

Systematic Literature Review: Implementation of Routine Screening with
Patient Health Questionnaire 9 (PHQ-9) of Adults with Crohn's Disease

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Literature Review

Introduction

Inflammatory Bowel Disease (IBD) is the categorical name for the two of conditions that are characterized by chronic inflammation of the gastrointestinal system; Crohn's disease (CD) and Ulcerative Colitis (UC) are the two conditions classified as IBD. There is no cure for CD; physical symptoms of CD may include, but are not limited to, abdominal pain, diarrhea, hematochezia, weight loss, fatigue, anemia, or vitamin deficiencies. The goals of CD treatment are preventing disease progression and achieving both clinical and endoscopic/histologic remission. Evaluation of medical comorbid conditions in CD is routine and considered standard of care; however routine depression screening has not been widely adopted as part of the total IBD care paradigm.

The psychological impact of CD on the individual's quality of life (QOL) as well as the relationship between these psychological factors has been studied from varying perspectives over the past 20 years. Recommendations for the integration of psychological care/screening have been made, yet the adoption of routine screening as an evidence-based standard of care for CD patients has not been realized in practice. Patients and providers alike have acknowledged that CD can impact mood and QOL (Rubin et al., 2021). The CD disease process and the symptoms associated can range from mild to debilitating, but regardless of severity, the impact on the individual's psychological well-being and QOL can be significant.

Modern paradigms for chronic care management recognize that there is a bidirectional relationship between depression and the chronic disease. The chronicity of CD requires that the individual be able to acknowledge and develop healthy coping skills (Keefer & Kane, 2017). Even when under the care of a gastroenterologist, the role of the individual in self-care and

active participation in disease treatment is crucial for successful long-term management.

Individuals with a chronic medical condition and a diagnosis of depression may potentially demonstrate deficits or characteristics contributing negatively to disease course and burden (Chang et al., 2017). Lorig & Holman (2003) identified three core self-management tasks that an individual must engage in to have the potential for optimal outcomes related to their chronic condition. The three core self-management tasks are:

1. Medical management, including all components of care from individual disease knowledge to decision making, to relationship development with the team involved in medical care.
2. The creation and maintenance of life roles which are meaningful while also learning to adjust to any limitations that may be related to the disease and the disease process.
3. Individual acknowledgment and development of strategies to manage the impacts of IBD over the psychological and emotional aspects of their life (Lorig & Holman, 2003).

The purpose of this systematic literature review was to explore the most recent literature published related to depression in adult patients (≥ 18 years of age) with CD, and to make the determination if the literature supports the implementation of routine screening for depression with Patient Health Questionnaire 9 (PHQ-9) of adults with CD in the outpatient gastroenterology clinic setting. The intention is not to imply or infer any relationships between depression and CD, but to evaluate the most current literature related to the conditions when comorbid and determine if evidence supports a practice change of screening for depression as part of routine care.

AIM statement

Increase screening of Crohn's disease adult patients with PHQ-9 in the outpatient gastroenterology clinic during a predetermined six-week timeframe and evaluate the provider perceptions regarding PHQ-9, comorbid depression and CD, and potential integration for practice change.

Search Strategy

A series of comprehensive literature searches of PubMed, APA PsycArticles, APA PsycInfo, CINAHL Plus with Full Text, Cochrane Central Register of Controlled Trials, Cochrane Clinical Answers, Cochrane Database of Systematic Reviews, Health Source: Nursing/Academic Edition, MEDLINE Complete were performed. Boolean search included terms/phrases: (IBD or inflammatory bowel disease or Crohn's disease) AND (depression or depressive disorder or depressive symptoms or major depressive disorder or mood disorder) NOT (IBS or irritable bowel syndrome) Filters included Humans, English, Adult: 18+ years, from January 1, 2016 – February 14, 2022. The yield of the searches was 505 articles. Systematic reviews were included in the initial search as a method to evaluate if any current (2016-2022) systematic reviews had been published related to this specific question. No systematic literature reviews were included in the final full text record review completed by this author.

Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was utilized as a structured guide for the evaluation of material from the above search (Figure 1). PRISMA provides a structured protocol to guide the evaluation of literature and minimize potential for unintentional bias (Page et al., 2021). Duplicates were removed from the initial 505 articles with a total of 277 articles remaining. The remaining articles then were title and abstract

screened. The remaining 97 articles were read in total and evaluated using inclusion and exclusion criteria stated below. Johns Hopkins Nursing Evidence-Based Practice (JHEBP) Model evidence rating scales were used as a component of inclusion/exclusion criteria to ensure only articles with evidence of adequate strength and quality were included, and to integrate a component of the Conceptual Framework for future practice integration utilized to support the proposed practice change (Dang & Dearholt, 2018).

The final number of articles selected for inclusion was 33. Four primary categories for material classification were identified after full articles were reviewed. The four categories are: prevalence of depressive symptoms in CD, impact/outcomes of comorbid depressive symptoms in CD, evaluation/measuring of depressive symptoms in CD, and CD patient perspectives. The final articles were then classified within the four categories identified by this author; there was potential for an article to be appropriate for more than one category dependent on content.

Inclusion Criteria:

- Articles generated by the search utilizing terms and limits/filters documented above.
- JHNEBP Evidence Rating Scales strength of the Evidence Level I, II, or III and the Quality of the Evidence being A (High) or B (Good) (Dang & Dearholt, 2018).
- Supportive content via independent searches was integrated into the final written work. Any supportive research materials were screened by the same standards as those for the systematic literature review; all materials met “Filter” criteria and were deemed to meet JHNEBP strength and quality inclusion criteria.

Exclusion Criteria:

- Systematic reviews of literature.

- JHNEBP Evidence Rating Scales strength of the Evidence being Level IV and V or Quality of the Evidence C (Low quality or major flaws) (Dang & Dearholt, 2018).
- No delineation between Crohn’s disease and Ulcerative Colitis in the body or results of the article.
- No relevance identified related to established subject categories.

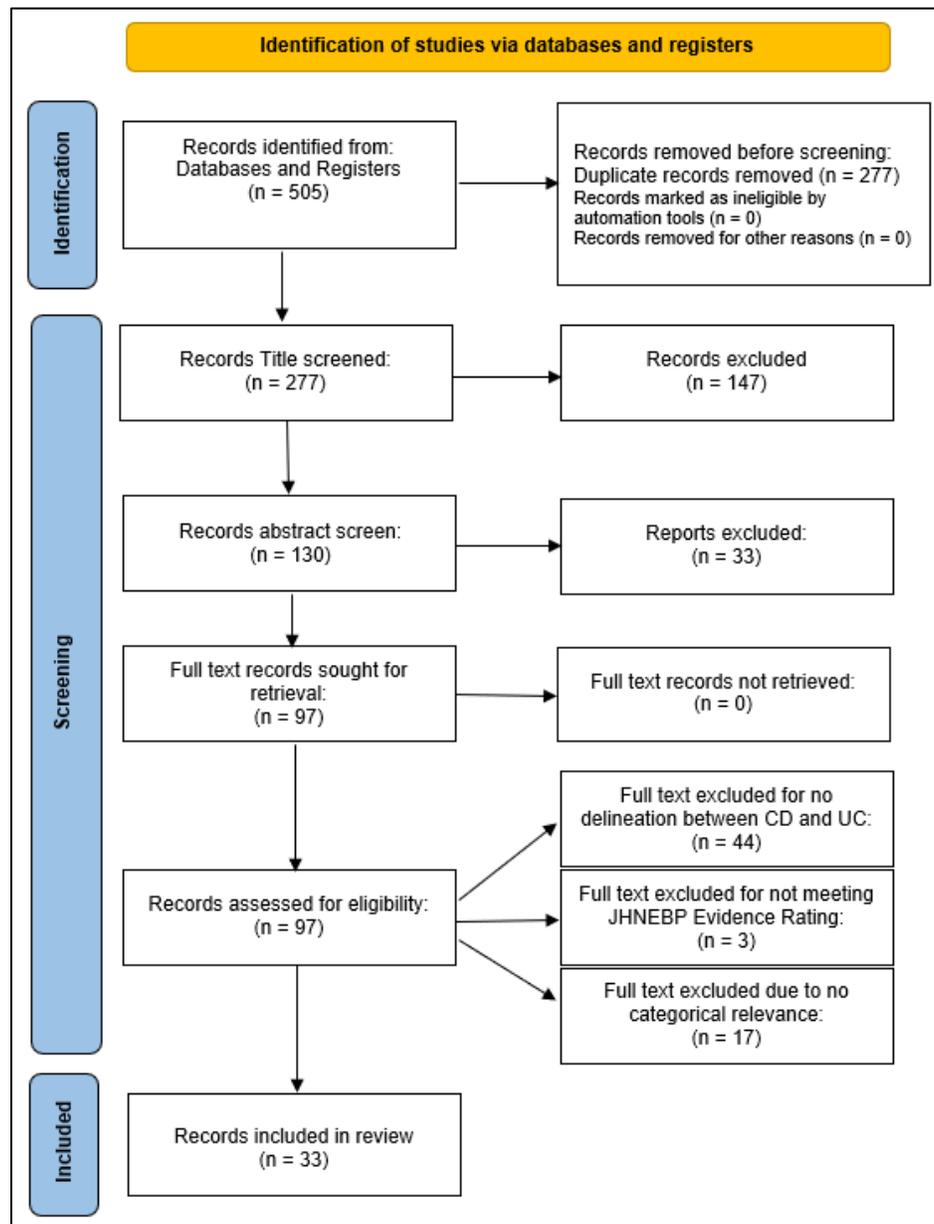


Figure 1. PRISMA Flow Diagram demonstrating the information flow through each phase of systematic review (Page et al., 2021).

Organizing Results

Prevalence of depressive symptoms in the adult CD population

Multiple studies have reported that the prevalence and incidence of depression is higher in the CD population when compared to the general population, with prevalence measured in some cohorts of up to 15-24% at least mild levels of depression with screening tools and up to 20% by patient self-report (Bernstein et al., 2019; Bhamre et al., 2018; Kim et al., 2016; Jackson et al., 2018; Kochar, Barnes, et al., 2018). The potential for underestimating and undervaluing the frequency and impact of depression in CD patients could result in irreparable psychological and physical damage; prevalence rates acquired by self-report have revealed that 61.7% of CD patients reported experiencing depression or anxiety related to their IBD during the two weeks prior to completing the questionnaire (Yan et al., 2020). A large retrospective matched cohort study revealed the presence of an increased rate ratio (IRR) for depression in males but not females compared to population controls; this indicates the potential for CD to serve as a precursor for depression in males with CD (Bernstein et al., 2019). The specific pathogenesis of depressive symptoms in the IBD population may be a topic of debate, yet it is undeniable there is an increased prevalence documented with IBD, and specifically CD.

Affective character traits are identified as: depressive, irritable, anxious, cyclothymic and hyperthymic; it is postulated that an individual with affective temperament would be more likely to be at risk for mood disorders. When comparing IBD patients against a control group regarding the presence of affective traits, it was identified that individuals with CD scored significantly higher in depressive, irritable and cyclothymic measurements when compared to UC. This increased presence of affective traits could suggest that individuals with CD may be at increased risk for mood disorders (Bieliński et al., 2018).

Symptoms of depression have been identified to occur at a frequency higher in the IBD population (49%) in contrast to the non-IBD population (23%). The same study with these findings utilized items 2 and 9 from the PHQ-9 to screen for depressive symptoms and identified that 8% of CD patients screened positively for depressive symptoms (Bhandari et al., 2017). A large nation-wide cross-sectional study in France, with the cohort majority diagnosed with CD (61%, n = 721), evaluated the overall disease burden of IBD using six validated questionnaires with results showing a higher than anticipated presence of depression (49.4%). These findings were consistent with similar depression rates (16%) from a study evaluating rates of depression in individuals with CD 5 years after a CD related surgery (Williet et al., 2017). There is potential for clinically active disease to serve as the only independent risk factor for major depression when comparing clinical remission versus clinically active disease; the overall risk of major depression with active CD has been documented to be as high as 42.4% and that 33.0% suffer with mild depression (Geiss et al., 2018).

CD patients with increased scores on the gastrointestinal (GI) Patient-Reported Outcomes Measurement Information System (PROMIS[®]) have been shown to also have increased scoring on measures of disease activity and decreased QOL indicators; these findings suggest that increased CD symptom burden may have a relationship with psychosocial dimensions impacting QOL (Kochar, Martin, et al., 2018). The increased disease severity of CD, identified as a score of ≥ 450 by Crohn's Disease Activity Index (CDAI) score has shown to correlate with a higher frequency of depression identified by a PHQ-9 cut off score of ≥ 10 for depression and Hamilton Depression Scale (HAM-D) ≥ 24 (Bhamre et al., 2018). A higher level of disease activity of CD patients in an outpatient Brazilian IBD clinic was found to be associated with higher anxiety scores, and decreased QOL; this same study found 100% (n=9) of

CD patients with positive disease activity scored by Harvey-Bradshaw Index (HBI) also scored positive for depression via Hospital Anxiety Depression Scale (HADS). Twenty percent of those CD patients with HBI indicating remission also scored positive for depression on HADS (Calixto et al., 2018). These findings suggest that depressive symptoms are present across the continuum of CD and that the relationship between symptom burden and psychosocial symptoms can be associated with negative impact on QOL.

Impact/outcomes of comorbid depressive symptoms in CD

Whether measurable or perceived, the impact of CD can affect disparate aspects of an individual's life, including financial burden related to increased expenditures associated with CD. The same can be said, and is documented about depression, and thus the presence of concomitant depression and CD could not only result in exacerbation of a medical condition, but also amplify the intensity in which other domains of life are affected. It has been suggested that there is a bidirectional relationship between depression and chronic disease. This bidirectionality of the relationship between depression and disease is suggested, in that, the presence of poor health resulting in poor self-management will result in continued poor health and additionally that inflammation can potentiate depression while depression can potentiate inflammation (Keefer & Kane, 2017). Araki et al. (2020) found that a majority (75%) of IBD patients believed that their disease could be exacerbated by psychological stress. A positive correlation was revealed through scatter plotting between increased Center for Epidemiologic Studies Depression (CES-D) scale scoring and elevated CDAI scores (Araki et al., 2020). Acceptance of the concept of bidirectionality between depression and disease highlights the importance of self-care, adherence to treatment, and advocacy by the individual in their treatment course (Keefer & Kane, 2017).

A relationship was demonstrated between scoring positive for depression on PROMIS[®] and scores indicative of increased disease activity one year later using Short Crohn's Disease Activity Index (SCDAI). Additional association has been observed between the odds of active CD and baseline t-scores indicating depression (Gaines et al., 2016). Depression and somatization have been shown to correspond with patient reported clinical disease activity without correlation to mucosal inflammation (Gracie et al., 2016). This is not indicative alone of one condition serving as a precursor for the other, but more so provides support for the need to identify and treat both depression and CD.

Higher Patient Health Questionnaire 8 (PHQ-8) scores (≥ 5 consistent with mild depression and ≥ 10 consistent with moderate to severe depression) have been correlated with poorer clinical outcomes and decreased time to clinical recurrence (Kochar, Barnes, et al., 2018). This same association between depression, and to a lesser degree anxiety, has been shown to correlate with decreased interval to clinical recurrence. The published research available demonstrates a statistically significant relationship between depression and clinical recurrence in both CD and UC patients who reported clinically relevant symptoms of depression (HADS score >7) that correlated to shorter intervals until clinical recurrence in comparison to their counterparts without depressive symptoms (Mikocka-Walus et al., 2016). Gaines et al. (2020) documented evidence supporting their hypothesis that the affective-cognitive dimension of depression can serve as a predictor of patient reported CD activity, but not the converse.

A trend was identified that CD patients were at increased risk for major depression when compared with UC patients; 42.4% of patients with active disease were identified to be at increased risk for major depression. These findings were further supported when a correlation between increased disease activity, elevated fecal calprotectin (biochemical measurement of

inflammation in the intestines), and decreased QOL scoring correlated with PHQ-9 scores indicative of depression (Geiss et al., 2018). Immunomodulator (IMM) therapy is considered escalated treatment in the medical care of IBD, and it has been identified that CD patients with symptoms of anxiety and depression were more likely to be treated with IMM in comparison to their UC counterparts. Increased corticosteroid utilization was also observed in CD patients with depression (Navabi et al., 2018). CD patients with symptoms of depression/anxiety demonstrated higher CDAI scores and higher simple endoscopic scores for CD (SES-CD) when compared to a matched cohort without depression/anxiety symptoms. The same cross-sectional study from the southwest China IBD referral center found those CD patients with depression/anxiety symptoms compared to those without depression/anxiety symptoms were prescribed corticosteroids more frequently (42% vs 28.3%) and had an increased likelihood of undergoing surgery related to CD (56.5% vs 41.5%) (Gao et al., 2021).

Active CD can result in disability related to the objective loss of functioning and the possible physical manifestations of the disease such as fatigue, diarrhea, abdominal pain, nutritional deficiencies, or arthralgias. Increased disability levels related to CD have been found with increased levels of depression, decreased QOL, and increased anxiety (Chan et al., 2017). Patients with CD have demonstrated markedly worse impairments of QOL compared with UC patients (IsHak et al., 2017). The observation of higher depression scores correlating with an increase in symptoms reported by Tomazoni & Benvegnù's (2018) in their cross-sectional survey supports that CD QOL may have a relationship with depressive symptom reporting and disease activity. The median duration of absenteeism in CD has been estimated at 120 days, and treatment with Tumor Necrosis Factor (TNF) antagonists/anti-TNF medication has been shown to be associated with work productivity loss (Williet et al., 2017). Anti-TNF medications are

utilized later for treatment in “step up” approach for severe disease or initially in severe disease phenotypes using the “top-down” approach (Tsui & Huynhb, 2018). This suggests that severe disease may impact potential work disability (Williet et al., 2017). This evidence should be of potential concern due to the findings of a two-year retrospective chart review identifying that when depressive symptoms, evaluated using a PHQ-9 (score ≥ 10), are present at baseline, they were associated with anti-TNF therapy non-adherence and that prevalence of depressive symptoms was higher in the population that stopped medication due to non-compliance rather than a medical reason (Calloway et al., 2017). Additionally, CD patients that were depressed at baseline via PHQ-8 were found to have a 2.5 times higher risk to be taking narcotics at 24-month follow-up (Kochar, Barnes, et al., 2018).

Evaluation of hospital readmission rates of CD patients post discharge demonstrated that the presence of depression increased the odds of hospital readmission within 90 days. Medicare insurance coverage was observed in 29% of those CD patients, and with increased readmission the potential for medical provider financial penalties could increase exponentially. These findings were highlighted in a retrospective cohort study utilizing data from 2013 obtained from the Nationwide Readmission Database. The findings include that IBD hospitalizations numbered 52,498 with 63% related to CD; and the median total readmission charges for patients with CD were \$25,862 (Barnes et al., 2017). Healthcare utilization for CD patients with anxiety and depressive symptoms was identified to be increased in the areas of hospitalization, imaging, surgical intervention, “no-show” clinic visits, IMM therapy, and corticosteroid usage. When evaluated separately there was no statistically significant difference between only depression or only anxiety (Navabi et al., 2018). Depression was correlated with a quantifiably significant increase in healthcare cost in commercially insured patients with CD; increased utilization was

identified in the areas of emergency department visits, likelihood of computed tomography (CT), and surgical interventions (Wong et al., 2019).

The findings discussed in this section support a relationship between depression and CD, and further support the concept of bidirectionality of these conditions without suggesting one as a precursor, but more of an interconnected relationship. Early identification through routine screening and subsequent intervention related to depression in the CD population may result in prevention of any potential negative relationship, overall improved disease outcomes, and promote the curtailing of increased healthcare utilization and associated costs.

Evaluation/measuring of depression in CD

The increased prevalence of depression in not only the IBD population, but more specifically the CD population, has repeatedly been documented. This supports the implementation of a well validated depression screening tool to be utilized as part the paradigm of CD patient care. There has been no significant research reported to date about what percentage of IBD patients have been screened for depression routinely, but one study found that only 36% of individuals with IBD and symptoms of depression had seen a mental health professional the year preceding survey completion (Bhandari et al., 2017). Use of PHQ-8 was demonstrated more sensitive than a single self-report question assessing depression. Higher PHQ-8 scores have been shown to correlate with poorer clinical outcomes and decreased time to clinical recurrence. In the same study, it was reported that 20% of CD patients self-reported being depressed at baseline with 38% scoring positive for depression per PHQ-8 scale ($p < 0.01$) (Kochar, Barnes, et al., 2018).

PHQ-9 is a nine-item self-administered screening tool specific for depression. PHQ-9 is the same tool as PHQ-8 with the addition of one question specifically focused on suicidal ideation (SI). It is a simple rapid tool with clear criteria for depression severity. PHQ-9 focuses on the

Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for Major Depressive Disorder (MDD) (Kroenke et al., 2001). PHQ-9 is provided online by the American Psychiatric Association as the Disorder-Specific Severity Measure for depression (American Psychiatric Association, 2022). PHQ-9 is available at no cost in the public domain and is currently being utilized routinely in clinical settings. When compared for both reliability and validity against Hamilton Depression Scale (HAMD-17) there was a statistically significant correlation between the two tools demonstrated, and this further supports the use of PHQ-9 for even the most severe levels of depression (Sun et al., 2020). The composition and content of PHQ-9 inclusive of criteria for MDD is vital due to individuals with CD being considered at increased risk for major depression when compared with individuals with UC (Geiss et al., 2018).

PHQ-9 has been found to have the highest sensitivity (95%) when evaluated against PHQ-2, Hospital Anxiety and Depression Scale, Kessler-6 Distress Scale, and PROMIS[®] for depression identification in the IBD population. None of the depression scales demonstrated superior psychometric properties, but all were considered valid. The use of a self-administered symptom scale, such as PHQ-9, has the benefits of time saved for patient and clinic, benefit of standardized scoring, and continuity of symptom severity monitoring (Bernstein et al., 2018). Multiple screening tools have been studied and implemented in published research. There is a question if the PHQ-9 could potentially overestimate depression due to some symptom overlap between IBD and depression, such as the symptoms of fatigue and appetite change, but when IBD patients that screened positive with PHQ-9 were evaluated, 90% had a depression diagnosis confirmed by a psychiatrist (Byrne et al., 2017).

There has not been a significant amount of research specifically related to suicidality in the IBD patient population. PHQ-9 specifically assesses suicidality in item 9 inquiring about thoughts self-harm and if the individual feels that they would be better off dead. These specific questions have been validated as a screen for suicide risk/suicidal ideation. SI has been documented to be prevalent in IBD patients with one study measuring SI at a rate of 5.25% with the majority patients being male, white, and having CD. This same study demonstrated direct correlation between SI and depression severity and decreased QOL related to IBD (Hashash et al., 2019). PHQ-9 has shown 100% sensitivity and 92.2% specificity for identification of SI in the IBD population; substantial agreement between the SI questions in the Structured Clinical Interview for DSM-IV and PHQ-9 has been observed (Litster et al., 2018). The presence of depression was also found to have a positive correlation with reported SI with both SCID and PHQ-9 (Litster et al., 2018). A Swedish nation-wide matched population cohort study, with an 11-year average follow up, found that individuals with IBD, CD and UC, had an increased frequency of suicide attempts, but that only the CD population had a statistically significant increase for completed suicide (Ludvigsson et al., 2021).

Patient perspectives

The evolving healthcare landscape has moved toward actively engaging the patient in the plan of care and trajectory of their healthcare experience. Autonomy for the well-informed patient/consumer is a driver in today's healthcare landscape. Support and education with the goal of allowing for an educated consumer involved in the decision-making process is valued, yet minimal current published research is available examining the perspective of the individual with CD and their viewpoint related to psychological health, desire for services, and perceptions of psychological care. The perceived severity of the impact of psychological factors of IBD by

providers and patients varies. Patients have reported that they believe that IBD can result in negative psychosocial impact and that there is an exacerbation of symptoms when they experience anxiety or depression. It has been reported that over 80% of providers disclosed never having asked about the impact of IBD on patient sexual life, and approximately 60% never inquired about the impact of disease on emotional state or in the workplace (Marín-Jiménez et al., 2017). A majority of patients reported that they feel it is important for their provider to inquire during regular visits about the impact of IBD on personal relationships and psychological wellness. Patients reported that treatment for psychological conditions should be part of their care, and that inclusion of a clinical psychologist as part of their treatment team was appropriate (Marín-Jiménez et al., 2017).

A mixed method research study that utilized qualitative semi-structured face to face interviews reported findings supporting that depressive and anxiety symptoms were prevalent in the IBD population with specific themes and subthemes identified related to those symptoms. Symptoms of low mood were associated with fear of judgement and stigma, with the subthemes of lack of others understanding of the disease and concerns of perceived cleanliness. Jordan et al. (2017) found that patient self-report, perceptions, and lived experiences were consistent with past literature; the predominant qualitative aspect of the study was integrated with the quantitative well validated screening tools Generalized Anxiety Disorder 7-item (GAD-7) and PHQ-9. Qualitatively, themes and subthemes related to symptoms of anxiety and depression have been consistent; while patients have additionally expressed the desire for psychological care from a specialist familiar with the IBD disease process (Jordan et al., 2017). Participant lived experience supports the integration of routine depression screening during care through both qualitative findings and participant reported desire for psychological care from a

professional with specialized IBD knowledge.

Discussion

My proposed recommendation for practice change is the integration of routine depression screening of CD patients in the outpatient gastroenterology clinic setting utilizing PHQ-9. Current research demonstrates a consistent presence and prevalence of depression as a comorbidity with CD. The impact and frequency of depression in the CD population has been associated with alterations in disease activity, measures related to QOL, disability, and potentially self-care. The American College of Gastroenterology (ACG) has acknowledged the potential role psychological conditions may play in CD and published the following recommendation in 2018:

Perceived stress, depression, and anxiety, which are common in IBD, are factors that lead to decreased health-related quality of life in patients with Crohn's disease, and lead to lower adherence to provider recommendations.

Assessment and management of stress, depression, and anxiety should be included as part of the comprehensive care of the Crohn's disease patient

(Strong recommendation, very low level of evidence) (Lichtenstein et al., 2018, p. 495).

Although the level of evidence was considered very low the recommendation was strong, I would encourage providers to adopt the ACG recommendation for depression screening of CD patients with the goal of integrated holistic treatment.

At the time of this review, the United States Preventive Services Task Force (USPSTF) published a recommendation related to depression screening in adults ≥ 18 years of age stating: "The USPSTF recommends screening for depression in the general adult population, including pregnant and postpartum women. Screening should be implemented with adequate systems in

place to ensure accurate diagnosis, effective treatment, and appropriate follow-up” (Siu et al., 2016, p.380). I would encourage gastroenterology providers to adopt the USPSTF recommendation as part of routine care in their adult CD patients and to utilize PHQ-9 for such routine screening. The PHQ-9 would be an ideal tool for practice integration because of patient self-administration, ease in rapid scoring, and high specificity.

The routine screening for depression would assist in the identification and proper referral/treatment addressing depression in this population of interest. Screening and treating/referring, as appropriate may improve the clinical course of CD patients as well as have the potential to improve domains of the individuals’ lives not directly measurable endoscopically, serologically, or histologically.

The primary limitation of this literature review was that only one reviewer, the author, engaged in the evaluation of the material from initial search to inclusion. This potential for bias was addressed and mitigated using the formally published methods and standards for literature review and evaluation, PRISMA and the JHEBNP evidence rating scales.

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