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Behavioral Interventions may Prolong Remission in Patients with Inflammatory Bowel Disease

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Abstract

Inflammatory Bowel Diseases (IBDs) are chronic, relapsing and remitting gastrointestinal conditions with no known cure. Previous studies have linked behavioral factors, including stress and medication adherence, to relapse.

Purpose—We sought to determine the effect of participation in a behavioral self-management program on incidence of flare within 12 months following behavioral intervention when compared to the natural history of flare incidence prior to program participation.

Results—Results from a 2-level regression model indicated that those participants in the treatment group were 57% less likely to flare in the following 12 months (compared to 18% in the control group). The decline in “flare odds” was about 2 times greater in treatment versus controls (OR=.52, t(34)=2.07, p<.05). Office visits, ER visits, and disease severity (all p<.05) were identified as moderators of flare risk.

Conclusions—We have demonstrated 1) a statistical model estimating the likelihood of flare rates in the 12 months following a behavioral intervention for IBD (compared to a control condition), and 2) that the introduction of a behavioral intervention can alter the natural course of a chronic, relapsing and remitting gastrointestinal condition such as IBD.

Keywords

IBD; Crohn’s Disease; Ulcerative Colitis; Behavioral Self-Management; Hypnotherapy; Remission

Introduction

Inflammatory bowel disease (IBD) refers to digestive symptoms resulting from chronic inflammation in the gut. Crohn's disease (CD) and ulcerative colitis (UC) are two of the most common forms of this disease. IBDs affect as many as 3 million people in North America (Loftus, 2004; Shanahan & Bernstein, 2009) and cost more than $25,000 *per*

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person, per year in medical expenditures, absenteeism and lost productivity (Gibson et al., 2008; Longobardi & Bernstein, 2007). IBDs are usually diagnosed in young adulthood and therefore have a direct impact on psychosocial development (Feagan, Bala, Yan, Olson, & Hanauer, 2005; Marri, 2005; Rogala et al., 2008). The course of IBD is chronic and marked by unpredictable disease flares, which may occur either spontaneously or in response to external triggers(Hanauer, 2004; Levenstein et al., 2000). There is no cure for IBD and treatment is suboptimal because 40–60% of patients will not benefit from the currently available therapies which include corticosteroids, immunomodulators, biologic agents and surgery (Katz, 2008).

IBD differs from benign digestive disorders such as Irritable Bowel Syndrome and Functional Dyspepsia in that it involves an immuno-inflammatory response to common bacterial antigens found in the gut. The main difference between UC and CD is that the latter is limited to the colon whereas CD is systemic and can affect the entire gut mucosa from mouth to anus(Bernstein, Fried, et al., 2010). CD is also different from UC in that it can be associated with extraintestinal symptoms such as mouth sores, eye inflammation, joint pain and skin lesions (Bernstein, 2002). Similar to other immune-mediated chronic diseases like multiple sclerosis and rheumatoid arthritis, IBDs are characterized by periods of remission interspersed with periods of acute flare. During flare, symptoms include abdominal pain, cramping and urgent diarrhea. In remission, patients struggle with consequences of intestinal damage, including abdominal pain, discomfort and bloating (Sandborn, Feagan, & Lichtenstein, 2007). Disability and impaired function are not uncommon in IBD (Ananthakrishnan et al., 2008; Gibson, et al., 2008)— patients with severe disease have the most impaired quality of life and psychological distress (Walker et al., 2008). We have previously demonstrated that IBD patients who have difficulty adapting to disease-related demands also report more bowel and systemic symptoms, more pain, less engagement in activities, higher perceived stress, an emotional representation of illness and higher health care use (Kiebles, Doerfler, & Keefer, 2010).

While not directly linked to the etiology of the disease, psychological factors are believed to play some role in the course of IBD. Data support the role of psychological stress in promoting flare *directly* through immunological pathways (Bernstein, Singh, et al., 2010; Farhadi, 2005; Mawdsley, Macey, Feakins, Langmead, & Rampton, 2006; Singh, Graff, & Bernstein, 2009; Tache, 2004) and *indirectly* through behaviors known to promote relapse (Bitton, 2003) such as poor medication adherence (Higgins, Rubin, Kaulback, Schoenfield, & Kane, 2009), smoking (Singh, et al., 2009) and depression (Walker, et al., 2008).

While not a substitute for coordinated medical care, well-defined and comprehensive disease management behavioral interventions have the potential to *modify risk of relapse* in IBD. We have previously reported on the promising role of hypnotherapy on quality of life and self-efficacy in IBD (Keefer & Keshavarzian, 2007; Keefer et al., 2010). Other behavioral therapies have been tested in this population with mixed results (Keller, 2004; Kennedy et al., 2004; Schwarz & Blanchard, 1991) in part due to lack of endpoints focused on disease activity or course. To investigate whether behavioral interventions might directly impact the occurrence of disease flare, we reviewed the medical records of 36 patients who had undergone a behavioral self-management program at our center. Our aim was to 1) determine each individual's historical rate of relapse (occurrence of flare) prior to their participation in a behavioral self-management program and 2) determine whether the introduction of such a program might reduce the likelihood of relapse in the year following participation.

Patients and Methods

Study Design

For this study, we extracted data from two independent behavioral clinical trials running simultaneously at our center: the Ulcerative Colitis Relapse Prevention Trial (UCRPT) (Keefer, Kiebles, & Barrett, 2008) and the Crohn's Disease Self-Management Project (CDSM). Each trial was designed to assess disease activity following a brief, skills-based behavioral intervention (hypnotherapy for UC or cognitive-behavioral therapy [CBT] for CD respectively). The Institutional Review Board (IRB) at Northwestern University approved study procedures and all participants signed consent forms, including one allowing review of medical records. Additional methodological detail on UCRPT is reported elsewhere (Keefer, et al., 2010).

Participants

We recruited adult men and women (age 18–70) with endoscopically documented IBD to participate. Participants with UC enrolled in UCRPT (N = 31) and were randomized to either gut-directed hypnotherapy (HYP) or an active attention control (CON). Five participants with CD who had participated in the CDSM were randomized to either a cognitive-behavioral self-management treatment or wait list (with optional crossover).

Inclusion criteria were similar for each study and included a flare frequency of ≥ once per year, quiescent disease at time of baseline, a stable medication regimen (> 30 days), and 12 full months of study participation. Exclusion criteria included active disease, history of severe or fulminant IBD, comorbidities including IBS, renal or hepatic disease, history of colon resection/ostomy, short bowel syndrome, or indeterminate colitis, steroid dependency, smoking cessation ≤ 30 days and contraindications for behavioral intervention (e.g., cognitive impairment, past sexual abuse, serious mental illness).

Treatment Conditions

All participants completed a 7-session behavioral protocol targeting improved management of their IBD using techniques known to enhance stress management, disease / medication knowledge, coping and medication adherence. Both experimental treatments provided patients with an IBD self-management tool (i.e. hypnosis or cognitive-behavioral coping strategies). All protocols were standardized and conducted on an individual, outpatient basis at a GI clinic in an academic medical center. Doctoral level health psychologists (LK, JLK) administered treatment on a weekly basis for 45–60 minute sessions (totaling approximately 5–6 face-to-face hours). Participants in the UC study (N = 31) were randomized to either hypnosis or an active control (i.e. mind-body therapy), also facilitated by a doctoral level therapist. The hypnotherapy and mind-body conditions have been previously described (Keefer, et al., 2010). In both of the active treatment conditions (UCRPT and CDSM), participants practiced newly learned behavioral strategies at home between sessions over the course of treatment.

Study Review Period and Clinical Parameters

For each study participant who had completed the entire year long follow-up period, two blinded research assistants (EC, AV) reviewed medical records from the time of first encounter at Northwestern Medical Faculty Foundation (NMFF) through the time of study completion. Clinical data were summarized from the first encounter through the study start and end dates. The following clinical data was collected from participants' medical records: frequency of outpatient visits, hospitalizations, Emergency Room (ER) visits, GI-specific surgeries, documented psychiatric conditions, health-related behaviors (e.g., smoking and alcohol consumption), disease severity and disease self-management ratings by physician,

and presence of flare events before ("PRE") and after ("POST") behavioral intervention. As is customary for clinical trials in quiescent UC, patients were considered to have a new flare event when they experienced daily rectal bleeding for past 7 days, a Mayo Score > 2 or any Mayo subscale score > 1(G. D'Haens et al., 2007; Mesalamine Study Group, 1996). As is customary in clinical trials for CD, a flare event was defined as: Crohn's Disease Activity Index(Best, 1976) > 150 and 1) an increase from baseline CDAI > 70 points (Thia et al., 2008) and/or 2) an intensified medical regimen in response to symptoms(G. R. D'Haens et al., 2009)

Statistical Approach

Our statistician (ZM) was blind to study condition and performed statistical analyses using PASW18.0 for Windows (SPSS Inc., Chicago IL). Sample characteristics are described in terms of frequencies, central tendency and variability. Participants from the active treatment group from each study (N = 24) were considered as a whole. Participants from UCRPT who had completed the attention control condition past the year follow-up period were designated as CON (N = 12). CDSM did not have a useable control group because of its crossover design.

Flare State Analyses Using Hierarchical Linear Modeling (HLM)

Treatment (n=24) and control (n=12) groups were compared on "per month flare state probabilities" derived from a multi-level regression model with a logistic link function. Rates were based on monthly flare state data from periods ranging from 12 to 36 months prior to beginning treatment versus 12 months after beginning treatment.

Flare State Assessment

Flare state was determined based on patient presentation to clinic due to onset of blood in stool, urgency and bowel discomfort, and corroborated by physician rating of flare activity during physician visit. Physician rating of flare is customary in our group practice and is therefore well-characterized in the patient's medical chart. Consistent with disease activity standards for clinical trials in quiescent UC, patients were considered to have relapsed if they experienced daily rectal bleeding for past 7 days, a Mayo Score(Schroeder, Tremaine, & Ilstrup, 1987) > 2 or any subscale score > 1. As is customary in clinical trials for CD, relapse was defined as: Crohn's Disease Activity Index(CDAI)(Best, 1976) > 150 and 1) an increase from baseline CDAI > 70 points and/or 2) an intensified medical regimen in response to symptoms.

Flare states were assessed for varying time periods prior to beginning treatment (depending on the available period for review) for not more than 36 months (i.e., 36 × 30 days) prior to beginning treatment. All cases were assessed for at least 12 months (again, defined as 30 day periods). If the PRE review period started at the same time as the first recorded flare onset, the reviewed PRE period began after the end date of that flare (to prevent bias associated with starting measurement because of a first flare onset). The POST review period consisted of 12 consecutive monthly periods after beginning treatment or control protocols. Each period was scored for the presence/absence of any flare activity during that period.

Statistical Model

A 2-level regression model was used (HLM-2L). At a first level, variation in Per Month Flare State (PMFS, binomial) was predicted by Time (PRE months versus POST months) within person. Random, correlated intercept and slope components were included, and a logistic link function was used. At the second level, intercept and slope variation was modeled as a function of treatment (versus control, dummy coded).

Level 1 logit(PMFS) = Intercept + Slope(Time) + Error

Level 2 Intercept = B_{00} + B_{01} Treatment + Error

Slope = B_{10} + B_{11} Treatment + Error

Exploratory analyses were conducted evaluating the potential moderating effects of 9 baseline factors, based on patient historical data before starting treatment or control protocols.

1. Number of outpatient GI visits
2. Number of hospitalizations
3. Number of ER visits
4. Number of Surgeries
5. Presence of a Psychiatric Diagnosis (binomial)
6. Smoker (binomial)
7. Alcohol Use (rated 1=none, 2=occasional, 3=social, or 4=heavy)
8. Disease Severity (rated 1=mild, 2=moderate, 3=severe, and 4=fulminant)
9. Disease Self-Management (rate 1=proactive, 2=adequate, 3=minimal, 4=poor)

To evaluate moderators, linear main effects and interactions were added to the level 2 model, as follows. Each potential moderator was assessed separately (without controlling for other moderators).

Level 1 logit(PMFS) = Intercept + Slope(Time) + Error

Level 2 Intercept = B_{00} + B_{01} Treatment + B_{02}Moderator + B_{03}(Treatment × Moderator) + Error

Slope = B_{10} + B_{11} Treatment + Error + B_{12}Moderator + B_{13}(Treatment × Moderator) + Error

Results

In this sample (N=36), 19 participants were women (53%), 31 had UC (86%), and 21 were rated as having “moderate” to “severe” disease (58%). The mean age of the sample was 38.3 years (SD=11.5, range 20–69) and the mean length of time with disease was 10.1 years (SD=8.9, range <1–35). Time from diagnosis to first encounter at our faculty practice was 7.0 years (SD=7.7, range 0–32) with only 7 participants diagnosed within our practice. Average duration of flare lasted 8.4 weeks (SD=6.8, range <1–28). Twenty-eight were non-smokers (78%), 24 were rated as “social drinkers” by their physician (67%) and 27 had no known psychiatric disorders (75%). The average amount of time between time of first encounter at our practice through the time of study completion was 4.2 years (SD=2.5, range 1–10). Table 1 provides an overview of the clinical parameters included in the 2-level regression model across the entire review period (PRE and POST).

Between Groups Comparison of Per Month Flare Rates Following Behavioral Intervention

Table 2 reports estimated Per Month Flare Rates during PRE and POST periods based on the 2-level model described above. Full sample estimates are based on a model excluding the treatment predictor. Odds ratios comparing POST divided by PRE flare odds are reported for the full sample, and separately within control and treatment groups, with associated

inferential tests. These within group odds (for treatment over control) were also contrasted, and again, associated inferential tests are reported.

In the treatment group, per month flare state odds declined by 57% (OR=0.43, t(34)=4.01, p<.001). In terms of simple rates, this corresponds to a drop from 13.1% to 6.1%. The decline in per month flare odds was less substantial in the control group, decreasing by 18% (OR=0.82, t(34)=0.83, p=.414). In terms of simple rates, this corresponds to an estimated drop in monthly flare rates from 10.2% to 8.5%. Overall, the decline in flare odds was about 2 times greater in treatment versus control groups (OR = .52, t(34)=2.07, p=.046).

Exploratory Analyses of Potential Moderators of Flare Rate

Table 3 reports results of the exploratory evaluation of effects of potential moderators on the pre-treatment flare odds and the POST:PRE ratio in flare odds, overall, within groups, and contrasting treatment groups. Three moderators were positively correlated with high PRE-treatment flare odds. Not surprisingly, pre-treatment flare odds were positively associated with number of outpatient visits (OR=1.07, t(34)=2.12, p=.041), number of ER visits (OR=1.30, t(34)=2.91, p=.006), and physician rated disease severity (OR=1.56, t(34)=2.41), p=.022). Only one of these effects was significant within groups, specifically within the control group, disease severity was associated with higher flare odds (OR=3.04, t(32)=2.82, p=.008). The effect of disease severity on flare odds during the pre-treatment period was significantly lower in the treatment group versus control group (OR=0.39, t(32)=2.04, p=.049), but this effect seems attributable to type 1 error (as there is no apparent systematic distinction between treatment and control during the pre-treatment period).

Only 1 significant moderator effect on POST versus PRE odds was detected in a 3-way interaction. Specifically, the effect of number of outpatient visits on POST:PRE flare odds was significantly **higher** for treatment versus control cases (OR=1.31, t(32)=2.30, p=.028). As exploratory analyses yielded few significant effects at modest significant levels, and given the number of tests performed, these findings may be best regarded as inconclusive at present.

Discussion

We sought to determine whether behavioral therapy could prolong remission above and beyond traditional medical therapy in patients with IBD. We reviewed medical records of the patients who had participated in one of two behavioral trials at our Center in order to determine each individual's historical rate of relapse prior to their participation in a behavioral trial and whether the introduction of a behavior therapy, either gut-directed hypnotherapy or CBT reduced their individual likelihood of relapse in the year following the intervention. As predicted, patients who received a brief, targeted behavioral intervention experienced a 57% reduction in their risk to relapse over the following year. Patients who received supportive therapy (active control) which did not directly target behavioral risk factors for flare experienced a much smaller effect on risk to relapse (18%). The decline in risk to relapse in the control group is likely a result of participants' effort towards self-management and/or expectancy for improved disease management, both of which have been shown to positively affect outcome (Sandborn, 2006). Overall, the decline in flare odds was about 2 times greater in the treatment versus control groups underscoring the potential for behavioral interventions to have a direct impact on disease course.

While the mechanisms of hypnotherapy and CBT on maintenance of remission are speculative at this point, stress management and increased self-efficacy are two possible explanations of prolonged remission associated with behavioral intervention. This is supported in our previous report of hypnotherapy in UC (Keefer & Keshavarzian, 2007;

Keefer, et al., 2010). Seventy-five patients with IBD identify stress as a trigger of relapse (Lewis, 1998; Moser, 1993) which is consistent with data from several small prospective studies(Levenstein, 2002; Levenstein, et al., 2000) and animal models (Mawdsley, et al., 2006; Milde, 2004) (Million, 1999) (Elson, 2002; Kiliaan, 1998). To the extent that brief behavioral interventions could address stress and improve coping, it is possible that they could prolong remission and thereby improve quality of life. Of note, the behavioral interventions featured in this trial were administered over an 8 week period yet the consequences of the treatment were maintained over time. This has important implications for the cost-effectiveness of a self-management program on IBD outcomes.

Three moderators were positively correlated with high pre-treatment flare odds: number of outpatient visits, number of ER visits and physician rated disease severity. This suggests that behavioral interventions may be effective at reducing health care use, particularly emergency health care use and more broadly impacting disease activity. However, these data were part of an exploratory analysis and thus remain inconclusive.

Limitations

The retrospective nature of this study and its relatively small sample size are its most significant limitations. However, the effect we detected between the behavioral intervention and the control group was substantial enough to support further investigation. The other limitation was that we combined behavioral interventions without considering the independent aspects of each. The majority of participants underwent hypnotherapy (86%), and therefore this data may not be fully generalizable to CBT. Future studies should delineate hypnotherapy and CBT due to mechanistic differences between these two interventions. This approach could provide additional support for the role of behavioral interventions on relapsing and remitting diseases.

Summary and Conclusions

In this study, patients with Inflammatory Bowel Disease who had received a brief behavioral intervention targeting stress and disease self-management at our Center experienced a 57% reduction in their risk to relapse over the following year, twice that of the supportive therapy condition. While preliminary, these results support the implementation of behavioral self-management programs for individuals with Crohn’s Disease and Ulcerative Colitis as a way of altering disease course and improving quality of life.

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Table 1

Clinical parameters of the Northwestern IBD Risk to Flare Participant Pool (*N*=36)

VARIABLES	Mean	Median	Standard Deviation & Range
Number of outpatient visits	7.5	6.0	4.1, 2.0–19.0
Number of outpatient visits (per yr/per person)	*2.4*	*1.8*	*1.7, 0.3–6.2*
Number of hospitalizations	0.4	0.0	0.8, 0.0–3.0
Number of Emergency Room visits	0.3	0.0	1.0, 0.0–4.0
Number of GI-related surgeries	0.4	0.0	0.8, 0.0–3.0
Alcohol use rating by physician	2.6	3.0	0.6, 1.0–3.0
Disease severity rating by physician	1.7	2.0	0.7, 1.0–3.0
Disease self-management rating by physician	2.4	2.0	0.9, 1.0–4.0

Abbreviations: NMFF=Northwestern Medical Faculty Foundation

Key: Alcohol use rating: 1=none,rare, 2=occasional, 3=social, 4=heavy; Disease severity rating: 1=mild, 2=moderate, 3=severe, 4=fulminant; Disease self-management rating: 1=proactive, 2=adequate, 3=minimal, 4=poor

Table 2

Estimated per month flare state rates, with Post versus Pre odds ratios and inferential tests both within groups, and contrasting treatment and control groups (N = 36)

Sample		Per Month Flare Rate (%)		Post:Pre Within Group			Treatment: Control		
	N	Pre	Post	OR	t	p	OR	t	p
ALL	36	12.1	6.8	.53	−3.82	< .001			
Control	12	10.2	8.5	.82	−0.83	.414	0.52	−2.07	.046
Treatment	24	13.1	6.1	.43	−4.01	<.001			

Table 3

Exploratory evaluation of effects of potential moderators on Pre-treatment flare odds and Post:Pre ratio in flare odds, overall, within groups, and contrasting treatment groups.

Effect on Intercept (i.e. Pre-Treatment Flare Odds)								
Predictor	**ALL**		**Control**		**Treatment**		**TX:CON**	
	OR	**t(p)**	**OR**	**t(p)**	**OR**	**t(p)**	**OR**	**t(p)**
#OutpatientVisits	**1.07**	**2.12(.041)**	1.11	1.86(0.72)	1.06	1.39(.174)	0.96	−0.59(.561)
# Hospitalizations	1.01	0.10(.923)	2.20	1.18(.245)	0.92	−0.43(.673)	0.42	−1.26(.218)
# ER visits	**1.30**	**2.91(.006)**	1.48	1.93(.062)	1.16	0.75(.459)	0.79	−0.84(.405)
# Surgeries	1.10	0.51(.613)	0.66	−0.93(.359)	1.19	0.82(.416)	1.79	−1.19(.242)
PsychiatricDx(s)	1.67	2.01(.052)	2.20	1.20(.239)	1.46	0.98(.335)	0.66	−0.54(.596)
Smoking	1.10	0.41(.685)	1.04	0.18(.860)	1.04	0.18(.860)	*	*
Alcohol	1.09	0.39(.702)	1.00	0.01(.994)	1.19	0.56(.582)	1.19	0.40(.693)
Disease Severity	**1.56**	**2.41(.022)**	**3.04**	**2.82(.008)**	1.19	0.77(.450)	**0.39**	**−2.04(.049)**
Self-Management	1.29	1.43(.163)	1.97	1.71(.098)	1.15	0.65(.520)	0.58	−1.21(.237)
Effect on Slope (i.e. Post:Pre Ratio of Flare Odds)								
Predictor	ALL		Control		Treatment		TX:CON	
	OR	t(p)	OR	t(p)	OR	t(p)	OR	t(p)
# OutpatientVisits	1.00	−0.04(.968)	0.84	0.09(.927)	1.10	1.40(.171)	**1.31**	**2.30(.028)**
# Hospitalizations	0.88	−0.85(.400)	0.48	−0.71(.483)	1.01	0.04(.942)	2.10	0.69(.497)
# ER visits	0.87	−1.76(.087)	0.85	−0.51(.616)	0.76	−0.77(.448)	0.90	−0.22(.825)
# Surgeries	0.92	−0.21(.832)	0.82	−0.27(.788)	0.98	−0.06(.955)	1.20	0.22(.824)
Psychiatric Dx(s)	0.54	−1.75(0.89)	0.48	−0.72(.478)	0.63	−0.73(.469)	1.32	0.23(.816)
Smoking	1.01	0.03(.976)	1.23	0.70(.487)	1.23	0.70(.487)	*	*
Alcohol	0.81	−0.75(.460)	0.56	−1.38(.177)	0.74	−0.67(.511)	1.32	0.53(.603)
Disease Severity	1.26	0.91(.371)	0.60	−0.80(.428)	2.03	1.69(.100)	3.38	1.60(.119)
Self-Management	0.91	−0.41(.683)	0.61	−0.78(.443)	1.03	0.07(.944)	1.68	0.72(.480)

*no interaction possible due to invariance (N = 1 smoker in control)

**All predictors are scaled such that high scores correspond to “less healthy” scores.