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To cite this article: Kathryn L. Prendergast, Marissa A. Gowe, Margaux J. Barnes, Caroline V. Keller, Caitlin Horne & John Young (2022) Treating anxiety and depression in inflammatory bowel disease: a systematic review, *Psychology & Health*, 37:1, 105-130, DOI: [10.1080/08870446.2020.1867135](https://doi.org/10.1080/08870446.2020.1867135)

To link to this article: <https://doi.org/10.1080/08870446.2020.1867135>



Published online: 26 Jan 2021.



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Treating anxiety and depression in inflammatory bowel disease: a systematic review

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ABSTRACT

Objective: Inflammatory Bowel Disease (IBD) is associated with higher rates of clinically significant anxiety and depression than in healthy populations. Psychosocial interventions targeting anxiety and depression in IBD have variable efficacy and disparate treatment approaches, making treatment recommendations difficult. The current study aimed to identify effective treatment components across psychosocial treatment approaches for anxiety and depression in IBD.

Design: A systematic review of psychosocial treatments for anxiety and depression in IBD was conducted. Based on the Distillation and Matching Model, treatments were coded and data aggregated by intervention components, or practice elements (PE), to elucidate replicable clinical techniques.

Main Outcome: The percentage of studies utilizing a given PE was the primary outcome.

Measures: Among all included studies, as well as among those finding favorable, significant effects on anxiety or depression, the percentage utilizing each PE and number of PEs utilized was determined.

Results: The most utilized PEs among included interventions were relaxation, IBD psychoeducation, cognitive restructuring, distraction, and social skills. Examining only interventions with favorable differences on specified outcomes (HRQoL, Anxiety, Depression, and/or Coping) indicated that relaxation, education, cognitive restructuring, and mindfulness were most utilized.

Conclusion: Implications for clinical practice are discussed, including the development and dissemination of treatment recommendations.

Abbreviations: IBD: Inflammatory Bowel Disease; HRQoL: Health Related Quality of Life; PE: Practice Element; CD: Crohn's Disease; UC: Ulcerative Colitis; DMM: Distillation and Matching Model; CBT: Cognitive Behavior Therapy; SFT: Solution Focused Therapy



ARTICLE HISTORY

Received 12 May 2020

Accepted 16 December 2020

KEYWORDS

Inflammatory bowel disease; anxiety; depression; treatment; systematic review

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Introduction

Inflammatory Bowel Disease (IBD) affects approximately 3 million US adults (Centers for Disease Control and Prevention, 2018). These diseases, including Crohn's Disease (CD) and Ulcerative Colitis (UC), develop due to chronic inflammation of the digestive tract commonly leading to diarrhea, abdominal pain, weight loss, nausea, and urgent bowel movements (NIH, 2014, 2017). Both conditions are characterized by periods of active disease followed by remission that may last from several weeks to years. A growing body of research has examined the association between physiological symptoms of IBD and the development of psychosocial difficulties. Specifically, it has been noted that emotional symptoms including anxiety and depression occur more frequently in individuals with IBD as compared to healthy peers (Greenley et al., 2010; Mackner et al., 2006; Mikocka-Walus et al., 2016). This may be due in part to high rates of maladaptive coping among individuals with IBD associated with poor disease outcomes and health-related quality of life (HRQoL; Danesh et al., 2015; Faust et al., 2012; Freitas et al., 2015; Mikocka-Walus et al., 2016; van Tilburg et al., 2015). Given these relations, researchers have begun to develop behavioral interventions that target the psychosocial comorbidities associated with IBD in pursuit of improving HRQoL and disease outcomes.

Anxiety, depression, and associated factors in IBD

Recent research has pointed toward a heightened prevalence of anxiety and depression in individuals diagnosed with IBD, reporting 19.1–21.1% with anxiety and 21.2–25.5% with depression, compared to 9.6% with anxiety and 13.4% with depression in healthy controls (Byrne et al., 2017; Mackner et al., 2006; Mikocka-Walus et al., 2016). The literature has also found higher rates of maladaptive coping in individuals with IBD, that in turn are associated with greater anxiety and depression, decreased quality of life (QoL), risk of active disease, and functional disability (Danesh et al., 2015; Faust et al., 2012; Freitas et al., 2015; Mikocka-Walus, et al., 2016; van Tilburg et al., 2015). Evidence further suggests that both maladaptive coping and depressive symptoms partially explain the relations between stressors and abdominal-pain distress in IBD (Reed-Knight et al., 2018), as do anxiety and depression independently (Mikocka-Walus et al., 2016).

A detailed review of additional factors associated with individual level of adjustment among people suffering from IBD indicated several other constructs involved in the etiology and maintenance of emotional difficulties (Jordan, Sin, Fear, & Chalder, 2016). These included gender (with females being at higher risk in some studies), personality variables (e.g. neuroticism), stress (i.e. perception of stress and coping strategies), emotions (e.g. alexithymia; self-consciousness; active emotional control), and maladaptive cognitions. The latter could be further subdivided into those cognitions related to IBD (e.g. perception of stigma for disease; lack of social support; health beliefs indicated severe outcomes) and more general cognitive errors likely to result to maladjustment and/or emotional duress (e.g. hopelessness; negative self-concept). The review particularly noted that negative emotion focused methods of coping with stress (i.e. avoidance or aggression) were particularly associated with negative

outcomes in terms of psychological distress and HRQoL. Given these associations, interventions targeting emotional symptoms in IBD have emphasized adaptive coping techniques for improving anxiety and depression as well as related factors of disability, risk of disease activity, and HRQoL (Ballou & Keefer, 2017; Mikocka-Walus et al., 2015; Yeh et al., 2017).

Health related quality of life (HRQoL)

The Centers for Disease Control (CDC) defines HRQoL as an individual's perceived psychological and physical health status across time (Centers for Disease Control and Prevention, 2000). Individuals with IBD report lower HRQoL than healthy individuals, and those with comorbid anxiety or depression report lower HRQoL than those without these emotional comorbidities (Faust et al., 2012; Magalhães et al., 2014). Impaired HRQoL in chronic illnesses can have negative psychosocial and interpersonal correlates on the individual level such as less adaptive coping strategies (e.g. lack of cognitive restructuring), poor body image, and poor relationships (Megari, 2013). From a societal standpoint, HRQoL is measured by the CDC to identify groups experiencing impairment and allocate effective public health programming aiming to prevent future disease or alleviate disease burden. Thus, impaired HRQoL is concerning not only because of the individual burden associated with emotional duress, but also because lower HRQoL in IBD has been linked with higher instance of emergency department visits and hospitalization (Regueiro et al., 2016), and thus higher longitudinal costs for sustained treatment. Given the associations between lower HRQoL, increased health-care utilization, and higher anxiety and depression in IBD populations, psychosocial treatment studies in this population have targeted HRQoL as a related outcome (Ballou & Keefer, 2017; Mikocka-Walus et al., 2015).

Disease activity

Disease activity is commonly studied as a factor related to emotional symptoms in IBD due to the heightened prevalence of anxiety and depression during and/or immediately preceding active states of the disease (Mikocka-Walus et al., 2016). For example, a recent study reported 66.4% of patients with active IBD vs. 28.2% of patients with inactive IBD indicated clinically significant anxiety symptoms, while 34.7% of patients with active IBD vs. 19.9% of patients with inactive IBD indicated clinically significant depressive symptoms (Mikocka-Walus et al., 2016). Additionally, active disease state is cross-sectionally associated with a four-fold risk of anxiety and depression in adult populations (Byrne et al., 2017; Mackner et al., 2006). Greater anxiety severity and/or depressed mood has also been associated with higher rates of relapse in terms of disease activity (Freitas et al., 2015; Mikocka-Walus, Pittet et al., 2016). The directionality of this relationship is yet unclear, and future research elucidating the causes of this association is warranted for treatment improvement.

Anxiety & depression treatment in IBD

There is great heterogeneity in the literature on treating anxiety and depression in IBD. Intervention studies, including pilot studies and randomized controlled trials (RCTs) targeting anxiety and depression in IBD, typically employ a wide range of measures and focus on a diverse array of outcome variables (Berrill et al., 2014; Reigada et al., 2013; Schoultz et al., 2015; Thompson et al. 2012). Additionally, as noted by Jordan, Ohlsen, Hayee, and Chalder (2018), the vast majority of existing trials have been conducted in samples of individuals who exhibited only subclinical emotional symptoms at treatment onset (thus potentially limiting the effects of intervention and biasing overall interpretation of treatment efficacy). To further compound systematic understanding of the extant literature, review studies have also been confounded by high variability of therapeutic approaches implemented in previous research. Some have classified disparate treatments as one broad category such as ‘psychotherapies’ (Timmer et al., 2011; Yeh et al., 2017), whereas others have examined disparate treatment types separately but noted limited evidence to recommend one intervention type over another (Ballou & Keefer, 2017; Goodhand et al., 2009; Knowles et al., 2013; McCombie et al., 2013; Von Wietersheim & Kessler, 2006). Examples of the heterogeneous set of interventions examined in the literature include Cognitive Behavioral Therapy (CBT), Solution-Focused Therapy (SFT), mindfulness-based therapies, relaxation, hypnosis, and psychodynamic therapies (Ballou & Keefer, 2017; Goodhand et al., 2009; Knowles et al., 2013; McCombie et al. 2013; Von Wietersheim & Kessler, 2006). There is mixed evidence for each of these treatment modalities despite robust support for the use of CBT, SFT, mindfulness, and relaxation for other chronic illness populations. Because of the lack of consensus for a superior treatment type, but some support for intervention more generally, aggregating the current evidence at the level of individual treatment techniques may be advantageous.

Practice elements & the distillation and matching model

‘Practice element’ (PE), defined as an individual technique entailed in multi-component interventions, is a term derived from the Distillation and Matching Model for evaluating large bodies of research findings (DMM; Chorpita & Daleiden, 2009). The DMM considers PEs as the units of analyses to facilitate aggregation of findings across treatment orientations. Chorpita and Daleiden (2009) applied the model across major mental health diagnoses in children and adolescents and were able to produce practice profiles linking evidentiary treatments to specific targets (irrespective of the theoretical orientation or branding of any specific treatment package). To our knowledge, no literature has yet to examine health psychology interventions using this model. In a burgeoning field with numerous disparate theoretical and practical approaches to treatment, understanding which individual techniques are associated with patient improvement would be useful in the selection and implementation of clinical interventions. Further, discerning individual PEs would potentially decrease some of the ambiguity in existing research between various theoretical approaches. As such, the purpose of this review is to aggregate findings of existing studies examining the efficacy of psychological treatment of anxiety and depression in IBD by analyzing PEs

(criteria delineated below) across broad treatment types. The results are also presented to facilitate clinical application, particularly in terms of informing readers of which PEs are most frequently associated with successful interventions.

Methods

Types of studies

Inclusion criteria were studies that (1) were published in a peer-reviewed journal as a paper or abstract with discernible eligibility criteria; (2) investigated the effect of a psychological intervention (i.e. the manipulation utilized at least one identified practice element with an accessible description), on anxiety, depression, and/or coping (3) were controlled evaluations of efficacy/effectiveness; (4) focused on populations with CD, UC, or combined UC and CD; (5) utilized group by time analyses or multi-level modeling equivalent; and (6) were written in English or Spanish. Among studies meeting these criteria the exclusion criteria were 1) a complete lack of practice description (i.e. no PEs could be discerned from the study's description) and 2) the reported data were from the same intervention as another included paper. In the case of multiple papers from the same intervention, the paper most relevant to the endpoints of the present review and most recent was considered the primary paper for inclusion and all other study papers were used as supplements during data extraction. The endpoints of anxiety, depression, and/or coping were selected as inclusion criteria over HRQoL and disease activity. This was due to studies investigating the effect of an intervention solely on HRQoL and/or disease activity often not explicitly targeting anxiety and depressive symptoms (i.e. investigated the effect of a psychological intervention on pain or fatigue regardless of anxiety or depression). These criteria were selected to elucidate the highest caliber of evidence for treatment related to anxiety and depression in IBD, in lieu of including poorer quality designs and accounting for study quality.

Search strategy

The primary investigator (KP), CK, and CH searched PSYCinfo, PubMed, Alt HealthWatch, Cochrane Library, and ScienceDirect, using the following terms: psychosocial intervention IBD, CBT IBD, psychotherapy IBD, anxiety intervention IBD, depression intervention IBD, mindfulness intervention IBD, acceptance-based intervention IBD. Within all databases, 'peer-reviewed' was selected for, within Cochrane Library, 'embase' was selected to reduce overlap with Pubmed, and finally within ScienceDirect 'research articles' was selected to reduce irrelevant sources and because selecting 'peer-reviewed' was not an option. Databases were searched through May 2019 with no specified start date. Other sources included additional records identified through previous reviews (found in database searching) and references offered by MG and MB. This search strategy was agreed upon by all authors, although no review protocol was registered. These sources led to 1,363 records after duplicates were removed, the titles and abstracts of which were reviewed for consistency with the goals of the current study twice (once by KP, and once by CK or CH), to ensure rigor.

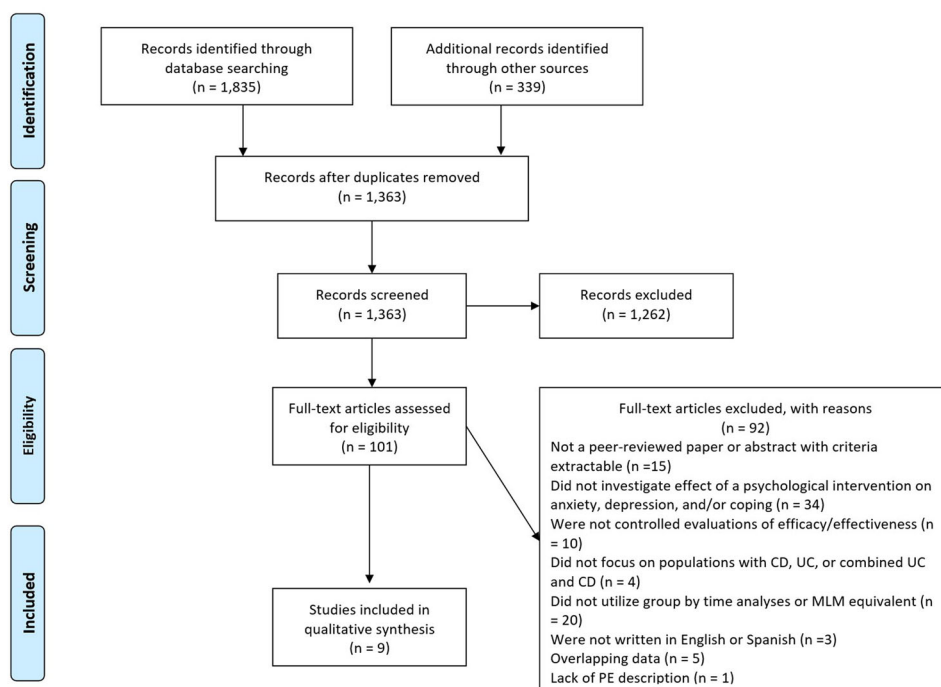


Figure 1. PRISMA flow diagram.

The final list resulted in 9 papers meeting inclusionary criteria, which are reviewed here (see [Figure 1](#)).

Data extraction

For each article, data were sought for the following variables: population age, intervention classification (CBT, mindfulness, SFT, etc.), and results of outcomes of interest (i.e. anxiety, depression, coping, QoL, disease activity). Practice elements were also extracted and coded in accordance with the general structure of the DMM, which relies on published descriptions of PEs for coding (cf., Chorpita et al., 2005; Chorpita & Daleiden, 2009). PE coding was conducted independently by KP and CK, and any discrepancies were resolved between the two and/or MG and MB. The PEs extracted in the course of the present study that were previously described by the DMM include: relaxation, cognitive (cognitive restructuring; here forth referred to as such), social skills, attending (i.e. differential attention parent training), self-monitoring, relapse prevention, problem solving, exposure, and assertiveness training (Chorpita & Daleiden, 2009). Additionally, because the DMM has heretofore not been applied to health psychology interventions, several codes for novel PEs not on the original list were also delineated as necessary. This resulted in the definition of five new or adapted PEs related specifically to clinical techniques seen in IBD literature, including: education (encompasses disease and/or psychoeducation delivered to any target; n = 7 observations across all studies); mindfulness meditation (involving a specific focus on mindful

awareness in meditation; $n = 2$); goal setting (adapted to reflect planned activities to improve mental and/or physical health, including healthy dietary and physical activities; $n = 2$), hypnotherapy (hypnosis used to target symptoms of anxiety, abdominal pain, and/or immune functioning; $n = 2$); distraction (direction of the patient's attention away from the pain/symptoms); biofeedback (the use of biotechnology to demonstrate physiological arousal levels and 'gameify' the reduction of these levels utilizing concurrent techniques; $n = 1$) and stress management (identification of various stressor types and corresponding tactics; $n = 1$). One additional study described the use of stress management, however it was referred to as an overarching approach (i.e. broken down into other PEs) rather than a PE itself; Thus, in this instance stress management was classified as the intervention approach rather than a PE so as not to not duplicate the same technique in multiple categories.

Data analysis

Similarly, data analysis was influenced by DMM methodology, which used frequency patterns evaluated with rigorous statistical methods (Chorpita & Daleiden, 2009). Due to the current small volume of evidence investigating interventions for anxiety and depression within IBD, this more detailed statistical method was not appropriate for the present review. Thus, the PEs from the studies reviewed are described and aggregated based on frequency of use alone. Separate PE frequency charts were generated for (1) all active interventions described in the included studies; (2) all interventions that produced evidence in the form of performing significantly better than one or more comparison groups over time (referred to as 'successful' interventions); and (3) successful interventions within individual outcome domains (i.e. anxiety; depression; QoL; disease activity).

Results

Of included studies ($n = 9$), 6 were conducted with samples of adults alone (age ≥ 18), 1 with adolescents alone (ages 11–17), 1 with younger children (ages 8–10) and adolescents, and 1 with all three age groups. For additional information on the sample criteria and study design for included studies, see [Table 1](#). The broad intervention classifications described in these papers were as follows: CBT ($n = 5$); relaxation ($n = 1$); mindfulness-based ($n = 2$); and stress-management ($n = 1$). Extracted practice elements were as follows: education, cognitive restructuring, self-monitoring, relaxation, hypnotherapy; social skills, distraction, differential attention, assertiveness training, exposure, goal setting, problem solving, mindfulness meditation, stress management, and biofeedback. For additional treatment characteristics, see [Table 2](#). Across all studies, frequency data indicated that relaxation and education were the most commonly implemented techniques, followed by cognitive restructuring, distraction, and social skills ([Figure 2](#)). The following studies were identified as successful interventions because results demonstrated significant group-by-time differences in one or more variables of interest, with one group demonstrating greater improvement(s): Schoultz

Table 1. Study designs.

Study	Sample size	Age Mean(SD)	Age range	IBD type(s)	Inclusion criteria	Exclusion criteria	Comparison condition
Mikocka-Walus et al. (2017); Some data obtained from earlier paper on same study: Mikocka-Walus et al. (2015)	CBT (N = 90) SC (N = 84)	Total sample: 46.5 (15.7)	≥18 y.o.	All types	1. Clinically established diagnosis of IBD 2. Current clinical remission or mild symptoms only for at least 3 months, 3. Sufficient English to answer questionnaires, 4. 18 y.o. or greater 5. Competence to consent 6. Willingness to complete CBT sessions	1. Diagnosis of substance dependence or serious mental illness 2. Currently in psychotherapy 3. Significant cognitive impairment	Standard care (SC)
Thompson et al. (2012)	PASCET-PI (N = 22) TAU (N = 19)	PASCET-PI 15.0 (2.3) TAU 15.1 (1.8)	11–17 y.o.	All types	1. 11–17 y.o. 2. Biopsy-confirmed IBD diagnosis 3. Children's Depression Inventory Score >= 9 on child- or parent-reported version 4. English speaking	1. Current major depressive, dysthymic, bipolar, psychotic, or substance use disorder by DSM-IV criteria 2. Antidepressant medications within 2 weeks of assessment 3. Substance use disorder or suicide attempt within 1 month of enrollment 4. Depression requiring psychiatric hospitalization 5. Failure of previous manual-based CBT of at least 8 sessions	Treatment as usual (TAU)
Schultz et al. (2015)	MBCT (N = 22) WC (N = 22)	MBCT 48.59 (12.05) WC 49.68 (15.37)	≥18 y.o.	Crohn's disease or ulcerative colitis	1. Sufficient English 2. Able to give informed consent 3. Age of 18 or older 4. Diagnosis of Crohn's disease or ulcerative colitis confirmed by clinician 5. Ability to do light exercise 6. Ability to attend the eight sessions and commit to up to 45 minutes of daily home practice 7. No recent change in antidepressants	1. Major psychiatric illness or alcohol dependency 2. Were scheduled for surgery during the study period 3. Already participating in other pharmacological or psychological intervention study 4. Recent prescriptions of antidepressants 5. Exacerbation of symptoms	Waitlist control (WC)
Jedel et al. (2014)	MBSR (N = 27) Control (N = 28)	MBSR 46.04 (12.8) Control 39.68 (11.06)	18–70 y.o.	Ulcerative colitis	1. Documented moderate UC 2. Inactive UC 3. One or more flares in previous 6 months 4. Colonic involvement of >15 cm from the anal verge 5. Age 18–70	1. History of colon resection 2. Antibiotic use within previous 30 days 3. Antidiarrheal medication use within previous 7 days 4. Use of non-allowed medication	Time/Attention control

(continued)

Table 1. Continued.

Study	Sample size	Age Mean(SD)	Age range	IBD type(s)	Inclusion criteria	Exclusion criteria	Comparison condition
Levy et al. (2016)	SLCBT (N = 91) ES (N = 94)	Total sample 13.5 (2.7)	8–17 y.o.	Crohn's disease or ulcerative colitis	<ol style="list-style-type: none"> 6. No IBD medication or on a stable dose 7. Willingness to complete an 8-week course 	<ol style="list-style-type: none"> 5. Unresolved history of abuse, current or past dissociative disorder, PTSD, psychosis, hospitalization for self-harm/SI 6. Resistance to intervention due to religious beliefs 7. Current pregnancy/lactation 8. Prior mind/body intervention training 9. Current chronic disorders 1. Chronic disease other than epilepsy 2. Major surgery within the past year unrelated to IBD 3. Developmental disabilities requiring full-time special education or impairing ability to communicate 4. Non-English speaking 	Education support (ES)
Mizrahi et al. (2012)	Treatment (N = 18) WC (N = 21)	Total sample 35.56 (13.38)	≥18 y.o.	All types	<ol style="list-style-type: none"> 1. 8–17 y.o. 2. 3+ months post-diagnosis of Crohn's or UC diagnosis 3. Lived with participating caregiver for 3+ months 4. Willing, able, and agreed to participate in the intervention and complete questionnaires 5. Medically approved to engage in normal activities 	<ol style="list-style-type: none"> 1. Expected surgery in the following two months 2. Diagnosed as suffering from an active psychosis or from active major depression 3. Undergoing psycho-pharmacotherapy 4. Participating in another research study 5. Acquainted with and already practicing relaxation techniques 	Waitlist control (WC)
McCombie et al. (2015)	CCBT (N = 113) TAU (N = 86)	CCBT 38.3 (12.8) TAU 39.6 (11.8)	18–65 y.o.	All types	<ol style="list-style-type: none"> 1. 18–65 y.o. 2. Diagnosed with IBD 3. Sufficient English 4. Willing to participate in the intervention and answer questionnaires 	<ol style="list-style-type: none"> 1. Disease too severe (recent major surgery or complicated disease) 2. Diagnosis of psychotic disorder 3. Receiving any psychological intervention 4. Those with an ileostomy or colostomy 	Treatment as usual (TAU)

(continued)

Table 1. Continued.

Study	Sample size	Age Mean(SD)	Age range	IBD type(s)	Inclusion criteria	Exclusion criteria	Comparison condition
Schwarz and Blanchard (1991)	Treatment (N = 11) Treated control (N = 10)	Treatment 45.3 (11.9) Treated control 42.3 (13.4)	≥18 y.o.	All types	1. >= 18 y.o. 2. Diagnosis of IBD by personal physician	1. Meet criteria for DSM-III-R major depressive disorder, bipolar disorder, or schizophrenia Intellectual disability	Self-monitoring treated control
Stapersma et al. (2018) – PE's in Szigethy et al. (2007)	CBT (N = 37) Control (N = 33)	18.62 (4.27) Control 17.69 (4.82)	10–25 y.o.	All types	1. Confirmed diagnoses of IBD (UC, CD, or IBD-undclassified) 2. Subclinical symptoms of anxiety and/or depression	1. Current pharmacological or psychological treatment for mental health problems 2. Insufficient mastery of Dutch language 3. Diagnosis of selective mutism, bipolar disorder, schizophrenia/psychotic disorder, autism spectrum disorders, obsessive-compulsive disorder, posttraumatic or acute stress-disorder, or substance use disorder 4. 8+ sessions of CBT in past year 5. Participating in another interventional study	Care as usual

Table 2. Treatment characteristics.

Study	Delivery mode	Number of sessions	Frequency of sessions	Length of session	Treatment family	Included PEs
Mikocka-Walus et al. (2017) – Some data obtained from earlier paper on same study: Mikocka-Walus et al. (2015)	Participants choice: Face to face (F2F, n = 22) or Online (n = 68)	10	F2F: 1/week, Online: Self-directed	2 hours	CBT	Education, Cognitive, Relaxation Techniques, Social Skills, Distraction, Assertiveness Training, Exposure
Thompson et al. (2012)	Predominantly face to face, with no more than 3 sessions delivered via telephone	9–11 individual youth sessions, 3 parent sessions	1/week	1 hour	CBT	Education, Cognitive, Relaxation, Hypnotherapy, Goal Setting, Problem Solving
Schultz et al. (2015)	Face-to-face	8 sessions	1/week	2 hours	Mindfulness-based cognitive therapy	Education, Cognitive, Mindfulness Meditation
Jedel et al. (2014)	Face-to-face	8 sessions	1/week	2–2.5 hours	Mindfulness-based stress reduction	Education, Mindfulness Meditation
Levy et al. (2016)	Face-to-face	3 sessions	1/week	Mean length = 70 minutes \pm 14.31	CBT	Cognitive, Relaxation, Attending (Parent Training), Stress Management
Mizrahi et al. (2012)	Face-to-face	3 sessions	1/2 weeks	50 minutes	Relaxation	Self-Monitoring, Relaxation
McCombie et al. (2015)	Self-administered on computer via Moodle	8 sessions	1/week	Not specified/self-directed	CBT	Education, Cognitive, Relaxation, Social Skills, Distraction, Assertiveness Training, Exposure
Schwarz and Blanchard (1991)	Face-to-face	12 sessions	2/week for first 4 weeks, 1/week for second four weeks	60 minutes	Stress management	Education, Self-Monitoring, Relaxation, Biofeedback
Stapelsma et al. (2018) – PE's in Szigethy et al. (2007)	Individual sessions: 6 face-to-face sessions, 7 via phone, family sessions: 3 face-to-face sessions	13 individual sessions, 3 family sessions (for those <20 years old)	1/week for first ten weeks, 1/month for following 3 months	Face-to-face = 60 min, phone = 30 min	CBT	Education, Cognitive, Relaxation, Hypnotherapy, Social Skills, Distraction, Goal Setting, Problem Solving

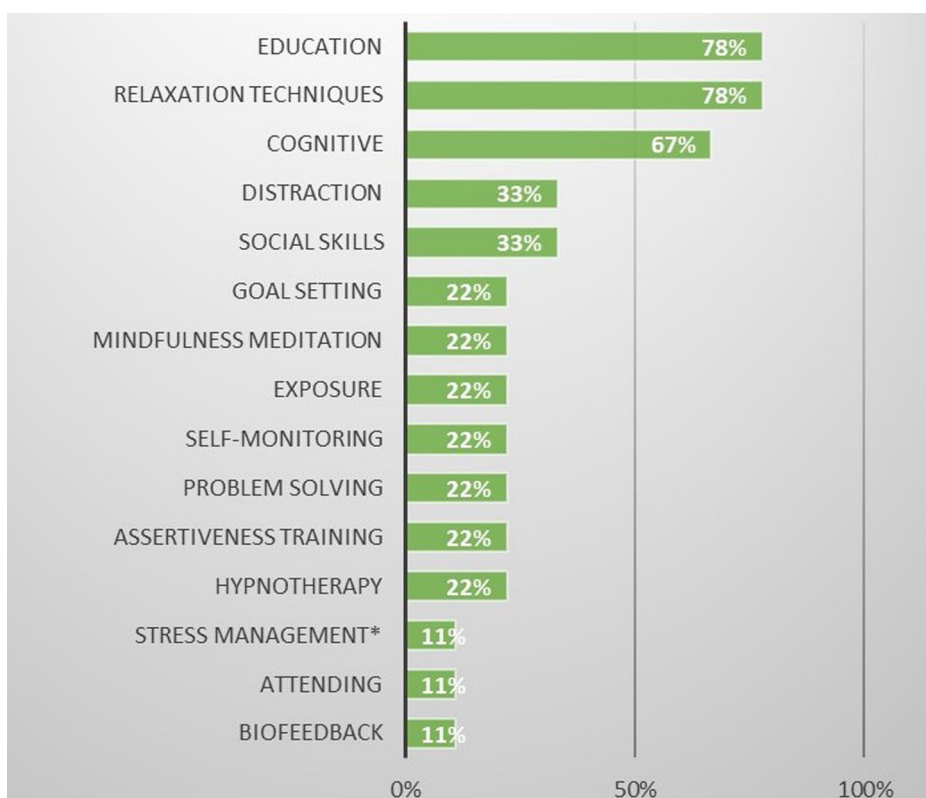


Figure 2. PE profile for included interventions ($n = 9$). *Refer to data extraction methods for additional details.

et al., 2015; Jedel et al., 2014; Levy et al., 2016; Mizrahi et al., 2012; Schwarz & Blanchard, 1991. For a summary of included studies' results, see Table 3.

The PE profile for successful interventions, however, exhibited some differences in comparison to the overall aggregate. Relaxation again accompanied education as the most frequently employed PEs, followed by cognitive restructuring, and then by mindfulness meditation and self-monitoring (Figure 3). PEs in treatments with significant group by time differences specific to psychosocial outcomes (HRQoL, Anxiety, Depression, and/or Coping; $n = 5$) were grouped together because there were few interventions examining these outcomes independently. The PE frequencies for these interventions were similar, with cognitive restructuring now accompanying relaxation and education as most frequent, followed by mindfulness meditation (Figure 4). A PE figure for Disease Activity was not generated because so few studies showed significant group by time improvement in this variable ($n = 2$).

To further characterize successful interventions, follow-up descriptive statistics of central tendency were run for the number of PEs employed in all included interventions, successful interventions, and remaining interventions. These results indicated that successful interventions utilized fewer PEs overall ($M = 3.67$, Median = 3.5), than non-successful interventions ($M = 7$, Median = 7.5), and all studies included ($M = 4.78$, Median = 4).

Table 3. Study results.

Study citation	Outcomes & measures	Main findings	Limitations	Classification of 'Successful' (Y/N)
Mikocka-Walus et al. (2017) – Some data obtained from earlier paper on same study: Mikocka-Walus et al. (2015)	Quality of life Short-Form 36 Health Questionnaire (SF-36) Disease activity Crohn's Disease Activity Index (CDAI), Simple Clinical Colitis Activity Index (SCCAI) Anxiety State Trait Anxiety Inventory (STAI) Depression Hospital Anxiety and Depression Scale (HADS) Stress Revised Social Readjustment Rating Scale (RSRRS) Coping Brief Coping Operations Preference Enquiry (Brief COPE), IBD Stages of Change Coping Questionnaire (IBDSCCOQ) Biomarkers C-Reactive Protein, Hemoglobin, Platelets, White Cell Count Depression Children's Depression Inventory, Child Report (CDI-C) and Parent-Report (CDI-P) Global/Adaptive functioning Children's Global Functioning Scale Anxiety STAI Depression Beck Depression Inventory II (BDI-II) Disease activity CDAI, SCCAI Disease-related quality of life	No significant multivariate effects of CBT on disease activity, anxiety, depression, coping, or biomarkers at 6, 12, or 24 months. An exploratory sub-analysis of participants in need (defined as those who recently transitioned from pediatric care (18–20 yo); CDAI > 180 or SCCAI > 5; poor coping, and/or high anxiety or depression) at 6 months revealed significant improvement in HADS scores which disappeared at 12 months.	Attrition at 12 months was high overall (39%). Attrition was significantly higher in the CBT group vs standard care ($p < .001$, 53% vs 24% respectively) and in the online vs in-person CBT option ($p = .02$, 60% vs 32% respectively).	N
Thompson et al. (2012)	Depression Children's Depression Inventory, Child Report (CDI-C) and Parent-Report (CDI-P) Global/Adaptive functioning Children's Global Functioning Scale Anxiety STAI Depression Beck Depression Inventory II (BDI-II) Disease activity CDAI, SCCAI Disease-related quality of life	Non-significant trends toward greater reduction in depressive symptoms (child and parent-report) at 12-month follow up Significantly greater improvement in global functioning (adaptive functioning) in the intervention group than the control. No significant changes in state anxiety, disease activity, or QOL. There was a significant group x time interaction for depression and trait anxiety.	Limited sample size Overall attrition Greater attrition in minority participants, Potential ceiling effect for depressive symptoms owing to exclusion of those with clinical depression 44% attrition in both groups Difficulty of assessing use of at home practice Lack of assessment of medication changes throughout intervention	N
Schultz et al. (2015)	Depression Beck Depression Inventory II (BDI-II) Disease activity CDAI, SCCAI Disease-related quality of life	Non-significant trends toward greater reduction in depressive symptoms (child and parent-report) at 12-month follow up Significantly greater improvement in global functioning (adaptive functioning) in the intervention group than the control. No significant changes in state anxiety, disease activity, or QOL. There was a significant group x time interaction for depression and trait anxiety.	Limited sample size Overall attrition Greater attrition in minority participants, Potential ceiling effect for depressive symptoms owing to exclusion of those with clinical depression 44% attrition in both groups Difficulty of assessing use of at home practice Lack of assessment of medication changes throughout intervention	Y

(continued)

Table 3. Continued.

Study citation	Outcomes & measures	Main findings	Limitations	Classification of 'Successful' (Y/N)
Jedel et al. (2014)	<p>Inflammatory Bowel Disease Questionnaire (IBDQ)</p> <p>Disease-related quality of life</p> <p>IBDQ</p> <p>Depression</p> <p>BDI-II</p> <p>Anxiety</p> <p>STAI</p> <p>Mindfulness</p> <p>Mindful Attention Awareness Scale (MAAS)</p> <p>Disease status</p> <p>Mayo UC-DAI Disease Activity, Rectal Bleeding Score, Sigmoidoscopy), Inflammation (Stool Calprotectin Levels, Interleukin-6, -8, and -10), Stress</p> <p>Serum adrenocorticotrophic hormone (ACTH), urinary cortisol, Perceived-Stress Questionnaire (PSQ)</p> <p>Perceived health competence</p> <p>Perceived Health Competence Scale</p> <p>IBD-Specific quality of life</p> <p>IMPACT-III</p> <p>Anxiety</p> <p>Multidimensional Anxiety Scale for Children (MASC)</p> <p>Coping skills</p> <p>Pain Response Inventory (PRI), Pain Beliefs Questionnaire (PBQ), Adults' Responses to Children's Symptoms (ARCS)</p> <p>Depression</p> <p>CDI-C and CDI-P</p> <p>Disease activity</p> <p>Pediatric Crohn's Disease/Ulcerative</p>	<p>They found significantly better QOL among flared participants in the treatment group, compared to flared subjects in the control group, as measured by the IBD-Q Total Scale and the bowel and emotion subscales. There were no differences between MBSR subjects who flared and control subjects who flared on measures of depression, anxiety mindfulness, perceived health competence, relapse rates or stool calprotectin.</p>	<p>Small sample size</p> <p>Could not investigate role of medication on outcomes</p> <p>Age difference in groups</p> <p>Potential influence of disease activity on assessments in those who flared</p>	Y
Levy et al. (2016)	<p>Perceived Health Competence Scale</p> <p>IBD-Specific quality of life</p> <p>IMPACT-III</p> <p>Anxiety</p> <p>Multidimensional Anxiety Scale for Children (MASC)</p> <p>Coping skills</p> <p>Pain Response Inventory (PRI), Pain Beliefs Questionnaire (PBQ), Adults' Responses to Children's Symptoms (ARCS)</p> <p>Depression</p> <p>CDI-C and CDI-P</p> <p>Disease activity</p> <p>Pediatric Crohn's Disease/Ulcerative</p>	<p>Significant differences in CDI, IMPACT and PRI (child-reported), missed school days, child problem-focused coping (Adult reported)</p> <p>Non significant findings for PRI (parent report), child problem focused coping (child-reported), emotion focused coping (PBQ), FDI, MASC, or hospital days</p>	<p>Study sample predominantly white, Parent sample comprised largely of mothers, Participants predominantly had inactive disease states</p>	Y

(continued)

Table 3. Continued.

Study citation	Outcomes & measures	Main findings	Limitations	Classification of 'Successful' (Y/N)
Mizrahi et al. (2012)	Colitis Activity Index (PCDAI/PUCAI)			
	Other			
	Functional Disability Inventory (FDI), Hospital Days, Missed School Days, Disease-related quality of life			
	IBDQ	Significant differences in IBDQ, anxiety (STAI), mood & stress (VAS)	Non-blinded study	Y
	Anxiety	No significant difference in Depression (VAS)	Small sample size Waitlist rather than attention control Lack of long-term follow-up	
McCombie et al. (2015)	STAI			
	Stress, depression and mood			
	Visual Analogue Scale (VAS)			
	HRQOL			
	Short Form 12 Health Questionnaire (SF-12)	Significant improvement in HRQOL (SF-12) for those who complete at least 50% of study	Participants were not blinded Lack of statistical power Low adherence Time single diagnosis not recorded Unknown if some participants began psychiatric treatment outside the boundaries of the study	Y
Schwarz and Blanchard (1991)	Anxiety and depression			
	HADS			
	Stress			
	Perceived stress scale (PSS-10), Coping			
	Brief COPE			
	Crohn's disease activity			
	Harvey Bradshaw Index			
	UC or IBD-unspecified disease activity			
	SCCAI			
	Other			
	Social Functioning Questionnaire (SFQ), Eysenck Personality Questionnaire- Brief Version (EPQ-BV)			
	Depression			
	BDI-II	Significant group by time difference in diarrhea and urge to defecate such that the group that only self-monitored symptoms showed greater improvement than group that also utilized relaxation and biofeedback skills.	Low sample size, Disproportionate representation of UC vs CD in each treatment group	Y
	Anxiety			
	STAI			
	Somatic symptoms			
	Psychosomatic Symptom Checklist (PSC)			
	Stress			

(continued)

Table 3. Continued.

Study citation	Outcomes & measures	Main findings	Limitations	Classification of 'Successful' (Y/N)
Stapersma et al. (2018) – PE's in Szigethy et al. (2007)	IBD Stress Index, Hassles Scale, Life Events Scale Anxiety Screen for Child Anxiety Related Disorders (SCARED; 10–20 y.o.), HADS (21–25 y.o.), Depression CDI (10–17 y.o.), BD-II (18–25 y.o.), HRQoL IMPACT-III (10–20 y.o.), IBDQ (21–25 y.o.) Disease activity PCDAI or PUCAI (10–20 y.o.), CDAI or partial Mayo score (21–25 y.o.)	No findings showed significant group by time changes	Statistical limitation of utilizing different instruments across the age spectrum of the study, Small sample size	N

Finally, modal PEs were examined, with frequency statistics showing the modal PE to be relaxation and education for all included interventions (78% each), all successful interventions (67% each), and interventions successful for psychosocial outcomes (60%). Ties for modal PEs and next-most frequently utilized PEs, however, were not quite as consistent between these groups. Cognitive restructuring was second-most frequent for all included interventions (67%), second-most frequent for all successful interventions (50%), and then accompanied relaxation and education as modal for interventions successful for psycho-social outcomes (60%). Similarly, mindfulness meditation and self-monitoring were more featured in successful PE profiles than the overall aggregate. Mindfulness meditation was used in 22% of all included interventions, 33% of all successful interventions, and 40% of interventions successful for psychosocial outcomes and ranked as second most-frequent for this group. Interestingly, self-monitoring was comparatively most featured in all successful interventions (33%), as opposed to all included interventions (22%) or interventions successful for psychosocial outcomes (20%). In total, among the entire set of all included interventions, relaxation and education (78%) were modal with only cognitive restructuring as a clear runner-up; however, when considering only interventions successful for psychosocial outcomes, all three of these PEs became modal (each at 60%), and mindfulness meditation (33%) became evident as the clear runner-up.

Discussion

The present study examined PE Profiles of effective interventions for anxiety and depression in IBD. Practice Element profiles reflect the great heterogeneity of this burgeoning literature, while simultaneously offering a new perspective on the content of successful interventions (as defined in the methods). For example, profiles were very similar for all successful interventions vs. psychosocial-specific successful interventions, yet distinct from the profile of all PEs studied. Although relaxation, education, and cognitive restructuring were the top three for each profile, successful interventions more frequently utilized mindfulness meditation and self-monitoring next, while in all included studies, distraction and social skills were next most frequent.

Modal practice elements

It is perhaps unsurprising that the Cognitive Behavioral techniques of cognitive restructuring was more frequent in interventions effective for psychosocial outcomes than those improving any outcome more broadly. It is noteworthy, however, that other traditional Cognitive Behavioral PEs of self-monitoring and exposure were not prominently featured in these treatment approaches. This stands in contrast to the literature examining CBT more broadly, which heavily emphasizes the combination of techniques such as self-monitoring, cognitive restructuring, and exposure in the traditional treatment of emotional disorders. This difference may result from a differential combination of PEs being more appropriate to the treatment of anxiety and depression in IBD. Given the close association between anxiety, depression, and disease activity, it is possible that techniques or combinations of techniques simultaneously



Figure 3. PE profile for successful interventions, any outcome (n=6). *Refer to data extraction methods for additional details.

targeting physiological aspects and affect dysregulation would be more effective. Subsequently, the combination of physiologically quieting PEs like relaxation and mindfulness meditation with cognitive restructuring techniques may have a positive impact on both anxiety or depression and disease symptoms (as opposed to solely cognitive/behavioral adaptations in response to these symptoms). This notion may be supported by a disparity showing up in the use of mindfulness meditation (22% in all included studies vs 40% in interventions with psychosocial success). This is consistent with the results of Yeh et al. (2017), who conducted a review of mind-body interventions for anxiety and depression in IBD and concluded that relaxation and mindfulness-based interventions may improve psychological functioning in adults with IBD (particularly those with high stress and concurrent IBS symptoms). Further, among successful interventions, cognitive restructuring was always utilized in combination with at least relaxation, mindfulness, or both. Thus, combining cognitive restructuring with one of these elements seems particularly salient for IBD populations.

Although it is possible that traditional CBT PEs such as self-monitoring and exposure were simply not well described within included studies, relying on published descriptions is the most empirical method of extracting PEs as it limits bias introduced

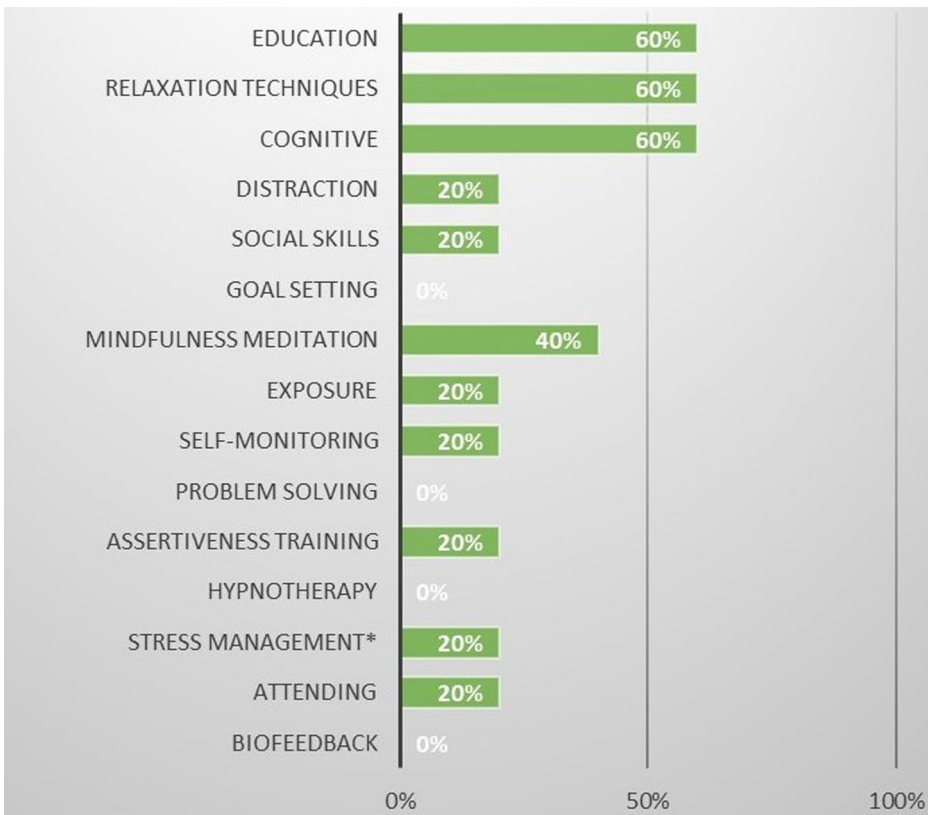


Figure 4. PE profile for successful interventions, psychosocial outcomes (n = 5). *Refer to data extraction methods for additional details.

by post-hoc descriptions of PEs. Combining this method with double coding and resolving discrepancies, our methods limit the impact of biased PE descriptions on these results. Further, although the PE of goal setting is typically considered a traditional component of CBT, our study specifically examined goal setting in the context of health behaviors such as diet and physical activity. Thus, we may have seen lower rates than expected for this PE, not because of the same reasons as self-monitoring and exposure, but because this PE may be better fitted for psychosocial interventions for adherence/compliance within IBD rather than for anxiety and depression. The traditional idea of goal setting within CBT is often accomplished through homework and collaborative goal setting. While many of these interventions described homework, collaborative goal setting was not described. Thus, homework was conceptualized as an integrated part of other PEs, such that there was homework specific to each of relaxation, self-monitoring, cognitive restructuring, etc.

For mindfulness meditation and relaxation, successful combinations demonstrated less ubiquity. Like cognitive restructuring, relaxation was most often used in combination with at least mindfulness, cognitive restructuring, or both, and mindfulness was used once in combination with at least relaxation, cognitive restructuring, or both among successful interventions. However, in two successful studies, cognitive restructuring was not utilized at all, and mindfulness or relaxation was utilized successfully in

combination with only one other PE. Mindfulness was in combination with only education in an intervention yielding group by time improvement in emotional and physical HRQOL. Relaxation was used in combination with only self-monitoring in an intervention resulting in significant group by time improvement in disease activity. This suggests prioritizing the inclusion of physiologically quieting interventions for psychological services in IBD, and perhaps prioritizing mindfulness meditation for psychosocial outcomes. Given that this generalization is based only on singular cases, however, it awaits further replication before being strongly supported as an overall change to clinical intervention more broadly. Additionally, it is important to consider the influence of the number of PEs utilized in these cases (2 PEs for each study) and whether this enhanced efficacy via increasing acceptability for patients.

The number of elements utilized across all observations should also be considered when interpreting the finding of education, relaxation, cognitive restructuring, and mindfulness as the top PEs utilized with success. In addition to the aforementioned cases utilizing only 2 PEs with success, these observations were supported by the disparity of elements used between successful and not successful interventions. The mean ($M = 3.67$) and median (3) number of PEs included for successful interventions were lower than those that were not successful ($M = 5.75$, median = 6.5). These findings, combined with the differential PE profiles, may suggest that focusing on three or less of the top four PEs (education, relaxation, cognitive restructuring, and mindfulness meditation—perhaps prioritizing the inclusion of at least one of relaxation or mindfulness meditation) and putting little to no focus on additional PEs would increase effectiveness of interventions for psychosocial outcomes in IBD.

Treatment group vs. practice elements

Many previous review studies lacked consensus in recommending one treatment group over another, and the current findings shed light as to why that may have been the case. First, the PEs with the highest frequencies in successful treatments were often nested within separate specific approaches (e.g. relaxation from relaxation programs; mindfulness from mindfulness meditation programs; cognitive restructuring from cognitive-behavioral programs). Second, the disparity in number of PEs utilized and variability in PE combinations utilized even between successful interventions represents variance in treatment outcome unaccounted for by treatment content alone. However, the totality of extraneous factors may not always be feasibly controlled, neither experimentally nor statistically. To do so in the course of even a single study can be difficult, but when considering an entire body of literature, it becomes exponentially more so. These difficulties are compounded when the literature is limited in the number of studies given novelty of inquiry in the area (i.e. meta-analytic approaches cannot be applied, and other methods of statistical aggregation are similarly limited). Thus, many of the variables that could be entailed in the 'extraneous factors' part of efficacious treatment has yet to be illuminated. The PE profiles and descriptive statistics produced in the current study represent the psychosocial content that one can control, implement, and disseminate, and have utility both in elucidating potential

foundational techniques for psychosocial treatment of IBD and illuminating currently unknown factors affecting treatment outcome.

Limitations and future directions: potential factors affecting outcome

Factors influencing variability in treatment outcome are numerous and raise questions about the feasibility of experimentally or statistically controlling for their influence. In terms of treatment factors, the length of intervention and/or contact hours, provider of intervention (i.e. nurse, psychologist, etc.), individual vs. group format, and timing of post-treatment assessments could all affect outcomes. The order and combination of PEs could also influence outcomes (i.e. dependent, additive effects of PEs delivered sequentially), as could discrepancies in labeling PEs (i.e. one study described their practice element as stress management, and this term could not be further broken down, whereas other studies described multiple PEs like relaxation and cognitive restructuring as making up a stress management approach). In terms of patient factors, differing inclusion criteria (e.g. age; those with clinically elevated anxiety and/or depression symptoms; those with elevated disease activity; individuals in remission or with comorbid IBS; etc.) could also affect outcomes, which has been noted by more recent reviews (Yeh et al., 2017). Additionally, separating analyses for treatment of anxiety vs. depression in IBD will eventually be necessary as work in this area continues to advance, as will research illuminating stress-related symptoms (i.e. distress due to fatigue, pain, weight loss, or social sequelae). The present study did not account for these differences, partially due to the limited literature and wide variety of inclusion criteria and post-assessment time frames utilized across interventions. Owing to these issues, the present study was limited by the number of included studies and scope of frequency and descriptive analyses. Future research investigating the influence of these factors on intervention efficacy is warranted.

Clinical implications

In spite of these limitations, the current findings may have important implications for clinical practice. Our finding that education (about the impact of IBD on both physiology and emotional symptoms) and relaxation were most prominent across successful interventions in participants across the lifespan offers some support for their application as a front-line intervention in the medical setting. Relaxation techniques and deep breathing require minimal teaching time and can be delivered by a wide variety of professionals including social workers, psychologists, or nurses. Mindfulness meditation and cognitive restructuring may also serve as effective first line treatments, given their prevalence in successful interventions for psychosocial outcomes, and they exhibit similar ease of training and adaptability in methods of implementation. Beyond these foundational techniques, our findings also point to implementation of self-monitoring. However, our findings also point toward the importance of carefully combining techniques to minimize PEs utilized to improve outcomes, with successful interventions suggesting the use of 3–4 of the following: relaxation, education, cognitive restructuring, and mindfulness meditation. Although the current findings do not

directly inform necessity or sequencing of these techniques, it is possible that more heavily cognitive PEs would be best applied after physiological quieting techniques or reductions in disease activity were achieved. Further research on the context, sequence, and optimal delivery methods of specific PEs in IBD treatment is necessary, and developing evidentiary guidelines for such considerations will be helpful in directing clinical resources and facilitating access to evidence-based care.

Summary

In conclusion, the current study found that effective psychological treatments of anxiety and depression in IBD most frequently employ education, relaxation, cognitive restructuring, and mindfulness techniques, consistent with a more recent review isolating studies employing physiologically calming techniques of relaxation and mindfulness. Effective treatments may also be characterized by the inclusion of self-monitoring and the use of fewer total practice elements. Although limited by the small the number of studies and scope of descriptive and frequency analyses, these results contribute to the understanding of how treatment content may influence outcome. This represents a step forward from the previously reported ambiguity over the advantage of one psychological treatment type over another for improving anxiety and depression in IBD. Future research examining additional factors related to treatment outcome other than treatment content are warranted. The clinical significance of the present results is indicated by their support of relaxation and education as potential first-line treatments of comorbid anxiety and depression while disease activity is treated, with the employment of additional cognitive and mindfulness techniques perhaps best suited for when anxiety and/or depression persist even beyond a reduction in disease activity. Thus, anxiety and depression may be successfully treated with evidence-based psychological treatment that prioritizes elements of relaxation and education before employing traditional cognitive behavioral techniques.

Disclosure statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from (kprender@uab.edu).

Funding

KLP was supported by the University of Alabama at Birmingham Center for Clinical and Translational Science under grant TL1TR001418 and the University of Alabama at Birmingham Nutrition Obesity Research Center pre-doctoral fellowship funded through the NIH T32 grant (T32HL105349) awarded by the Heart, Lung and Blood Disease Institute (NHLBI). MAG was supported by the Agency for Healthcare Research and Quality/University of Alabama at Birmingham K12 in Patient-Centered Outcomes Research Program under grant K12HS023009. This work has been supported in part by funding awarded to MJB from The University of Alabama at Birmingham Nutrition and Obesity Research Center Pilot and Feasibility Program under grant DK056336 and the Kaul Pediatric Research Institute (no grant number assigned).

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Data availability statement

The data that support the findings of this study are available from the corresponding author, KP, upon reasonable request.

Summary

The present systematic review suggests clinical techniques of relaxation, cognitive restructuring, education, and mindfulness meditation are most frequently successful in treating anxiety and depression in IBD.

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