Digital Behavioral Interventions in Inflammatory Bowel Disease

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1) Background/Significance

Crohn's disease and ulcerative colitis, together known as IBD, are conditions of chronic intestinal inflammation that often have a relapsing and remitting course in affected individuals. Historically, IBD was considered a condition almost exclusively affecting individuals of European ancestry, while IBD is now increasingly recognized in diverse populations. [1-3] Previous studies have shown worse clinical outcomes among African American and Hispanic IBD patients that has been attributed in part to psychosocial factors.[4,5]

Psychological distress specifically has been linked to increased disease activity in IBD.[6] A recent study, in fact, found evidence for bi-directional effects between IBD disease activity and psychological distress, whereby increased psychological distress exacerbates disease activity and vice versa.[7] Compared to healthy controls, individuals with IBD have increased prevalence of anxiety and depression: 9.6% versus 19.1% and 13.4% versus 21.2%, respectively.[8]

Given elevated levels of psychological distress and its relationship to disease activity in IBD, studies have promoted increased psychosocial screening though people of color are under-represented in these studies. For example, the NIH PROMIS measures are patient-reported outcome tools based on Item Response Theory and calibrated on large samples of the general population that have gained popularity for their rigorous testing.[9,10] PROMIS measures have been tested in IBD using disease-specific activity and HRQoL instruments with results suggesting construct validity.[11] Notably, however, the racial composition in one of the main trials was about 92% White and only 2-3% African American or Hispanic. As recent estimates of the prevalence of IBD in the US suggest that up to approximately 25% are people of color,[12] there is clearly under-representation of people of color in IBD psychosocial screening studies. It is also unclear whether people of color are adequately represented in studies focused on interventions to address psychological distress in IBD.

Among the proposed interventions to address psychological distress in IBD, cognitive behavioral therapy (CBT) has the most evidence of effectiveness.[13,14] CBT is a form of psychotherapy in which individuals are taught to identify and modify maladaptive thinking and behavior in order to improve their psychological status and coping skills. Results of previous studies suggest that the positive effects of CBT on depression symptoms and quality of life in IBD are experienced within subgroups of patients, such as those with elevated psychological distress, rather than unselected IBD patients. Of the few trials that make up the literature on this intervention in IBD, there is no mention of focusing on people of color.

In the largest trial using CBT in IBD patients, subjects were offered their choice of either in-person CBT or internet-based cognitive behavioral therapy (iCBT).[14] Nearly all participants chose iCBT, which is CBT delivered through a digital platform. Importantly, the mode of CBT delivery was not associated with the outcome in the trial, suggesting that patients who use iCBT derive similar benefits as those receiving in-person CBT. Results of the trial indicated that quality of life was significantly improved only among the select group of those classified at baseline as "in need" (e.g. high IBD disease activity, poor mental health). The study was not designed to test the effect of iCBT in patients specifically with psychological distress and further research is needed to test iCBT among these individuals. Notably, the racial demographics of this trial were not specified.

2) Study Design

We propose a 1:1 randomized trial design to evaluate the efficacy of iCBT among a population of Black and Latinx IBD patients and to assess factors influencing its implementation. Patients within our integrated health system at Montefiore Medical Center will be actively recruited and screened to identify those with elevated psychological distress. Eligible patients will be randomized to receive 4~~8~~ weeks of iCBT or digital mood tracking to evaluate the effect of iCBT on levels of psychological distress, HRQoL and disease activity post-intervention. We will also evaluate individual and process level barriers and facilitators to iCBT implementation via surveys and semi-structured interviews. The study objectives will be achieved through the following specific aims:

Aim 1: Investigate the efficacy of iCBT among Black and Latinx IBD patients with elevated psychological distress

We predict that compared to those who receive digital mood tracking, patients who are allocated to iCBT will have (a) lower psychological distress, as measured by the National Institutes of Health (NIH) Patient Reported Outcomes Measurement Information System (PROMIS) anxiety and depression scores and NIH Toolbox Perceived Stress Scale scores, (b) higher HRQoL on overall PROMIS-29 scores and (c) lower disease activity, as measured by patient-reported disease activity indices.

Aim 2: Evaluate implementation of iCBT among Black and Latinx IBD patients

We predict that (a) behavioral factors, such as elevated psychological distress, high self-efficacy, coping, and spirituality will be the strongest predictors of acceptance of iCBT and that other factors such as younger age, higher educational attainment, recent IBD diagnosis, and high disease activity will be associated with higher iCBT use and (b) modifiable individual and process level barriers and facilitators of iCBT use will be identified.

Participants will have IBD and elevated psychological distress and be recruited from the two outpatient clinical sites where the research physician and senior key personnel practice. The total estimated IBD population with clinical visits at Einstein/Montefiore is approximately 1,200 patients. In an average week, about 34 unique IBD patients receive care at one of the two study sites of which about 19% are Black and 30% are Latinx. About 85% have internet access, using active patient portal registration in the electronic medical record as a rough proxy. Based on estimates from the literature, the prevalence of anxiety or depression in IBD is around 20% and up to 66% with active disease.[8] Thus, we estimate that on a weekly basis at least 6 and up to 22 Black or Latinx IBD patients attending a study site will have elevated anxiety or depression.

All consenting participants will complete a baseline questionnaire. Eligible participants will undergo 1:1 randomization using computer-generated variable 2 and 4 block allocation to either the iCBT or the digital mood tracking study arm. Allocation sequence will be concealed from the study team using opaque sealed envelopes. At the time of participant consent, the research physician will select the next consecutive envelope that will determine participant group assignment to either iCBT or digital mood tracking. All participants will receive a one-page brochure on mental health recommendations from the National Institute of Mental Health. Participants initially randomized to the digital mood tracking app will be offered ~~8~~4 weeks of iCBT after completing the post-intervention study assessment/interview.

The digital mood tracking application (app) selected for this study (Pixel™) allows participants to log their mood each day by way of a facial expression emoji and a free-text box. This app is commercially available free of charge through iOS and Android app stores with English and Spanish language options.

The iCBT platform selected for use in this study (Sanvello™) is an evidence-based mobile app created by clinical experts that has been shown to decrease depression, anxiety, and stress and to increase self-efficacy in a non-IBD population.[15] App features include: daily mood tracking; guided journeys (e.g. psychoeducational content providing background information about cognitive behavioral therapy and instructing users on how to use app tools to maintain motivation and interest); coping tools (e.g. meditation, goal setting, and negative thought redirecting activities); weekly progress assessments; community support board. Study participants will receive a 2-month subscription for the app. Subscription is covered by

various health insurance plans. The cost for individuals who do not qualify for health insurance coverage will come from the study budget. Participants will be instructed to export from the app a weekly data use report to the research physician's Montefiore email. ~~The research physician will be linked to participant usage and progress through the app.~~ There is an emergency resources section within the app that includes information on crisis help-lines and other resources for users in emergency situations. The app is available for use in iOS and Android systems as well as online through any web browser. App content is available in English with text translations in Spanish.

All participants will receive a unique link to complete a follow-up questionnaire at 4~~8~~ weeks post intervention (Table 1). Non-responders will receive a reminder phone call twice weekly for 2 weeks and thereafter be considered lost to follow-up.

Table 1. Timeline and Sources of Data

Baseline - REDCap Questionnaire (completed by patient at office visit or remotely)		
Socio-demographics	**Assessment Tools**	**Clinical features**
▪ Age ▪ Race/ethnicity ▪ Sex ▪ Birthplace ▪ Primary language ▪ Educational attainment ▪ Employment status ▪ Health insurance ▪ Marital status	▪ IBD disease activity index: Short Crohn's Disease Activity Index for Crohn's disease *or* Simple Clinical Colitis Activity Index for ulcerative colitis ▪ PROMIS-29 ▪ Perceived Stress Scale ▪ PROMIS Self-efficacy Managing Emotions ▪ PhenX Toolkit – Spirituality ▪ Brief Resilient Coping Scale	▪ IBD phenotype ▪ Disease duration ▪ IBD medications ▪ Previous/current psychiatric diagnosis, suicidal ideation or hospitalization
Follow-up at ~~8~~4 weeks REDCap Questionnaire (completed by patient remotely)		
	Assessment Tools	
	▪ IBD disease activity index: Short Crohn's Disease Activity Index for Crohn's disease *or* Simple Clinical Colitis Activity Index for ulcerative colitis ▪ PROMIS-29 ▪ Perceived Stress Scale ▪ PROMIS Self-efficacy Managing Emotions	

3) **Study Population**

We aim to recruit 25 patients in each study arm for a total of 50 participants. Eligibility will be restricted to:

- age ≥ 18 years
- race/ethnicity self-identified as Black/African American or Hispanic/Latinx
- established diagnosis of Crohn's disease or ulcerative colitis
- elevated psychological distress: at least one T-score within two standard deviations above the mean in the domains of anxiety or depression on the National Institutes of Health Patient Reported Outcomes Measurement Information System-29 (PROMIS-29) with or without a T-score within two standard deviations above the mean for perceived stress on the National Institute of Health Toolbox Perceived Stress Scale (Perceived Stress Scale)
- internet access (smartphone/mobile device with data plan, computer with internet)
- ability to provide informed consent in English or Spanish

Exclusion criteria are:

- PROMIS-29 anxiety or depression T-scores in the severe range (above 2 standard deviations)
- Current suicidal ideation, past suicidal attempt or hospitalization

4) Participant Recruitment

Recruitment will be active and occur during in-person study site visits. If in-person visits are not possible (e.g. ongoing public health crisis), recruitment will occur via telemedicine visits. All IBD patients will be invited to participate. We anticipate enrolling 1-2 participants weekly into the trial.

For patients recruited during an in-person visit, the research physician/assistant will approach patients during their visit who meet the screening questions (based on age, race/ethnicity, diagnosis of IBD, internet access) to confirm eligibility. After the informed consent process, patients will complete a study questionnaire via a REDCap survey on a study site computer. Responses to this initial questionnaire will determine eligibility for randomization into the study based on the inclusion/exclusion criteria. Upon completion of the questionnaire, computer-automated scores will be generated. Patients with severe psychiatric distress or suicidality will be linked to psychiatric services at Montefiore. The research physician/assistant will inform patients of their eligibility to be randomized into the trial.

In the event in-person visits are not possible, patients will be recruited at the time of a telemedicine visit and asked the same initial screening questions to confirm eligibility. The informed consent process would take place over the telephone (see next section for details), and patients will be sent a unique link to the REDCap survey. Patients completing the questionnaire outside of an in-person visit will access and complete it on their own personal device. The research physician will receive a daily report of newly completed questionnaires to ensure adequate follow-up. Patients with severe psychiatric distress or suicidality will be linked to psychiatric services at Montefiore. The research physician/assistant will inform patients of their eligibility to be randomized into the trial.

5) Informed Consent

Patients eligible for inclusion in the trial after confirmation of initial screening factors (age, race/ethnicity, diagnosis of IBD, internet access) will undergo an informed consent process using the attached consent form that includes discussion of study procedures, risks and benefits. The research physician/assistant will perform the informed consent process at the time of an office visit. If in-person office visits are not possible, patients will receive a copy of the informed consent form (emailed) in advance of the informed consent process, which would be conducted over the telephone by the research physician/assistant.

Participants may receive a total of $40 for completing the two study questionnaires. They will receive a $20 gift card for completing a questionnaire at the beginning of the study and another $20 gift card if they complete a questionnaire at the end of the study.

6) Risk/Benefit

Risks of the study include a loss of confidentiality or privacy. Only the research study team will have access to study related documents and participants questionnaires. Study documents in a paper form will be stored in a study binder in a locked cabinet in the research physician's office and accessed only by the research team. Study documents in digital form will be password protected and accessed only by the study team. Study questionnaires will be stored on the secure password protected online platform REDCap. Only the study team will have REDCap access to the study questionnaires.

Other risks of the study are the risk of discomfort or distress answering questions about mental health and discomfort or distress addressing mental health through a digital platform. It will be made clear to participants that they may choose not to answer any questions they feel uncomfortable with and that use of the iCBT application is completely voluntary. Participants are also directed to seek immediate medical attention in case of any severe psychological distress e.g. suicidality. The research physician will have a password-protected provider interface to the iCBT platform that enables aggregate information regarding individual participant iCBT data usage.

7) Data Analysis

Aim 1: Investigate the efficacy of iCBT among Black and Latinx IBD patients with elevated psychological distress

The primary outcome will be the level of psychological distress (scores in the domains of anxiety and/or depression on the PROMIS-29 assessment tool) at ~~8~~4 weeks between study arms. PROMIS-29 is a 29-item form that includes 4 questions in each of the domains of anxiety and depression.[16] Higher scores indicate a greater level of the measured trait, and raw scores are converted to a T-score that centers at a mean of 50 with a standard deviation of 10 in the general population. The minimum clinically significant change in the domains of anxiety and depression has been shown to be 2.3-5.5 points.[17,18] The other PROMIS-29 domains of physical function, fatigue, sleep disturbance, ability to participate in social roles, pain intensity and interference together give a measure of HRQoL.

Secondary outcomes will be the change in perceived stress, overall HRQoL and IBD disease activity. Perceived stress will be measured with the 10-item Perceived Stress Scale. Like PROMIS-29, higher scores indicate a higher level of the measured trait, and raw scores are converted to a T-score. The overall HRQoL will be measured with the PROMIS-29 including the non-anxiety/depression domains. Disease activity will be measured by the Short Crohn's Activity Index (for participants with Crohn's disease) or Mayo sub-scores (for participants with ulcerative colitis).

Primary analysis will be by intention-to-treat with participants analyzed in the group to which they were randomized. We will use descriptive statistics to summarize socio-demographic and disease characteristics of both study groups and of app usage in the iCBT group: number of modules completed; weekly time spent on app; participation in community support groups. Our primary hypothesis is that participants in the iCBT group will have lower psychological distress scores compared to those in the digital mood tracking group post-intervention. To test the association between psychological distress (T-score for anxiety, depression) and study group, we will use Student's t-test if the normality assumption is met, or the Mann-Whitney U test if normality is appreciably violated. Assuming a minimum clinically significant change of a 5.5 points difference in T-scores between study groups with a standard deviation of ± 6 points, a sample size of 40 participants (20 in each arm) will be needed to have 80% power at an alpha of 0.05. Targeting a recruitment sample size of 50 participants (25 in each arm) would allow for roughly 20% drop-out rate.

Our secondary hypotheses are that participants in the iCBT group will have lower perceived stress scores and higher HRQoL. To test these hypotheses, we will again use Student's t-test if the normality assumption is met or the Mann-Whitney U test if normality is appreciably violated. Finally, we hypothesize that elevated disease activity at baseline (Short Crohn's Disease Activity Index ≥ 150 or Mayo sub-scores ≥ 2) will be associated with achieving a minimum clinically significant change in T-score. To test the association between high baseline disease activity and minimum clinically significant change (as a dichotomous outcome), we will perform Chi-squared or Fisher's exact test.

Aim 2: Evaluate implementation of iCBT among Black and Latinx IBD patients

Participants randomized to iCBT will complete a survey as part of their follow-up assessment at ~~8~~4 weeks to evaluate their acceptance of and satisfaction with iCBT. Participants will have the option to complete the post-intervention survey at the study site or off-site on their own personal device. Survey responses will be recorded and stored in REDCap. Participants will be asked a series of questions aimed at evaluating attitudes about receiving psychotherapy via a mobile application and how useful they found iCBT. Likert scale from strongly agree to strongly disagree will be used. At the end of the survey, participants will be invited to participate in semi-structured interviews. The interviews will be conducted by the research physician to elicit personal and logistical factors that may have influenced participant iCBT use.

Post-intervention surveys will be categorized with respect to level of participant acceptance of iCBT, while app usage will be analyzed as continuous (e.g. time spent on

app) and categorical (e.g. used during all 4~~8~~ weeks). We hypothesize that participants more likely to accept iCBT will be those with: high self-efficacy (T-score above the mean of 50) compared to low self-efficacy (T-score at or below the mean of 50); high coping (Brief Resilient Coping Scale score ≥ 17) compared to low coping (score < 17); high spirituality (score ≥ 16) compared to low spirituality (score < 16); younger age (less than 40 years) compared to older age (at or over 40 years); higher educational attainment (high school graduate) compared to lower educational attainment (less than high school); recently diagnosed (within 2 years) compared to longstanding disease (over 2 years); and high disease activity (Short Crohn's Disease Activity Index ≥ 150 or Mayo sub-scores ≥ 2) compared to low disease activity (Short Crohn's Disease Activity Index < 150 or Mayo sub-scores < 2). We will use descriptive statistics to summarize behavioral, socio-demographic and clinical factors associated with iCBT acceptance and greater app usage, and we will perform Chi-squared or Fischer's exact tests to examine the associations. Interview responses will be examined for themes, and individual and process level barriers and facilitators to iCBT use will be summarized with respect to potentially modifiable features.

8) Data quality control and database management.

All study questionnaire responses will be entered and stored on REDCap, which will be password protected and accessed only by the research study team. Deidentified data from REDCap will be exported and analyzed on statistical software (e.g. Stata).

9) Data Safety Monitoring – this is REQUIRED for greater than minimal risk research - researchers can be alerted to use our policy here as guidance
https://www.einstein.yu.edu/docs/administration/institutional-review-board/policies/dsm.pdf
See attached document

10) References:

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