

The inclusion criteria included:

1. Patients who were 18 years old or older.

2. Patients diagnosed with CD.
3. Patients who were proficient in English.

The exclusion criteria included:

1. Patients who were younger than 18 years old.
2. Patients who had significant cognitive impairment.

Assessment of Health Literacy

Health literacy of CD patients was screened by a Newest Vital Sign (NVS) questionnaire in the parent study (Appendix 1). The NVS questionnaire, a reliable and quick screening instrument with a high sensitivity for limited health literacy in English-speaking patients, not only evaluates the reading and comprehending abilities, but also assesses the quantitative-numerical and abstract reasoning skills.⁵⁶ The score of NVS ranged from 0 to 5; a score of 4-5 was defined as adequate of health literacy, while a score of < 3 suggested limited health literacy (Appendix 1).

Assessment of Medication Use

Data on current and past medication use was collected at the time of clinical disease activity assessments (clinical remission vs. active disease). Medication use was defined by medication selection and medication self-discontinuation. Medication selection was measured by examining the medications that were being taken at the time of the recruitment by patients who were on monotherapy from the IBD Health Literacy

study. Medication self-discontinuation was defined as whether patients discontinued the medication without physician recommendation. This data was collected from medical records (provider office visit notes). Based on provider documentation, discontinuation was categorized as either patient-directed or provider-directed. Medications reported included 5-ASA, immunomodulators (including thiopurines and methotrexate), biologics, and prednisone.

Assessment of Clinical Remission

Data on clinical remission was collected at the time of recruitment in the IBD Health Literacy study. Thus, the data represented whether the patients were in remission (vs. had active disease) at the time when the data on medication use and health literacy levels were collected. Clinical remission of CD was assessed using the patient-reported Harvey-Bradshaw Index (HBI) scores (Appendix 2). Based on prior literature, a score <5 was defined as clinical remission.^{9,10}

Confounders

Additional measures, considered to be potential confounders, were obtained in this study: age, race/ethnicity, education levels, CD disease behavior and CD disease location. These measures were defined: Age was defined as the age at recruitment; race/ethnicity was grouped as Caucasians vs. other races; educational levels were categorized into higher education level with a college or above education and lower education level with a range from illiterate to high school graduate; CD disease behavior

and location was measured by the Montreal classification and was collected from medical records from the IBD Health Literacy study.

Statistical Analysis

Demographic characteristics including age, gender, race/ethnicity, disease duration, education level, and financial status were assessed using descriptive statistics. Baseline measures were compared between the limited health literacy and adequate health literacy using the Fisher's exact test for categorical variables and Student's t-test for continuous variables. If any of these demographic variables showed a significant difference ($p < 0.20$) between limited and adequate health literacy subgroups, they were considered as potential confounders. However, an analysis controlling for potential confounders could not be performed due to sample size limitations and lack of available information about other key variables including medication dosage and time to initiation of medications.

Differences of medication use between limited and adequate health literacy subgroups were analyzed using a univariate logistic regression because both variables were dichotomized. Detailed descriptions on the seven patients who were taking prednisone at the time of recruitment were presented (because all of them were on combination therapy). Because HBI score for clinical remission was also dichotomous, a univariate logistic regression was performed to analyze the associations of medication self-discontinuation with clinical remission. The effect modification analysis of health

literacy was conducted by comparing the magnitude of the crude estimator with that of stratum-specific estimator in limited and adequate health literacy subgroups.

All statistical analyses were performed in R. A $p < 0.05$ was considered as statistically significant for the results from logistic regressions.

RESULTS

Baseline Characteristics

From the dataset of the previous IBD Health Literacy study, 99 patients were enrolled for initial screening of the present study based on the inclusion/exclusion criteria. 38 patients were excluded because they were diagnosed with either UC or indeterminate colitis. Within the 61 patients who were enrolled in this study, 26 (43%) had limited health literacy ($NVS \leq 3$) and 35 (57%) had adequate health literacy ($NVS > 3$). The mean age of overall patients was 46.54 yr ($SD = 17.66$). 40 (66%) patients were female, 39 (64%) patients were Caucasian, 40 (66%) patients have an education with college or above, and 33 (54%) patients achieved clinical remission at the time of visit. The information of the medication monotherapy patients were on at the time of recruitment were obtained from medical records: five patients on 5-ASA, three patients on thiopurines, three patients on MTX, fourteen patients on biologics. Seven patients who were on prednisone at the time of visit were all taking combination therapies. There were twenty-five patients on single medication, twenty-six patients on two or three medications concurrently, and nine patients not on any medication at the time of recruitment.

Table 2. Baseline Characteristics

Baseline Characteristics	Limited HL* (n=26) (NVS≤3)	Adequate HL (n=35) (NVS>3)
Age (mean, SD)	49.6(16.2)	44.3(18.6)
Age ≥65 yr (%)	4(15%)	8(23%)
Female (%)	17(65%)	23(66%)
Caucasian race (%)	10(38%)	29(83%)
Education with college or above (%)	10(38%)	30(86%)
CD location** (%)		
L1 (ileal)	4(15%)	12(34%)
L2 (colonic)	7(21%)	6(17%)
L3 (ileocolonic)	13(50%)	17(49%)
CD behavior** (%)		
B2 (stricturing)	5(19%)	9(26%)
B3 (penetrating)	5(19%)	7(20%)
P (perianal)	10(38%)	14(40%)
Medication at visit*** (%)		
5-ASAs*	3(12%)	2(6%)
Thiopurines	1(4%)	2(6%)
Methotrexate	1(4%)	2(6%)
Biologics	4(15%)	10(29%)
Medication self-DC (%)		
Thiopurines	5(19%)	4(11%)
Biologics	3(12%)	2(6%)
Clinical Remission (%)	9(35%)	24(69%)

* HL = health literacy; medication self-DC = medication self-discontinuation; 5-ASAs= 5-aminosalicylates.

** CD locations and behaviors are classified by Montreal classification.

*** Patients who were on monotherapy at the time of visit.

p < .05 indicated by bold text.

Table 2 showed the comparison of baseline characteristics between limited health literacy and adequate health literacy. Patients who had limited health literacy were older and had a higher percentage of self-discontinuing medications (eg. thiopurines and biologics); however, such differences were not statistically significant. The distribution of gender in both subgroups was approximately equal. A significantly higher percent of patients with adequate health literacy were Caucasian race ($p < 0.05$) and had received a higher education with college or above ($p < 0.05$). No significant differences in CD location and disease behavior were found between limited and adequate health literacy subgroups.

Differences of Medication Use in Health Literacy

A significant association between health literacy and clinical remission was found in the previous IBD Health Literacy study. The results for the difference of medication selection between limited and adequate health literacy were shown in Table 3. Patients who were on biologics at the time of visit were considered reference group in this analysis. The odds ratios for 5-ASAs and immunomodulators comparing to biologics were 3.75 (95%CI (0.46-38.26), $p = 0.22$) and 1.25 (95%CI (0.13-9.67), $p = 0.83$). These ORs suggested that patients who were on 5-ASAs were almost four times more likely to have limited health literacy than patients who were on biologics at the time of visit, and the likelihood of those who were on immunomodulators at the time of visit were slightly higher than those who were on biologics. Although these differences were clinically meaningful to some extent, none of them was statistically significant.

Differences of medication self-discontinuation in different health literacy levels were shown in Table 4. The odds ratios showed some clinically meaningful trends, but there was no statistically significant difference of medication self-discontinuation between limited and adequate health literacy. The odds ratio for patients who self-discontinued thiopurines versus those who did not self-discontinue the same medication was 1.98 (95%CI (0.44-9.46), $p = 0.37$); the odds ratio for those who self-discontinued biologics against those who did not was 2.67 (95%CI (0.38-23.30), $p = 0.33$). This suggested that patients with limited health literacy were more likely to discontinue these two medications without physician recommendations than those with adequate health literacy who were on the same medication. The results of patients who self-discontinued any medications versus those who did not were also presented; the odds ratio was 1.62 (95%CI (0.42-6.24), $p = 0.48$). Although the trend remains the same, the odds ratio was lower than thiopurines and biologics groups in separate. This indicated that there might be some other factors interfering the associations.

Table 3. Unadjusted analysis on differences of medication selection at the time of visit in health literacy.

	Limited Health Literacy		
	OR	95%CI	P-value
(Intercept)* (n=14)	-	-	-
5-ASAs (n=5)	3.75	0.46-38.26	0.22
Immunomodulators** (n=6)	1.25	0.13-9.67	0.83

* Intercept represents patients who were on *biologics* monotherapy at the time of recruitment in IBD Health Literacy study.

** Immunomodulators include *methotrexate* and *thiopurines*.

Table 4. Unadjusted analysis on differences of medication self-discontinuation in health literacy.

	Limited Health Literacy		
	OR	95%CI	P-value
Thiopurine			
(Intercept)* (n=31)	-	-	-
Self-DC** (n=9)	1.98	0.44-9.46	0.37
Biologics			
(Intercept)* (n=25)	-	-	-
Self-DC (n=5)	2.67	0.38-23.30	0.33
Total medications***			
(Intercept)* (n=34)	-	-	-
Self-DC (n=12)	1.62	0.42-6.24	0.48

* Intercept represents patients who did not discontinue the same medication without physician recommendation.

** Patients who discontinued the medication without physician recommendation.

*** Patients who ever self-discontinued any medications vs. those who did not; the numbers of patients do not add up because there were patients who were on both medications.

Medication Self-discontinuation and Clinical Remission of CD

Table 5 showed the results for the differences of medication self-discontinuation in clinical remission of CD. There were no statistically significant differences in clinical remission of CD, even though the trends had some clinical meaning. Patients who self-discontinued thiopurines and biologics were less likely to be in clinical remission of CD than those who did not self-discontinue the same medication; the odds ratios were 0.55 (95%CI (0.11-2.81), $p = 0.47$) and 0.15 (95%CI (0.01-1.21), $p = 0.11$), respectively. The results of patients who self-discontinued any medication versus those who did not showed that patients who ever had discontinued their medication without physician recommendation were less likely to be in clinical remission of CD, and the odds ratio for this association was 0.46 (95%CI (0.1-1.85), $p = 0.27$).

Health Literacy Associated Differences in the Associations Between Medication Use and Clinical Remission (Effect Modification by Health Literacy)

Although the associations between medication selection and clinical remission were analyzed by this study (Appendix 3), this study failed to detect health literacy associated differences in this association due to the small sample size. There was no effect modification by health literacy in association between thiopurine self-discontinuation and clinical remission of CD, meaning that there were no health literacy associated differences in this association (Table 6). The odds ratios for the associations between thiopurines self-discontinuation and clinical remission were 1.0 (95%CI (0.10-9.12), $p = 1.0$) in the limited health literacy subgroup and 0.57 (95%CI (0.04-14.16), $p =$

0.68) in the adequate health literacy subgroup. This might suggest that patients with adequate health literacy who self-discontinued thiopurines were less likely to be in clinical remission (compared to patients with limited health literacy who self-discontinued the same medication), but the results in both health literacy subgroups were not statistically significant and the statistical power for this difference was small. Table 7 showed the results on health literacy associated difference in the association between biologics self-discontinuation and clinical remission. However, this difference was undetectable because there were no patients with limited health literacy who were in clinical remission and had a history of biologics self-discontinuation simultaneously.

Health literacy associated difference in the associations between total medication self-discontinuation and clinical remission were showed in Table 8. Although odds ratios for both health literacy subgroups (OR = 0.6, 95% CI (0.06-4.58) for limited health literacy and OR = 0.5, 95%CI (0.06-4.62) for adequate health literacy) showed that patients with both limited and adequate health literacy who had self-discontinued any medication were less likely to be in clinical remission, the difference (of the association between medication self-discontinuation and clinical remission of CD) between limited and adequate health literacy groups was not significant.

Table 5. Unadjusted associations between medication self-discontinuation and clinical remission of CD.

	Clinical Remission of CD (HBI<5)		
	OR	95%CI	P-value
Thiopurines			
(Intercept)* (n=31)	-	-	-
Self-DC** (n=9)	0.55	0.11-2.81	0.47
Biologics			
(Intercept)* (n=25)	-	-	-
Self-DC (n=5)	0.15	0.01-1.21	0.11
Total medications			
(Intercept)* (n=34)	-	-	-
Self-DC (n=12)	0.46	0.11-1.85	0.27

* Intercept represents patients who did not discontinue the same medication without physician recommendation.

** Patients who discontinued the medication without physician recommendation.

*** Patients who ever self-discontinued any medications vs. those who did not; the numbers of patients do not add up because there were patients who were on both medications.

Table 6. Health literacy associated differences in the association between thiopurines self-discontinuation and clinical remission.

	No self-DC*	Thiopurines self-DC	OR (95%CI) for thiopurines self-DC within each stratum of HL
	N with/without clinical remission	N with/without clinical remission	
Limited HL**	4/6	2/3	1.0 (0.10-9.12), p = 1.0
Adequate HL	14/4	2/1	0.57 (0.04-14.16), p = 0.68

* Self-DC refers to patients who discontinued the medication without physician recommendation.

** HL = Health Literacy.

Table 7. Health literacy associated differences in the association between biologics self-discontinuation and clinical remission.

	No self-DC*	Biologics self-DC	OR (95%CI) for biologics self-DC within each stratum of HL
	N with/without clinical remission	N with/without clinical remission	
Limited HL**	4/4	0/3	NA
Adequate HL	11/5	1/1	0.45 (0.02-13.08), p = 0.60

* Self-DC refers to patients who discontinued the medication without physician recommendation.

** HL = Health Literacy.

Table 8. Health literacy associated differences in the association between total medication self-discontinuation and clinical remission.

	No self-DC	Medication self-DC*	OR (95%CI) for total medication self-DC within each stratum of HL
	N with/without clinical remission	N with/without clinical remission	
Limited HL**	5/6	2/4	0.6 (0.06-4.58), p = 0.63
Adequate HL	15/5	3/2	0.5 (0.06-4.62), p = 0.51

* This analyzed patients whoever discontinued any medication without physician recommendation vs. those who did not; self-DC = self-discontinuation.

** HL = Health Literacy.

Table 9. Details on the 7 patients who were taking prednisone at the time of visit.

ID	1	2	3	4	5	6	7
Age^a	48	33	47	63	67	36	46
Sex	F	F	F	F	M	F	M
Caucasian	Y	N	Y	Y	Y	N	Y
Education^b	N	N	Y	N	N	N	N
HL^c	A	L	A	L	A	L	A
HBI^d	-	R	-	-	-	R	-
5-ASA^e	-	-	-	Y	-	-	-
Thiopurines	-	Y	-	-	-	Y	-
MTX^f	Y	-	-	-	Y	-	-
Biologics	Y	-	Y	Y	-	Y	Y

^a Age at the visit
^b Education with college or above (Y: Yes, N: No)
^c HL = Health Literacy (A = Adequate, L = Limited)
^d Assessment of clinical remission of CD (R: Remission(HBI<5))
^e 5-ASAs = 5-Aminosalicylates (Y: Yes)
^f MTX = Methotrexate

DISCUSSION

This study first explored the difference in medication use (defined by medication selection and medication self-discontinuation) between CD patients with limited and adequate health literacy. Next, the difference in medication use between patients with and without clinical remission was investigated. Finally, health literacy associated differences in the associations between medication self-discontinuation and clinical remission of CD were examined.

Unadjusted analysis revealed that there was no statistically significant difference in medication selection between patients with limited and adequate health literacy who received monotherapy of 5-ASAs, biologics, and immunomodulators. Medication self-discontinuation rate was not significantly different across the health literacy spectrum. Moreover, prior medication self-discontinuation appeared to have no difference in current clinical disease activity (remission vs. active disease). Lastly, there was no health literacy associated differences in the association between medication self-discontinuation and clinical remission of CD.

Study Population

This study was conducted by analyzing an existing dataset from the IBD Health Literacy study within the GI department at Boston Medical Center. The distribution of age at diagnosis in this study population revealed a peak between 20 and 30 years old and a median age of 28 years old. Also, approximately 65% patients in this study were

female. These findings were similar to prior studies: a retrospective study in the United Kingdom found that 62% were female and the median age of diagnosis was 30 years old^{57,58}; a retrospective study in Olmsted County, Minnesota, United States showed that 54% of the study population were female and the median age of diagnosis was 29.5 years old^{58,59}; another prospective study found a female predominance and a median of age at diagnosis of 31 years old.^{58,60} In addition, there was predominance in Caucasian race (64%) and a smaller percentage in African American (20%) in this study, which was roughly similar to the prevalence of general CD population. Therefore, the results of this study suggest generalizability to the CD population at large but with caution due to other potential differences such as socioeconomic status and cultural differences.

Differences of Medication Use in Patients' Health Literacy Levels

The treatment for CD is a shared decision making process that requires patients to make preference-sensitive decisions in order to optimize the treatment response and improve adherence to treatment.^{55,61} Health literacy is crucial to this process in that low health literacy limits the patients' ability to communicate with health care providers, understand disease-associated knowledge, and participate in the shared-decision making process.⁶² However, the magnitude of the influence by patients' limited health literacy in this process remains unknown. The absence of a significant difference of medication selection between patients with limited and adequate health literacy suggests that the effective medications were equally used across the health literacy spectrum in this population.

While patients' desire to be actively involved in the preference-sensitive decision-making process, Siegel et al discovered that gastroenterologists lack the approach and tools to implement the shared-decision making process.⁶³ This could be another reason for the lack of observable difference in medication selection across health literacy levels. In some instances, gastroenterologists may take a more paternalistic approach, thereby diminishing the impact of the patient's health literacy on a treatment selection. (Something like – “In contrast to those with adequate health literacy, patients with limited health literacy often feel less empowered and are more likely to report dissatisfaction with patient-provider communication and shared-decision making (I think you can find a study from my paper that reported something like this). They may be more likely to experience a paternalistic approach, which often fails to adequately engage the patient and ascertain patient preferences as part of the decision making process). A lack of engagement in the treatment decision may increase patients' vulnerability to the potential harms of treatment through multiple potential mechanisms: lack of understanding of treatment benefits, risks, alternatives and expectations as well as inadequate strategies for self-management and involving the provider, when confronting troubles. Therefore, as it appears effective medications are likely to be equally used in limited and adequate health literacy subgroups, health care providers need to be cognizant of health literacy challenges and work to create a supportive and engaging environment for vulnerable patients

If we accept a premise that medication self-discontinuation can be either intentional (i.e., deliberate discontinuation due to dissatisfaction with the medication) or unintentional (i.e., lack of knowledge or awareness about the need to “refill” a medication), then this concept has similarities to intentional and unintentional non-adherence. This is a complex concept as it relates to health literacy. When looking broadly at adherence, studies have failed to find a consistent link with health literacy: Dharmapuri et al reported that almost one quarter of adolescents had worse medication adherence, independent of health literacy.⁶⁴ Lyles et al also failed to find an association between health literacy and medication adherence.⁶⁵ Similar to the present study, these studies did not distinguish between intentional and unintentional non-adherence either.

Other studies have shown that patients with limited health literacy are more prone to unintentional non-adherence, but not necessarily intentional non-adherence.^{66,67} Frequently less empowered to make health decisions, patients with limited health literacy may be less likely to intentionally self-discontinue their medications without direction from their doctor, but they may still be more prone to unintentional self-discontinuation. Findings from the present study failed to show differences of self-discontinuation of thiopurines and biologics between CD patients with limited and adequate health literacy, possibly because the distinction between intentional and unintentional behaviors could not be made.

That said, it is worthwhile to note that there are a few studies that have found significant association between health literacy and medication adherence overall. Waite et al found that HIV patients with limited health literacy were 3.3 times more likely to be non-adherent to antiretroviral regimens.⁶⁸ Noureldin et al also found that patients with limited health literacy had lower adherence to cardiovascular drugs than those with adequate health literacy.⁶⁹ Despite the small sample size of the present study, the odds ratios for medication self-discontinuation according to health literacy still reflect a trend that patients with limited health literacy were more likely to discontinue their medications without physician recommendation. One major difference between the studies that had statistically significant results and the present study was the sample size: Waite et al recruited 204 patients and Noureldin et al had 314 patients. The trend, which is consistent with the trends in the two aforementioned studies, suggests that there is a possibility that the difference in medication self-discontinuation between limited and adequate health literacy can be detected with a larger sample size.

Contrary to the trends detected in the present study, one study by Michael et al found a reverse trend: low health literacy was associated with higher odds of medication adherence in HIV populations in a longitudinal study.⁷⁰ While this may also be the situation in CD populations, such that patients who self-discontinue thiopurines and biologics do so because they think they have better understanding of when to stop their medications, the present study is not able to distinguish the actual motivation, whether it is due to limited health literacy or adequate health literacy. However, the HIV population

is different from CD population in many aspects such as age, sex and race. For example, there are more male patients than females in HIV population,⁷¹ but in this study females are the predominant sex. Some studies have shown that women are more vulnerable to nonadherence and men are more adherent to medications.⁷²⁻⁷⁴ Therefore, relationship between low health literacy and adherence may be unique for male-dominant HIV populations but not suitable for CD populations. The trends found in the present study, on the contrary, may provide a foundation for health literacy associated differences in medication use specifically for CD populations.

Associations Between Medication Self-discontinuation and Clinical Remission of CD

At first glance, the lack of significant differences between medication self-discontinuation behavior and the clinical remission of CD in the current study suggests a potential departure from prior studies. In a case-control study examining the role of medication adherence in IBD, Feagins et al found that medication adherence was significantly different in disease activities and that medication non-adherence was significantly associated with IBD flares.⁷⁵ The CD population in the Feagins et al. study was similar in size to the present study; however, the difference of medication adherence in different disease activities was found amongst the entire IBD population, and therefore included patients with UC. It is notable that UC is a much more homogenous disease than CD. On the contrary, a longitudinal study conducted by Mantzaris et al in a solely CD population with a smaller sample size of 30 patients did not find a significant relationship between medication adherence and clinical remission.⁷⁶ Studies examining medication

adherence and clinical remission in CD populations may be limited in their ability to detect a difference in part due to disease heterogeneity. Studies, including the present study, may also require larger sample sizes than examined in order to detect these differences.

When compared to other studies in CD that examined differences in medication use according to clinical disease activity (remission vs. active disease), there are several notable differences that likely contribute to the lack of significant findings in this study. First, key variables including disease location, disease severity, medication duration and dosage were closely associated with the clinical remission of CD and were able to be controlled for in the aforementioned studies. For example: Ho et al reported increased risk of treatment failure of corticosteroids in patients with fistulizing and stricturing CD at diagnosis;⁷⁷ Summers et al, Malchow et al, and Van Hees et al demonstrated 5-ASA at dosage between 3-6g/day to be a benefit over placebo in inducing remission in patients with mild to moderate CD;⁷⁸⁻⁸⁰ Finally, Patel et al provided evidence that low dose methotrexate (15mg/week) was superior to placebo for maintenance of remission in CD.²⁵ However, specific information about medication dosage and duration of use was not uniformly available in this study's dataset, thus limiting the ability of the present study to adjust for these factors. Information regarding disease location and severity was available; however, the present study could not account for these factors due to the small sample size.

Health Literacy Associated Differences in the Associations Between Medication Self-discontinuation and Clinical Remission of CD

Despite the lack of significant difference in medication self-discontinuation across health literacy levels, there was a significant difference in the clinical remission rate across health literacy level in this study sample (found in the IBD Health Literacy study). Therefore, it is reasonable to look at whether health literacy would impact the relationship between medication self-discontinuation and clinical remission. The results showed that there was no effect modification by health literacy in the associations between medication self-discontinuation and clinical remission of CD, meaning that there was no significant health literacy associated difference in these associations. The odds ratio was undetectable in patients who self-discontinued biologics and had limited health literacy because there were no patients in this subgroup in clinical remission. The odds ratios of thiopurine self-discontinuation in clinical remission were 1.0 (95%CI (0.10-9.12)) in limited health literacy and 0.57 (95%CI (0.04-14.16)) in adequate health literacy; however, the “crude estimator” (OR=0.55, 95%CI (0.11-2.81)) was not in between the stratum-specific odds ratios. In addition, the “crude estimator” (OR = 0.46, 95%CI (0.11-1.85), $p = 0.27$) of total medication self-discontinuation was not in between the stratum-specific odds ratios for adequate (OR = 0.5, 95%CI (0.06-4.62), $p = 0.51$) and limited health literacy subgroups (OR = 0.6, 95%CI (0.06-4.58), $p = 0.63$).

The observed trend in the association between medication self-discontinuation and clinical remission of CD did not vary according to health literacy level. The lack of significant health literacy-based differences may be due to the ambiguity of the term “self-discontinuation”, the small sample size of the present study or a true null result. In the case of the latter, it suggests that patients with both limited and adequate health literacy require support from health care providers throughout the treatment course. Health care providers not only need to consider patient preferences when prescribing medication, but also need to educate and engage patients in open communication about medication concerns, irrespective of health literacy. However, we hypothesize that the nature of the concerns, the support needed and the form in which this takes may vary according to health literacy, and further studies could seek to explore this.

Limitations

Several limitations related to sample size, assessments, confounders and analytic methods could affect the validity of the results. The small sample size limited statistical power, and thus reduced the chance of detecting a true effect. The small sample size of this study also limited the ability to control for various potential confounders. This might be the reason that the results have shown some trends that were reasonable in clinical care but not statistically significant. A sample size calculation and a power test were thus recommended in future analysis before initiating the study.

Another limitation would be the failure to control for factors that could potentially affect the associations investigated in this study. Race and education level are associated with health literacy. Caucasians and people who received a college education or above were found to have higher health literacy. Disease location, disease severity and disease-associated complications are critical when making treatment decisions.² Dosage of medications was also important and many prior studies have analyzed a medication dose-related association with CD remission.^{25,81} Route of administration can also affect patient's adherence to medications and the benefits of therapy.⁸² Time to initiation of immunomodulators could affect the efficacy of treatment for CD. Corticosteroids usually take 1-2 week to show benefits; therapeutic onset of thiopurines is about 12-17 weeks from initiation.^{11,14,15} The failure to control for these factors in the present study was due to multiple reasons. Some factors such as race, education level, disease location, disease severity and disease-associated complications, were collected but not analyzed because of small sample size; others were unavailable from the original dataset. The associations investigated in this study could either be strengthened or diminished if these factors are controlled.

Although the assessment of self-discontinuation can partially reflect medication adherence, it is still limited in the ability to accurately represent the actual conditions. Patients who may not have self-discontinued the medication, but could have been modifying the frequency of their use because of intolerance (i.e. - adverse effects) or self-titrating the dose to achieve a desired effect. These patients would not have been

captured as “self-discontinuing” their medication, but also would not meet the standard definition of “adherent”. The low specificity of self-discontinuation could reduce the observable difference in clinical remission between patients who self-discontinued the medication and who did not. There are many validated assessments of medication adherence in previous studies and one of them is Medication Possession Ratio (MPR). MPR is the sum of the days’ supply for all fills of a given drug in a certain period of time, divided by the numbers of days in this period.⁸³ If a patient missed a few refills during this period, then the MPR would be low; MPR would also be low if a patient self-discontinued the medication. Therefore, MPR has a wider coverage of medication adherence.

This study also failed to differentiate whether the patient was in an induction period or a maintenance period of remission. This is important because medications such as thiopurines and biologics can be used in both processes while other medications were more effective in one process than the other. Medication and clinical remission data were collected at one time point rather than longitudinally; it would be difficult for a cross sectional study to determine whether the patient is newly induced into remission or has been in the remission for a longer period of time. A longitudinal dataset would better describe such difference.

As the data of self-discontinuation was obtained from medical records by researchers in the Health Literacy IBD study, there was a risk of researcher bias in this

process. Even though the criteria for determining provider-directed discontinuation versus patient-directed discontinuation were predefined, the researchers might find it hard to determine the boundary between the two. There is a chance that the medical records showed that the patients stopped the medication because of patient-reported side effects, and one researcher consider it as a self-discontinuation while another researcher consider it as a suspension by the provider. If the number of these types of discrepancies is large enough, then there could be either an increase or a decrease in the effect of self-discontinuation on the clinical remission of CD.

Future Directions

Future studies are necessary to explore how health literacy affects the treatment and health outcomes in CD populations in order to support the results of present study. A larger sample size is a must in order to increase the power of detecting the differences of health literacy on medications and clinical remission of CD. Studies of the same design with a larger sample size need to adjust for several factors, including race, education, disease location, disease severity, disease-associated complications. A prospective cohort study on the differences of medication adherence between patients with limited and adequate health literacy specifically in CD is an option; a prospective or retrospective cohort study on the relationships of health literacy to self-discontinuation behaviors (intentional or nonintentional) in CD patients can be another choice. These studies would potentially help better understand the impact of variable health literacy on the treatment CD, and also improve the health care system to provide sufficient support for self-

management of medications. (i.e. – “Future studies involving patients at all levels of health literacy should consider using mixed methods to explore health system elements needed to address aspects of medication management support and shared decision making in order to achieve health equity.”)

Conclusions

This cross-sectional study investigated differences in medication use between CD patients with limited and adequate health literacy, differences in medication self-discontinuation between patients with and without clinical remission of CD, and health literacy associated differences in the association between medication self-discontinuation and clinical remission of CD. No significant health literacy associated differences were found in medication use, or between medication self-discontinuation and clinical remission of CD. Lack of differences in medication use between patients with limited and adequate health literacy suggests that effective medications are likely being used equally amongst limited and adequate health literacy subgroups in this population. The lack of a health literacy effect on the observable trend in the association between medication self-discontinuation and clinical remission of CD suggests that open communication and self-management support is needed for patients across all health literacy levels, though the most effective form of support may vary and needs further exploration. Despite limitations, the findings of this study offer valuable knowledge regarding health literacy associated differences in medication selection, medication self-discontinuation, and clinical disease activity in CD. This knowledge could be used to support future work to

optimize the efficacy of treatment for CD by improving health care system delivery support for patients across health literacy levels.

APPENDIX 1



Dear Healthcare Professional:

Thank you for your interest in the Newest Vital Sign (NVS), the first tool available to assess health literacy in English and Spanish.

Research shows that patients with low health literacy are less likely to comply with prescribed treatment and medical instructions from their physician. Identifying patients who are at risk for low health literacy allows physicians to apply specific clear health communication techniques that may enhance understanding. The Newest Vital Sign is a simple and fast way to identify those patients. The tool, which tests literacy skills for both numbers and words*, has been validated against a previously validated measure of health literacy (the TOFHLA), and has been shown to take approximately three minutes to administer.

In addition to the NVS tool, we are also including information to help enhance patient-provider communication. In this folder you will find the following materials:

- NVS Tool (nutrition label and scoring sheet tear-off pad, both two-sided in English/Spanish)
- NVS Implementation Guide
- *Ask Me 3* (fact sheet on free educational materials from the non-profit Partnership for Clear Health Communication)
- *Help Your Patients Succeed* (tips for improving communication with your patients)
- *Why Does An Ice Cream Label Work . . .* (fact sheet explaining the design of the NVS)

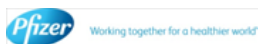
The Newest Vital Sign is Pfizer Inc's most recent contribution to the health literacy movement. For more than nine years, Pfizer has been committed to raising awareness of developing solutions for low health literacy. The overall goal of our Clear Health Communication Initiative is to positively impact the health care system by enhancing patient-provider communication to increase compliance and improve patient health outcomes.

The Newest Vital Sign and companion materials are available to medical and public health providers at no cost. To learn more about our efforts to improve health literacy, please visit www.pfizerhealthliteracy.com.

Sincerely,

Richard C. Hubbard, M.D.
Senior Director, External Medical Affairs
Pfizer Inc

*Literacy is defined as the understanding and application of words (prose), numbers (numeracy), and forms, etc. (document).



February 2011



Implementation Guide for the Newest Vital Sign

Health literacy— the ability to read, understand and act upon health information — is now known to be vital to good patient care and positive health outcomes. According to the Institute of Medicine’s groundbreaking report on health literacy, nearly half of all American adults — 90 million people — have difficulty understanding and using health information. When patients lack the ability to understand and act upon medical information, it can put their health at risk.

The Newest Vital Sign is a new tool designed to quickly and simply assess a patient’s health literacy skills. It can be administered in only 3 minutes and is available in English and Spanish. The patient is given a specially designed ice cream nutrition label to review and is asked a series of questions about it. Based on the number of correct answers, health care providers can assess the patient’s health literacy level and adjust the way they communicate to ensure patient understanding.

There are many ways to integrate the Newest Vital Sign (NVS) into a private practice or clinic setting to improve communication with patients. Improved communication can help increase your patients’ ability to understand and act upon the information you provide; ultimately improving patient satisfaction and health outcomes.

How To Use the Newest Vital Sign

1. Who and when to administer the Newest Vital Sign.

- **A nurse (or other trained clinic staff)** is the preferred administrator of the Newest Vital Sign.
- Administer at the same time that other vital signs are being taken.

2. Ask the patient to participate.

A useful way to ask the patient is an explanation similar to this:

“We are asking our patients to help us learn how well patients can understand the medical information that doctors give them. Would you be willing to help us by looking at some health information and then answering a few questions about that information? Your answers will help our doctors learn how to provide medical information in ways that patients will understand. It will only take about 3 minutes.”

3. Hand the nutrition label to the patient.

The patient can and should retain the nutrition label throughout administration of the Newest Vital Sign. The patient can refer to the label as often as desired.

More...

4. Start Asking the 6 questions, one by one, giving the patient as much time as needed to refer to the nutrition label to answer the questions.

- There is no maximum time allowed to answer the questions. The average time needed to complete all 6 questions is about 3 minutes. However, if a patient is still struggling with the first or second question after 2 or 3 minutes, the likelihood is that the patient has limited literacy and you can stop the assessment.
- **Ask the questions in sequence.** Continue even if the patient gets the first few questions wrong. However, **if question 5 is answered incorrectly, do not ask question 6.**
- **You can stop asking questions if a patient gets the first four correct.** With four correct responses, the patient almost certainly has adequate literacy.
- **Do not prompt patients who are unable to answer a question.** Prompting may jeopardize the accuracy of the test. Just say, “Well, then let’s go on to the next question.”
- **Do not show the score sheet to patients.** If they ask to see it, tell them that “I can’t show it to you because it contains the answers, and showing you the answers spoils the whole point of asking you the questions.”
- **Do not tell patients if they have answered correctly or incorrectly.** If patients ask, say something like: “I can’t show you the answers till you are finished, but for now you are doing fine. Now let’s go on to the next question.”

5. Score by giving 1 point for each correct answer (maximum 6 points).

- **Score of 0-1** suggests high likelihood (50% or more) of limited literacy.
- **Score of 2-3** indicates the possibility of limited literacy.
- **Score of 4-6** almost always indicates adequate literacy.

Record the NVS score in the patient’s medical record, preferably near other vital sign measures.

Best Practices for Implementation: Summary

- A nurse (or other trained clinic staff) is the preferred administrator of the Newest Vital Sign.
- Administer the NVS at the same time that the patient’s other vital signs are being taken.
- Record the NVS score in the patient’s chart, preferably near other vital sign measures.
- Tailor communication to ensure patient understanding.



Why Does an Ice Cream Label Work as a Predictor of the Ability To Understand Medical Instructions?

A patient's ability to read and analyze any kind of nutrition label requires the same analytical and conceptual skills that are needed to understand and follow a provider's medical instructions. The skills, which are known as *health literacy*, are defined as the understanding and application of words (prose), numbers (numeracy), and forms (documents).

The use of an ice cream label is especially relevant as recent research in the *American Journal of Preventive Medicine* (November 2006) has shown that poor comprehension of food labels correlated highly with low-level literacy and numeracy skills. However, the study found that even patients with better reading skills could have difficulties interpreting the labels.

Whether reading a food label or following medical instructions, patients need to:

- remember numbers and make mathematical calculations.
- identify and be mindful of different ingredients that could be potentially harmful to them.
- make decisions about their actions based on the given information.

PROSE LITERACY:

Clinical example: The patient has scheduled some blood tests and is instructed in writing to fast the night before the tests. The skill needed to follow this instruction is **Prose Literacy**.

Ice cream label example: The patient needs this skill to read the label and determine if he can eat the ice cream if he is allergic to peanuts.

NUMERACY:

Clinical example: A patient is given a prescription for a new medication that needs to be taken at a certain dosage twice a day. The skill needed to take the medication properly is **Numeracy**.

Ice cream label example: The patient needs this same skill to calculate how many calories are in a serving of ice cream.

DOCUMENT LITERACY:

Clinical example: The patient is told to buy a glucose meter and use it 30 minutes before each meal and before going to bed. If the number is higher than 200, he should call the office. The skill needed to follow this instruction is **Document Literacy**.

Ice cream label example: The patient needs this skill to identify the amount of saturated fat in a serving of ice cream and how it will affect his daily diet if he doesn't eat it.

Nutrition Facts

Serving Size $\frac{1}{2}$ cup
Servings per container 4

Amount per serving

Calories 250 Fat Cal 120

%DV

Total Fat 13g 20%

Sat Fat 9g 40%

Cholesterol 28mg 12%

Sodium 55mg 2%

Total Carbohydrate 30g 12%

Dietary Fiber 2g

Sugars 23g

Protein 4g 8%

*Percentage Daily Values (DV) are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.

Ingredients: Cream, Skim Milk, Liquid Sugar, Water, Egg Yolks, Brown Sugar, Milkfat, Peanut Oil, Sugar, Butter, Salt, Carrageenan, Vanilla Extract.

APPENDIX 2

For formulary coverage:

Harvey-Bradshaw Index (HBI) — A simple index of Crohn's disease activity¹

Patient name: _____

Date of HBI calculation: _____

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

1. General well-being (yesterday)	<input type="checkbox"/> Very well = 0 <input type="checkbox"/> Slightly below par = 1 <input type="checkbox"/> Poor = 2 <input type="checkbox"/> Very poor = 3 <input type="checkbox"/> Terrible = 4
2. Abdominal pain (yesterday)	<input type="checkbox"/> None = 0 <input type="checkbox"/> Mild = 1 <input type="checkbox"/> Moderate = 2 <input type="checkbox"/> Severe = 3
3. Number of liquid or soft stools per day (yesterday) = _____	
4. Abdominal mass	<input type="checkbox"/> None = 0 <input type="checkbox"/> Dubious = 1 <input type="checkbox"/> Definite = 2 <input type="checkbox"/> Definite and tender = 3
5. Complications (check any that apply; score one per item except for first box)	<input type="checkbox"/> None <input type="checkbox"/> Arthralgia <input type="checkbox"/> Uveitis <input type="checkbox"/> Erythema nodosum <input type="checkbox"/> Aphthous ulcers <input type="checkbox"/> Pyoderma gangrenosum <input type="checkbox"/> Anal fissure <input type="checkbox"/> New fistula <input type="checkbox"/> Abscess

Harvey-Bradshaw Index score²=

(please add scores of questions
1 through 5)

Remission	<5
Mild disease	5-7
Moderate disease	8-16
Severe disease	>16

References: 1. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet*. 1980;315(8167):514. 2. British Columbia Ministry of Health Services. Worksheet based on the Harvey-Bradshaw Index. British Columbia Ministry of Health Services website. <https://www.health.gov.bc.ca/exforms/pharmacare/5374fil.pdf>. Accessed September 23, 2010.

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APPENDIX 3

Unadjusted analysis on differences of medication selection at the time of visit in patients' disease activities (remission vs. active disease).

	Clinical Remission of CD (HBI<5)		
	OR	95%CI	P-value
(Intercept)* (n=14)	-	-	-
5-ASAs (n=5)	0.30	0.03-2.46	0.27
Immunomodulator** (n=6)	0.89	0.11-8.37	0.91

* Intercept represents patients who were on *biologics* monotherapy at the time of visit

** Immunomodulator include *methotrexate* and *thiopurines*

LIST OF JOURNAL ABBREVIATIONS

<p>Cev'Rcgf kcv".....Cev'Rcgf kcvlec="kvgtpcvkqpcn'lwtpcn'qh "....."Rcgf kcvleu"</p>	<p>Aliment Pharmacol Ther Alimentary Pharmacology & Therapeutics</p> <p>Am Heart J Ao gtlecp"J gctv'lwtpcn</p> <p>Am J Gastroenterol The American Journal of Gastroenterology</p> <p>Am J Health Behav American Journal of Health Behavior</p> <p>Am J Respir Crit Care Med Co gtlecp'lwtpcn'qh'T gur kcvqt { "cpf 'EtklecnEctg O gf kelpg"</p> <p>Ann Fam Med Annals of Family Medicine</p> <p>Arch Intern Med Archives of Internal Medicine</p> <p>Arthritis Res Ther Arthritis Research & Therapy</p> <p>Blood Press Monit Blood Pressure Monitoring</p> <p>Ecpegt "kpxguv".....Ecpegt "kpxguki cvkqp" "</p> <p>Clin Gastroenterol Hepatol Clinical Gastroenterology and Hepatology</p> <p>Cochrane Database Syst Rev The Cochrane Database of Systemcve Reviews</p> <p>Consult Pharm The Consultant Pharmacist: The Journal of the American Society of Consultant Pharmacistu</p> <p>Ewt't'J KXICF UTgr ".....Ewt'tgpv'J KXICF UTgr qtu" "</p> <p>Curr Opin Gastroenterol Current Opinion in Gastroenterology</p> <p>Dicdgyu'Gf ve The Dibetes Educator</p> <p>Dig Dis Digestive Diseaseu (Basel, Switerland)</p>
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Expert Rev Gastroenterol Hepatol	Expert Review of Gastroenterology & Hepatology
Expert Opin Pharmacother	Expert Opinion on Pharmacotherapy
Fam Med	Family Medicine
Inflamm Bowel Dis	Inflammatory Bowel Diseases
JAMA	Journal of the American Medical Association
J Adv Nurs	Journal of Advanced Nursing
J Crohns Colitis	Journal of Crohn's & Colitis
J Gen Intern Med	Journal of General Internal Medicine
J Pediatr	The Journal of Pediatrics
J Pediatr Gastroenterol Nutr	Journal of Pediatric Gastroenterology and Nutrition
Med Arh	Medicinski Arhiv
NEJM	New England Journal of Medicine
Natl Cent Educ Stat	National Center for Education Statistics
Respir Med	Respiratory Medicine
Ther Adv Chronic Dis	Therapeutic Advances in Chronic Disease
World J Gastroenterol	World Journal of Gastroenterology

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CURRICULUM VITAE

