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Review

Influence of the Gut-Brain Axis on Psychiatric Comorbidity in Inflammatory Bowel Disease

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Abstract

Individuals living with inflammatory bowel disease are at a heightened risk of developing certain psychiatric disorders and the gut–brain axis has been proposed as a potential contributor. In the context of the relationship between inflammatory bowel disease and psychiatric disorders, this comprehensive review examines the influence of the gut–brain axis by addressing (i) psychiatric comorbidity, (ii) the role of the gut microbiome and its metabolites, (iii) therapeutic approaches for depression and anxiety, and (iv) psychosocial stressors and microbiome interactions. There is a bidirectional relationship between inflammatory bowel disease and psychiatric conditions, particularly anxiety and depression, which arises from a complex interplay of genetic susceptibility, dysregulation of the gut–brain axis, and neuroimmune processes. Disturbances in gut microbiome composition represent a core mechanism underlying psychiatric comorbidities related to inflammatory bowel disease, although a substantial body of the current knowledge is derived from preclinical models. The integration of microbiome-based therapies into routine clinical practice is still in its early stages, which highlights the need for further research to establish their safety and effectiveness. A deeper understanding of the differences between Crohn's disease and ulcerative colitis is also pivotal for interpreting therapeutic responses. Ultimately, innovations in nutritional psychiatry and precision medicine hold promise for improving the lives of patients affected by these physical and mental comorbid conditions.

Keywords: inflammatory bowel disease; Crohn's disease; ulcerative colitis; gut–brain axis; gut microbiome; microbial metabolites; psychiatric disorders; anxiety; depression; therapeutic approaches

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1. Introduction

Autoimmune diseases comprise a heterogeneous group of chronic systemic conditions marked by exaggerated immune activation, persistent inflammation, and the widespread deposition of immune complexes within tissues and organs, often induced by abnormal immune responses, including aberrant B and T cell reactivity to self-tissues and the production of autoantibodies [1]. These disorders arise from the failure of the immune system to accurately distinguish self from non-self, a process commonly referred to as the loss or breakdown of immunological tolerance. Understanding the mechanisms underlying this loss of tolerance is essential for elucidating the pathophysiology of autoimmune diseases [2]. Their development is complex and multifactorial, influenced by genetic susceptibility, alterations in immune regulation, and environmental determinants such as lifestyle habits, dietary factors, and pharmacological exposures [3].

Immune-mediated inflammatory diseases constitute a group of chronic disorders driven by aberrant immune responses and sustained inflammation. This category encompasses conditions such as multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease (IBD) [4]. IBD is a relapsing autoimmune disorder that includes Crohn's disease (CD) and ulcerative colitis (UC). It primarily affects the gastrointestinal (GI) tract and results from a complex interplay between genetic susceptibility, environmental exposures, and alterations in the gut microbiome (GM) [5]. Over recent decades, both the incidence and prevalence of IBD have shown an increasing trend and are expected to continue rising through 2050, with disease onset most commonly occurring between the second and fourth decades of life [6,7]. For instance, the predicted incidence of IBD in various geographical contexts exhibited notable fluctuations: (i) in Canada, ranging from 0.65% in 2014 to 0.83% in 2025, 0.96% in 2035, and 1.05% in 2043; (ii) in Denmark, from 0.86% in 2014 to 1.19% in 2025, 1.44% in 2035, and 1.59% in 2043; and (iii) in Scotland, from 0.74% in 2014 to 1.04% in 2025, 1.32% in 2035, and 1.51% in 2043 [6]. Importantly, individuals with IBD often experience fatigue, anxiety, and depression during active disease phases, with some of these symptoms being perceived as more burdensome than diarrhea, flatulence, or pain [8,9]. In fact, these manifestations represent the most frequent extraintestinal symptoms associated with IBD and occur independently of direct GI involvement [10–12].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) [13] defines depressive disorders as conditions characterized by a persistent sad, empty, or irritable mood, accompanied by cognitive and somatic changes that substantially impair daily functioning. Major depressive disorder (MDD) is diagnosed when individuals exhibit at least five characteristic symptoms, which may include depressed mood, loss of interest or pleasure (i.e., anhedonia), significant fluctuations in weight, psychomotor agitation or retardation, persistent fatigue or diminished energy, feelings of worthlessness or excessive guilt, sleep disturbances such as insomnia or hypersomnia, reduced concentration or decisiveness, and recurrent thoughts of death or suicidal ideation [13]. As in IBD, the etiology and pathogenesis of depression is multifactorial, influenced by an interplay of psychological, biochemical, genetic, and social determinants [14].

Individuals living with IBD are at a heightened risk of developing certain mental disorders, particularly depression and anxiety, partly as a result of the chronic course of the condition and the ongoing need to implement coping and self-management strategies [15]. Nevertheless, elevated rates of depression and anxiety have been documented even in the years preceding an IBD diagnosis, implying that such psychiatric manifestations are not uniquely reactive to the burden of chronic illness [15,16]. Thus, they may also reflect underlying dysregulation of physiological pathways common to both conditions [15,16]. Evidence from retrospective cohort studies further indicates that the presence of depression increases the subsequent risk of developing IBD, whereas antidepressant use appears to mitigate this risk [16]. In turn, pharmacological treatments typically prescribed for IBD have also been shown to alleviate depressive symptoms [17].

Disruptions in the GM constitute another factor strongly implicated in the pathogenesis of IBD. In this respect, several review studies have documented an increased abundance of pathogenic bacterial taxa, such as *Escherichia coli* and *Klebsiella* spp., accompanied by a notable depletion of beneficial microorganisms, including *Clostridium* spp. and *Bacteroides fragilis*, in individuals with IBD [18–21]. In addition to bacteria, both viral and fungal communities contribute to disease modulation. Indeed, certain viruses have been shown to exert anti-inflammatory or protective effects [22], whereas others, such as norovirus, can aggravate intestinal inflammation [23]. Regarding the fungal domain, increased colonization by *Malassezia restricta* has been linked to the exacerbation of IBD symptoms in murine

models [24]. Conversely, supplementation with *Saccharomyces cerevisiae* has demonstrated preventive and therapeutic benefits, attenuating UC manifestations in mice [25].

Within the conceptual framework of the gut–brain axis (GBA), evidence has revealed both phenotypic correlations and shared genetic factors linking IBD to various psychiatric disorders [26]. Communication within the GBA appears to be influenced by numerous biological and environmental agents, which collectively play a pivotal role in mediating the bidirectional interactions between the gut and the central nervous system (CNS) [27]. Proposed mechanisms underlying this relationship include the activation of neuroinflammatory pathways, disruption of blood–brain barrier (BBB) integrity, and alterations in GM composition [28]. In recent years, considerable research has focused on elucidating the connections between IBD and psychiatric disorders, between psychiatric disorders and GM dysbiosis, and between GM dysbiosis and IBD [29–32]. In this context, evidence suggest that perturbations in the GBA may partially contribute to the elevated comorbidity observed between GI disorders and psychiatric disorders [33,34].

The relationship between psychiatric disorders and IBD appears to be multifaceted, bidirectional, and is not yet fully understood. Inflammatory activity, GM disturbances, and adverse effects of pharmacological treatments may constitute key factors influencing the psychological well-being of individuals with IBD [35]. Given the notably high prevalence of depression and anxiety within this population, current clinical guidelines could benefit from explicit recommendations for the routine evaluation and management of mental health issues in IBD patients. Consequently, systematic monitoring for mood disorders in IBD should be integrated into a multidisciplinary approach to patient care. This comprehensive review examines the contribution of the GBA to the relationship between IBD and psychiatric disorders by addressing (i) psychiatric comorbidity in IBD, (ii) the role of the GM and its metabolites in IBD and psychiatric disorders, (iii) therapeutic approaches for depression and anxiety in IBD, and (iv) psychosocial stressors and microbiome interactions in IBD.

2. Method

A non-systematic narrative approach was adopted to integrate a wide range of literature addressing multiple facets of the topic under examination. The literature search was conducted using the PubMed, Scopus, and Web of Science databases, without temporal or language restrictions. In addition, reference lists from relevant articles were reviewed to identify further studies of interest. The selection process consisted of two steps. First, titles and abstracts were screened to exclude studies deemed irrelevant. Subsequently, the full texts of the remaining articles were reviewed, and only those that met the established criteria were retained. The inclusion criteria focused on studies exploring the relationship between IBD and psychiatric comorbidities, the influence of the GBA in this relationship, mechanisms linking GM dysbiosis to psychiatric disorders, therapeutic approaches for anxiety and depression in the context of IBD, and psychosocial factors associated with IBD. Exclusion criteria encompassed studies that did not involve IBD patients or were not directly or indirectly relevant to the relationship between IBD, psychiatric conditions, and the GBA. Theses, conference abstracts, and letters were also excluded. Given the narrative nature of this review, no formal analysis of study quality was conducted. Data extracted from the selected studies were synthesized and organized into thematic sections, providing structure to the review.

3. Psychiatric Comorbidity in IBD

As previously noted, research has reported a higher prevalence of neuropsychiatric disorders among individuals with IBD, ranging from mild depressive symptoms to se-

vere forms of schizophrenia and dementia. However, estimates of these prevalence rates vary across studies. As outlined by Fousekis et al. [36], the spectrum of mental health conditions associated with IBD can be classified into four main categories: (i) psychiatric disorders, including depression, anxiety, bipolar disorder (BD), and schizophrenia; (ii) dementias, such as Alzheimer's disease (AD), Parkinson's disease (PD), and vascular dementia; (iii) autism spectrum disorders (ASD); and (iv) genetic syndromes, such as Down, Turner, and Williams syndromes.

A systematic review has shown that individuals with IBD exhibit a higher prevalence of anxiety and depression compared to the general population, with reported rates of 19.1% versus 9.6% for anxiety and 21.2% versus 13.4% for depression, respectively [37]. These rates were reported to be notably elevated during periods of active disease. Risk factors contributing to depression in IBD patients include age, disease severity, lifestyle, socioeconomic and sociodemographic characteristics, family history, and environmental stressors (e.g., the COVID-19 lockdown) [38–40]. Furthermore, various studies indicate that suicidal ideation occurs in approximately 6% of patients with IBD [41,42]. In turn, the association between BD and IBD remains inconsistent. A population-based cohort study conducted in the United States and New Zealand reported lower rates of BD among IBD patients compared with controls [43]. In contrast, a cross-sectional study in Taiwan found an increased likelihood of BD in IBD patients [44], while a national cohort study in Denmark observed elevated risk only in patients with CD [45]. Regarding schizophrenia, two Canadian cohort studies reported higher incidence rate ratios among IBD patients relative to age- and sex-matched controls, although findings were not entirely consistent [4,46]. Conversely, a general population-based study in the United Kingdom found no evidence of an increased risk of schizophrenia in patients with CD or UC compared with the general population [47].

A systematic review and meta-analysis conducted by Barberio et al. [10], which included subgroup analyses based on country, gender, location and activity of the disease, and the methods used to define anxiety and depression, reported a high prevalence of psychiatric symptoms among patients with IBD. Approximately one-third of patients exhibited anxiety symptoms, while around one-quarter experienced depression symptoms. It is important to note that the prevalence of depression in IBD may be underestimated, as overlapping symptoms such as fatigue, sleep disturbances, or somatic complaints can resemble active GI disease or other psychiatric comorbidities, potentially resulting in misdiagnosis or delays in recognition. This diagnostic complexity likely contributes to the variability noted across studies and underscores the importance of implementing standardized screening protocols in clinical practice. In a separate review, Arp et al. [48] identified 69 studies encompassing an average cohort size of 60,114 patients. Pooled prevalence estimates indicated that mood disorders affected 10% of patients, anxiety disorders 12%, substance misuse 3%, personality disorders 3%, psychotic disorders 2%; behavioral disorders 1%, developmental disorders 1%, and emotion-related disorders with onset typically during childhood 1%. Moreover, seven studies reported an increased risk of suicide in patients with IBD relative to control populations. More recently, a systematic review including 26 studies confirmed a significantly higher overall prevalence of psychiatric comorbidities in IBD patients compared with the general population. Meta-analytic results revealed significant associations between IBD and depression and anxiety. A significant association was also observed for BD, although notable heterogeneity was reported. In contrast, only three studies addressed the relationship between schizophrenia and IBD, yielding heterogeneous and inconclusive findings [49]. Table 1 summarizes the prevalence of psychiatric disorders in patients with IBD.

Table 1. Prevalence of psychiatric disorders in patients with IBD.

Study/Country	Study Design	IBD Subjects	IBD Diagnosis	Effects Estimates (95% CI)
Bernstein et al., 2019 [46]/Canada	Retrospective cohort	*N* = 6119 IBD patients Control: *N* = 30,573 Follow up 10 years	ICD-9-CM/ICD-10-CA codes	D: IRR = 1.58 [1.41–1.76] A: IRR = 1.39 [1.26–1.53] BD: IRR = 1.82 [1.44–2.30] S: IRR = 1.64 [0.95–2.84]
Bernstein et al., 2021 [50]/Canada	Retrospective cohort	*N* = 4623 IBD patients Control: *N* = 22,207 Follow up 16 years	ICD-9-CM/ICD-10-CA codes	BD: OR = 1.68
Bhamre et al., 2018 [51]/India	Prospective case–control	*N* = 70 IBD patients Control: *N* = 100	D: PHQ-9/HAM-D A: SCL-A20/HAM-A	D: OR = 9.4 A: OR = 11.17
Bhandari et al., 2017 [52]/USA	Retrospective cohort	*N* = 2,235,226 IBD patients Control: *N* = 190,269,933	D: questionnaire on any depressive symptoms	D: OR = 3.1
Bisgaard et al., 2023 [53]/Denmark	Nationwide population-based cohort	*N* = 22,103 IBD patients Control: *N* = 110,515 Follow up 9.7–10 years	ICD-10 codes	D: OR = 1.4 and 1.5 after 10 years A: OR = 1.4 and 1.3 after 10 years BD: OR = 0.9
Blackwell et al., 2021 [54]/UK and Denmark	Nested case–control	*N* = 10,829 patients with UC, *N* = 4531 patients with CD, Control: *N* = 15,360 Follow up 7.4 years	Codes from CPRD	D: OR = 1.47 UC; OR = 1.41 CD
Choi et al., 2019 [55]/Korea	Nationwide population-based cohort	*N* = 15,569 IBD patients Control: *N* = 46,707 Follow up 6 years	ICD-10 codes	D: OR = 2.06 CD; OR = 1.93 UC A: HR = 1.58 [1.43–1.74] CD; HR = 1.58 [1.38–1.82] UC
Cooney et al., 2024 [56]/UK	Retrospective, observational study	*N* = 3898 IBD patients Control: *N* = 15,571	ICD-10 codes	D: aHR = 1.34 [1.16–1.56] A: aHR = 1.25 [1.06–1.48] BD: aHR = 0.74 [0.34, 1.59]
Fuller-Thomson et al., 2015 [57]/Canada	Cross-sectional survey	*N* = 269 IBD patients Control: *N* = 22,522	GAD	A: OR = 2.18
Hernández Camba et al., 2022 [58]/Spain	Cross-sectional survey	*N* = 61 patients with UC, and *N* = 36 patients with CD Control: *N* = 596	DASS-21	D: OR = 2.46 A: OR = 1.35
Irving et al., 2021 [59]/UK	Retrospective cohort	N = 19,011 IBD patients Control: N = 76,044 Follow up 1 year	Algorithms validated in UK primary care	D: OR = 1.31 A: OR = 1.15
Kao et al., 2019 [44]/Taiwan	Cross-sectional survey	*N* = 3590 IBD patients Control: *N* = 14,360	ICD-9-CM codes	BD: OR = 2.10
Kim et al., 2023 [60]/Korea	Retrospective cohort	*N* = 32,867 IBD patients Follow up 6 years	ICD-10 codes	D: OR = 1.39
Larussa et al., 2020 [61]/Italy	Cross-sectional survey	*N* = 143 patients with UC and *N* = 59 patients with CD	S-IBDQ, HADS, B-IPQ	D: OR = 2.45
Liu et al., 2025 [38]/UK	Prospective cohort from a UK biobank	*N* = 2851 patients with UC and *N* = 1200 patients with CD Control: *N* = 394,851 Follow up 13,6 years	ICD-10 codes	PDs: HR = 1.21 [1.11–1.33] UC; HR = 1.15 [1.01–1.31] CD
Ludvigsson et al., 2021 [62]/Sweden	Nationwide population-based cohort	*N* = 69,865 IBD patients Control: *N* = 3,472,913 Follow up 8 years	National patient register	D: HR = 1.4 [1.4–1.5] A: HR = 1.3 [1.3–1.4] BD: HR = 1.1 [1.1–1.2]
Ma et al., 2023 [39]/UK	Prospective cohort from a UK biobank	*N* = 3561 IBD patients Control: *N* = 493,573 Follow up 13.3 years	ICD-10 codes	D: HR = 1.56 [1.39–1.76] overall, HR = 1.54 [1.25–1.90] CD, HR = 1.52 [1.30–1.78] UC
Marrie et al., 2017 [4]/Canada	Retrospective cohort	*N* = 6119 IBD patients Control: *N* = 97,727 Follow up 23 years	ICD-9-CM/ICD-10-CA codes	D: IRR = 1.71 [1.64–1.79] A: IRR = 1.34 [1.29–1.40] BD: IRR = 1.68 [1.52–1.85] S: IRR = 1.32 [1.03–1.69]
Marrie et al., 2018 [63]/Canada	Retrospective cohort	*N* = 8695 IBD patients Control: *N* = 43,465 Follow up 12.6 years	Validated case definitions	D: OR = 1.45 A: OR = 1.26 BD: OR = 1.44
Roderburg et al., 2024 [64]/Germany	Retrospective cohort	*N* = 9073 patients with UC and *N* = 6761 patients with CD Control: *N* = 31,728 Follow up 5 years	ICD-10 codes	D: HR = 1.4 CD; HR = 1.32 UC A: HR = 1.21 CD; HR = 1.28 UC
Tarar et al., 2022 [65]/USA	Retrospective cohort	*N* = 192,724 IBD patients Control: *N* = 12,848,266	ICD-10 codes	D: OR = 1.28 CD; OR = 1.55 UC A: OR = 1.4 overall

Table 1. *Cont.*

Study/Country	Study Design	IBD Subjects	IBD Diagnosis	Effects Estimates (95% CI)
Thavamani et al., 2019 [66]/USA	Retrospective case–control	*N* = 58,020 IBD patients Control: *N* = 11,316,450	SNOMED-CT	D: OR = 3.94 A: OR = 4.05
Umar et al., 2022 [67]/UK	Retrospective cohort	*N* = 48,799 IBD patients Control: *N* = 190,075	THIN	D: IRR = 1.36 [1.31–1.42] overall, HR = 1.36 [1.26–1.47] CD, HR = 1.30 [1.23–1.36] UC A: IRR = 1.17 [1.11–1.24] overall, HR = 1.38 [1.16–1.65] CD, HR = 1.26 [1.07–1.47] UC
Vigod et al., 2019 [68]/Canada	Retrospective cohort	*N* = 3721 IBD patients Control: *N* = 58,020	ICD-9-CM/ICD-10-CA codes, DSM-IV	D: HR = 1.12 [1.05–1.23] CD, HR = 1.12 [1.05–1.20] UC
Zhang et al., 2022 [69]/Taiwan	Retrospective cohort	*N* = 422 IBD patients Control: *N* = 2148 Follow up 11 years	Depressive disorder	D: OR = 9.43

D, depression; A, anxiety; BD, bipolar disorder; S, schizophrenia; PDs, psychiatric disorders; OR, odds ratio; HR, hazard ratio; aHR, adjusted hazard ratio; IRR, incidence rate ratio; CD, Crohn's disease; UC, ulcerative colitis; ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual of Mental Disorders; PHQ-9, patient health questionnaire-9; HAM-D, Hamilton depression scale; SCL-A20, symptom checklist anxiety scale; HAM-A, Hamilton anxiety scale; CPRD, Clinical Practice Research Datalink; GAD, generalized anxiety disorder; SNOMED-CT, Systematized Nomenclature of Medicine-Clinical Terms; THIN, The health improvement network; S-IBDQ, short inflammatory bowel disease questionnaire; HADS, hospital anxiety and depression scale; B-IPQ, brief illness perception questionnaire; DASS-21, depression anxiety stress scales-short form.

Research has reported that children with ASD frequently experience GI symptoms, including diarrhea, constipation, abdominal pain, and bloating, particularly among those exhibiting more pronounced behavioral challenges such as social withdrawal, sleep disturbances, and self-injurious behaviors [70]. A meta-analysis found that children with ASD have three times higher risk of GI symptoms compared to neurotypical peers [71]. More recently, four case–control studies have shown an increased prevalence IBD in individuals with ASD in comparison to matched controls [72]. In a population-based study including over 48,000 children with ASD, both CD and UC were more prevalent in the ASD cohort compared with control populations [73]. In addition, a retrospective analysis across four Boston hospitals reported a higher prevalence of IBD among hospitalized children with ASD compared with the general inpatient population (0.83% vs. 0.54%) [74].

The elevated risk of dementia among patients with IBD points to be multifactorial, involving chronic systemic inflammation, accelerated atherosclerosis, and hypercoagulable states [36]. Evidence suggests that persistent inflammation may accelerate the progression of AD through BBB disruption and microglial activation [75]. Moreover, the GBA may play a role in the development of PD in IBD patients. In this respect, animal models indicate that alterations in the GM can trigger PD pathology [76], and epidemiological evidence has linked GI infections to an increased risk of PD [77]. IBD has also been associated with heightened risk of thromboembolic events and stroke, likely driven by hyperhomocysteinemia, thrombocytosis, coagulation anomalies, and hyperlipidemia, thereby contributing to the onset of vascular dementia [78]. Notably, vascular dementia accounts for approximately 15% of all dementia cases [79].

3.1. Association Between Psychiatric Comorbidities and IBD Activity

As previously noted, psychiatric comorbidities, especially anxiety and depression, are prevalent among individuals with IBD. Indeed, estimates suggest that approximately 20–30% of patients with IBD experience mood disturbances, with the occurrence of psychiatric disorders tending to rise in conjunction with periods of active intestinal inflammation [80]. For this reason, considerable research has focused on the potential link between psychiatric disorders and the activity of IBD. In general terms, evidence indicates a positive association between active IBD and the presence of depressive or anxiety symptoms, with higher disease activity tending to correlate with increased prevalence and severity of psychiatric comorbidities. Moreover, several studies have proposed that depressive symptoms

may unfavorably influence the disease trajectory [81,82], contributing to poorer clinical outcomes. Some investigations have further indicated that active disease serves as a significant predictor of depression [83,84]. In addition, Chan et al. [85] reported a relationship between depressive symptom severity and IBD-related functional impairment. In contrast, Fairbrass et al. [86] observed that patients exhibiting persistently elevated anxiety or depression scores showed greater healthcare resource use, although this was not accompanied by a higher risk of future adverse disease events. Other studies failed to establish a consistent temporal association between psychiatric symptoms and disease activity [83–85]. Interestingly, Jordi et al. [81] identified allelic variants of two single nucleotide polymorphisms (SNPs) that were inversely correlated with depressive symptoms, one of which was also linked to lower IBD activity. In early stages of IBD, factors associated with anxiety included female sex, a diagnosis of CD, and stressful life events prior to diagnosis, while the only variable related to depressive symptoms was the presence of medical comorbidities [87]. Furthermore, in a large retrospective observational study comprising 3898 individuals with IBD aged between 5 and 25 years, Cooney et al. [56] demonstrated that patients with IBD exhibited a significantly increased risk of developing several psychiatric conditions. Specifically, adjusted hazard ratios (aHR) indicated elevated risks for anxiety, depression, eating disorders, post-traumatic stress disorder, self-harm, and sleep disturbances. The subgroup analysis revealed that male patients aged 12–17 years and those diagnosed with CD had the greatest susceptibility to new-onset mental health conditions. In line with these findings, Rasmussen et al. [88] reported that both CD and UC are associated with a heightened likelihood of psychiatric morbidity, largely attributable to a greater incidence of emotional disorders and increased use of psychotropic medications. In contrast, Askar et al. [89] found no significant association between the severity of depression and anxiety and the severity of UC or CD. These results could be attributed to differences in the studied populations and in the methods employed to assess mental health conditions [89]. Table 2 summarizes several studies exploring the connection between depressive and anxious symptomatology and IBD activity.

Table 2. Studies on the connection between depression and anxiety symptoms and IBD activity.

Study/Country	Study Design	Population	Diagnostic Methods	Results/Outcomes
Askar et al., 2021 [89]/Egypt	Cross-sectional observational study	*N* = 105 patients (23 with CD and 82 with UC) Mean age: 33.2 years	SCID I, HAM-D, and HAM-A	Although the prevalence of depression or anxiety in patients was high (56.1% and 37.1%, respectively), there was no correlation between both the severity of depression and anxiety and the severity of IBD, either UC or CD.
Bernabeu et al., 2024 [87]/Spain	Prospective, multi-center, observational study	*N* = 156 patients (80 with CD and 76 with UC) Mean age: 42.3 years	HADS, IBDQ-32, and PSS	A total of 37.2% of patients exhibited symptoms of anxiety, while 17.3% exhibited symptoms of depression. Quality of life was impaired in 30.1% of patients. Factors associated with anxiety in the early stages of IBD included being female and having CD. The only factor related to depression was the presence of comorbidity. Impaired quality of life was associated with being female and experiencing previous stressful life events.
Byrne et al., 2017 [83]/Canada	Retrospective chart review	*N* = 327 patient chart with CD and UC Age: >18 years	PHQ-9, GAD-7, or by diagnosis through psychiatric interview	Rates of depression and anxiety were 25.8% and 21.2%, with 30.3% of patients suffering from depression and/or anxiety. Disease activity was significantly related to depression and/or to anxiety. Females were more likely to experience anxiety.

Table 2. *Cont.*

Study/Country	Study Design	Population	Diagnostic Methods	Results/Outcomes
Cadogan et al., 2025 [90]/Canada	Cross-sectional study	*N* = 154 patients with IBD (63% CD) Age: >18 years	SCID I and DSM-5 categorization	Of 154 IBD participants, 57% had at least one psychiatric comorbidity with 27% having more than one psychiatric diagnosis. The prevalence was MDD (41.7%), anxiety disorders (39.6), SUD (16.2%), PTSD (5.3%), OCD (4.9%), and BD (2.0%). Of those with >1 psychiatric disorder > 70% had MDD and a comorbid anxiety disorder. Individuals with one or more psychiatric comorbidities were more likely to be current smokers and to exhibit higher IBD activity scores compared to those without psychiatric comorbidities.
Chan et al., 2017 [85]/Singapore	Cross-sectional study	*N* = 200 patients (95 with CD and 105 with UC) Age: >18 years	IBD-DI, HADS, and IBDQ	Symptoms related to anxiety and depression were common in this cohort of IBD and were strongly associated with IBD-related disability.
Cooney et al., 2024 [56]/UK	Retrospective, observational study	*N* = 3898 patients with IBD Age: 5–25 years	ICD-10	IBD patients were significantly more likely to develop new PTSD, eating disorders, self-harm, sleep disturbance, depression, anxiety, and any mental health condition. Male IBD patients aged 12 to 17 years, and patients with CD seem to exhibit the highest risk for the onset of new mental disorders.
Fairbrass et al., 2023 [86]/UK	Longitudinal study. Follow up for 12 months	*N* = 1548 patients with IBD Age: >18 years	HADS, PHQ-12, and SIBDQ	Only subjects with persistently abnormal or worsening depression scores were more likely to be referred to a gastroenterologist or IBD nurse specialist in the outpatient clinic.
Gao et al., 2021 [91]/China	Cross-sectional study	*N* = 341 patients (221 with CD and 120 with UC) Mean age: 33 years	HADS	The prevalence of anxiety/depression symptoms in IBD patients was 33.1%. Those with CD experiencing these symptoms tended to show higher endoscopic severity scores compared to those without anxiety or depression.
García-Alanís et al., 2021 [92]/Mexico	Cross-sectional study	*N* = 104 patients (12 with CD and 92 with UC) Mean age: 41.8 years	IBDQ-32 and SCID-I	The prevalence of any major mental disorder in IBD patients was 56.7%, with specific rates for anxiety (44.2%), mood disorders (27.9%), SUD (12.2%), and other psychiatric conditions (17.3%). From total, 29.8% of the patients presented three or more comorbid diagnoses. SUD was associated with lower digestive quality. MDD, social phobia, PTSD, and GAD were found to be significantly related to lower life quality.
Jordi et al., 2022 [81]/Switzerland	Prospective cohort study	*N* = 1973 patients (1137 with CD and 836 with UC) Age: 24.6–50 years	HADS	The prevalence of depression was found to be high in IBD patients, with active disease further increasing the risk for depression. Conversely, depressive symptoms also independently increased the risk for IBD flare-ups over time and appear to have a negative impact on various disease outcomes. In addition, the alleles of two SNPs (*rs588765-TC*, *rs2522833 C* allele) were found to be negatively associated with depressive symptoms in IBD patients, with the *rs588765-TC* allele combination also linked to lower IBD activity.
Nadeem et al., 2024 [93]/USA	Retrospective, cohort study	*N* = 69,105 patients with IBD Age: >18 years	ICD-10	Patients with active IBD were significantly more likely to develop MDD, anxiety, BD, alcohol use disorder, opiate use disorder, ADHD, and OCD. In addition, these patients were also more likely to use a wide range of psychotropic drugs, such as antidepressants, antipsychotics, anxiolytics, sedatives, hypnotics, mood stabilizers, stimulants, and medications employed for SUD.
Oyama et al., 2022 [82]/Japan	Case–control study based in a nationwide database	*N* = 159,481 patients (78,230 with CD and 81,251 with UC) Age: >18 years	ICD-10	The study found an association between a more severe clinical course of UC and depression. This finding suggests that depression could be related to increased disease activity in patients with UC, but the causal relationship remains unclear. In the analysis of CD, only steroid treatments were found to be associated with depression.

Table 2. *Cont.*

Study/Country	Study Design	Population	Diagnostic Methods	Results/Outcomes
Rasmussen et al., 2025 [88]/Denmark	Nationwide register-based retrospective cohort study	*N* = 4904 patients with CD, *N* = 5794 with UC, and *N* = 94,802 matched references Age: <25 years and follow up until 30 years	ICD-10 K50 and K51 codes	Patients with CD diagnosed before the age of 18 had an increased risk of anxiety (IRR = 1.58), while those diagnosed between the ages of 18 and 24 faced a higher risk of both anxiety and mood disorders. Patients with UC diagnosed before age 18 also showed a higher risk of anxiety (IRR = 1.39). Overall, patients with CD and UC are at an elevated risk for mental health conditions, particularly emotional disorders, and have higher rates of psychotropic drug use.
Riggott et al., 2025 [94]/UK	Prospective longitudinal study. Follow-up 5 years	*N* = 804 IBD patients Mean age: 44 years	HADS and PHQ-15	Among 717 participants with clinical activity data and 187 with both clinical and biochemical activity data, the rates of adverse outcomes were higher with increasing disease activity and greater psychological comorbidity.
Tribbick et al., 2015 [95]/Australia	Outpatient cohort	*N* = 81 IBD patients Mean age: 35 years	HADS, Manitoba Index, and MINI	A percentage of 19.8% participants had at least one anxiety-related disorder, while 11.1% were diagnosed with a depressive disorder. Active IBD was related to higher prevalence rates of both anxiety and depression. GAD was the most common anxiety-related condition (14.8%), and MDD was the most common depressive condition (6.2%).
van den Brink et al., 2018 [84]/The Netherlands	Prospective cohort study	*N* = 374 IBD patients Age: 10–25 years	HADS and SCARED	Mild anxiety or depressive symptoms were present in 35.2% of patients, while severe symptoms were reported in 12.4%. Elevated symptoms of anxiety (28.3%), depression (2.9%), or both (15.8%) were observed, with no significant differences between adolescents (10–17 years) and young adults (18–25 years). Active disease significantly predicted depressive symptoms. Female, active disease, and a shorter disease duration significantly predicted anxiety and/or depressive symptoms.

SCID-I, Structured Clinical Interview for DSM-IV; HAM-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale; PHQ, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder-7 self-report questionnaire; IBD-DI, IBD-Disability Index; HADS, Hospital Anxiety and Depression Scale; IBDQ, IBD questionnaire; SIBDQ, short IBD questionnaire; SNPs, single nucleotide polymorphisms; ICD-10, International Classification of Diseases, 10th Revision; SCARED, Screen for Child Anxiety-related Disorders; MINI, Mini-International Neuropsychiatric Interview; IRR, incidence rate ratio; PSS, Perceived Stress Scale; PTSD, posttraumatic stress disorder; MDD, major depressive disorder; GAD, generalized anxiety disorder; SUD, substance use disorder; BD, bipolar disorder; OCD, obsessive–compulsive disorder; ADHD, attention deficit hyperactivity disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; CD, Crohn's disease; UC, ulcerative colitis.

In summary, the prevalence of depression in IBD varied across studies, with estimates ranging from 11.1% to 56.1% [89,95]. Similarly, anxiety prevalence ranged from 17.3% to 44.2% [87,92]. Despite the high rates of these mood disorders, the existing literature suggested a potential link between anxiety, depression, and IBD flare-ups. Several factors were identified as contributing to the risk of depression and anxiety in patients with CD and UC, including gender [83,87], quality of life [92], genetic influences [81], medication use [93], and age [56,84,88].

3.2. Genetic and Genomic Correlates of Anxiety and Depression in IBD

Evidence suggests that first-degree relatives of individuals diagnosed with CD or UC face a markedly increased risk of developing these disorders themselves [96]. Similarly, anxiety disorders tend to occur within families, with heritability estimates indicating that individuals with an affected relative are four to six times more likely to experience an anxiety disorder [97]. The potential genetic interplay between IBD and mood or anxiety disorders remains complex, underscoring the importance of clinical cohort studies aimed at clarifying the genetic correlations underlying the comorbidity between IBD and psychiatric disorders [98]. Supporting this notion, a population-based cohort study including more than 2.19 million Swedish children born between 1991 and 2011 and their parents demonstrated that offspring of parents diagnosed with anxiety or stress-related disorders

exhibited a modestly increased risk of developing IBD [99]. Nevertheless, the observational nature of such cohort studies makes it difficult to rule out residual confounding, which limits the ability to infer direct causality. Despite this, advances in next-generation sequencing and genomic research now provide powerful tools for elucidating the genetic features of these associations.

The coexistence of IBD with anxiety and depression has been established in both experimental and clinical contexts. In preclinical research, one study utilizing a murine model of dextran sulfate sodium (DSS)-induced colitis analyzed forebrain tissue through RNA sequencing to explore molecular mechanisms underlying this association. Pathway enrichment analysis identified multiple inflammation-related processes, including those involving the IL-17 signaling cascade, modulation of the inflammatory response, and antimicrobial peptide activity. Notably, genes linked to neuroinflammation, such as prostaglandin-endoperoxide synthase 2 (*Ptgs2*), S100 calcium-binding proteins S100A8 and S100A9, and lipocalin 2 (*Lcn2*), were significantly upregulated in DSS-treated mice [100]. Building on these findings, subsequent RNA-sequencing research revealed that *Lcn2* expression was markedly elevated in the paraventricular thalamic nucleus (PVT) of mice exhibiting DSS-induced depressive-like phenotypes. Importantly, targeted silencing of *Lcn2* within the PVT was found to alleviate these depressive behaviors, suggesting a potential mechanistic link between intestinal inflammation, neuroinflammatory signaling, and mood regulation [101].

In a clinical study, transcriptomic profiles from 630 IBD samples retrieved from the Gene Expression Omnibus (GEO) database were examined to identify differentially expressed genes (DEGs) exhibiting significant dysregulation compared to healthy controls. Cross-comparison of these DEGs with a curated set of 153 genes previously associated with depression revealed 33 hub genes that may contribute to the molecular mechanisms underlying the comorbidity of depression and IBD [102]. In another clinical study, patients with IBD presenting depressive symptoms displayed notably reduced expression of two genes related to circadian rhythm in peripheral blood samples compared to IBD patients without mood disturbances. Specifically, circadian locomotor output cycles kaput (*CLOCK*) and nuclear receptor subfamily 1 group D member 1 (*NR1D1*) [103]. Parallel research has focused on identifying molecular signatures common to both IBD and MDD through integrative analyses of DEGs, aiming to clarify the shared biological pathways that may underpin this bidirectional relationship [104,105].

Genome-wide association studies (GWAS) represent an essential component of modern genomics, providing a powerful approach for identifying genetic variants linked to complex phenotypes across the entire genome. Using this methodology, Shaw et al. [106] revealed significant genetic correlations between IBD and psychiatric traits, particularly those related to anxiety and depression. Complementary bidirectional Mendelian randomization (MR) analyses further clarified the causal direction of this relationship. In this respect, genetic liability to IBD did not appear to increase the risk of MDD, but the reverse association (i.e., genetic predisposition to depression influences IBD susceptibility) was statistically significant [107]. Consistent with these findings, a separate investigation reported that individuals carrying a higher genetic risk for depression had an increased likelihood of developing IBD. In contrast, reverse MR analyses revealed no significant causal effect of genetic susceptibility to IBD, or to its subtypes, on depression risk [108].

Also in the context of depression, GWAS analyses of 44 SNPs identified enrichment across 19 biological pathways, many of which were linked to immune regulation and pro-inflammatory cytokine signaling [109]. In a MR study focused on candidate genes, a functional SNP located in the promoter region of the *IL6R* gene was found to influence circulating levels of C-reactive protein (CRP) and interleukin-6 (IL-6), as well as the severity

of depressive symptoms in a large population-based cohort [110]. Moreover, integrative analyses combining GWAS data with human brain proteomic profiling implicated genetic variation in *P2RX7*, which encodes the purinergic receptor P2X7, as a contributor to the pathophysiology of depression [111]. The biological significance of *P2RX7* extends beyond neuropsychiatric pathways, as this receptor modulates activation of the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome, which constitutes an essential regulator of innate immune responses that has also been implicated in the pathogenesis of IBD [112].

A loss-of-function SNP in the *PTPN2* gene, known for its regulatory role in T cell signaling and immunological processes, has been implicated in the pathogenesis of both IBD and psychiatric disorders. Within T cells, *PTPN2* acts as a negative regulator of antigen receptor signaling by dephosphorylating kinases associated with the T cell receptor (TCR) complex. In addition to this function, *PTPN2* is central for maintaining intestinal epithelial integrity, modulating cytokine signaling, and orchestrating T cell differentiation [113]. In experimental studies using *PTPN2*-deficient mouse models, the absence of this gene resulted in impaired insulin secretion and a pronounced reduction in the central release of key neurotransmitters, including norepinephrine, dopamine, and serotonin (5-HT), culminating in alterations consistent with anxiety-like behavioral phenotypes [114].

Lasconi et al. [115] noted a potential shared genetic basis between IBD and depression, emphasizing the central involvement of the hypothalamus and the hypothalamic–pituitary–adrenal (HPA) axis in this connection. Utilizing publicly available GWAS datasets related to both depression and IBD, the authors identified significant genetic correlations between the two conditions, supporting the existence of overlapping genetic determinants and suggesting a mechanistic link between intestinal inflammation and mood dysregulation. Their analysis further revealed that IBD-associated genetic variants were enriched within open chromatin regions of hypothalamic-like neurons and colonoids, implicating hypothalamic pathways in the genetic susceptibility to IBD. Notably, several genes located in hypothalamic cells and associated with IBD risk were found to participate in stress-response signaling, including cAMP-responsive element modulator (*CREM*), ciliary neurotrophic factor (*CNTF*), and Ras homolog family member A (*RHOA*). *CREM* encodes a protein that modulates stress-related transcriptional activity, *CNTF* constitutes a neurotrophic factor released during acute stress that is essential for cortical norepinephrine synthesis and HPA axis regulation, and *RHOA* contributes to the modulation of social stress and depressive-like behaviors by influencing dendritic remodeling within motivational and reward-related neuronal circuits [115]. In addition, a recent integrative study combining gene expression profiling with proteomic analyses identified four genes that appear to play central roles in both IBD and MDD. Specifically, hepatocyte growth factor (*HGF*), secreted protein acidic and cysteine-rich (*SPARC*), a disintegrin and metalloproteinase 12 (*ADAM12*), and matrix metallopeptidase 8 (*MMP8*) were highlighted as key biomarkers involved in inflammatory signaling and immune dysregulation. These findings provide insights on molecular pathways that may link IBD and psychiatric disorders, reinforcing the concept of shared immunological mechanisms that contribute to the pathophysiology of both conditions [104]. Thus, building on the aforementioned, the accumulated evidence indicates that clinical cohort studies and genetic investigations together offer more robust support for a causal effect of depression on the development of IBD, whereas genetic data substantiating a direct causal influence of IBD on depression remain relatively scarce.

3.3. Neurofunctional and Morphological Alterations During IBD

Neuroimaging research has aimed to determine whether individuals with IBD exhibit structural brain alterations compared to healthy controls. Such changes may include varia-

tions in regional brain volumes, although research has also been focused on determining differences in neural activity patterns. Most of this research has been carried out in patients with quiescent disease, largely because corticosteroids, which is the primary treatment for disease flares, are known to exert neuropsychiatric side effects and can influence brain morphology [116].

One of the earliest investigations reporting functional brain alterations in UC employed functional magnetic resonance imaging (fMRI) during a task involving emotionally salient visual stimuli [117]. Patients with UC demonstrated reduced blood oxygen level-dependent (BOLD) responses in the amygdala, thalamus, and cerebellum when exposed to emotionally charged images, suggesting diminished sensitivity to emotional content. More recently, a study integrating structural MRI with resting-state fMRI identified modifications in frontotemporal networks among remitted patients with UC or CD [118]. Interestingly, these network alterations appeared more pronounced in UC than CD, potentially reflecting differences in disease localization that may influence gut–brain signaling and central processing pathways. A separate study of a German UC cohort revealed decreased gray matter volume in the frontal cortex and anterior insula compared to healthy controls [119], findings that align with observations from CD populations [120]. However, other investigations failed to detect significant gray matter changes [121], which may be attributable to differences in previous disease activity or limited sample sizes. In a small-scale study involving nine CD patients, Gray et al. [122] examined the effects of anti-TNF-α therapy on brain function using fMRI and psychological assessments conducted before and after treatment. Administration of anti-TNF-α agents was associated with reduced visceral sensitivity and enhanced cognitive-affective processing, accompanied by functional changes in limbic regions, particularly the amygdala [122].

Although most neuroimaging research has focused on patients with quiescent IBD, studies investigating brain activity in individuals with active disease remain limited. For example, a fMRI study of patients with mild to moderately active UC who had not used corticosteroids in the preceding six months revealed altered activation within the limbic system, particularly in the hippocampus and frontal cortical regions, as well as disrupted functional connectivity between these areas [123]. These neural alterations were associated with deficits in working memory, attention, and executive function, consistent with the established cognitive roles of the affected brain regions. Similarly, Thapaliya et al. [124] assessed brain morphology in patients with active CD, including both those receiving immunosuppressive therapy and those in remission. Compared with healthy controls, patients exhibited reductions in gray and white matter volumes and cortical thickness, particularly within the left motor cortex. Conversely, increases in gray or white matter volume were observed in regions such as the right orbitofrontal cortex and left anterior cingulate cortex. Notably, many of these morphological alterations appeared independent of current disease activity, suggesting that they may represent chronic, enduring changes rather than transient effects of inflammation. However, within the same cohort, CD patients experiencing abdominal pain or extraintestinal manifestations demonstrated region-specific gray matter reductions and cortical thinning compared to patients without such symptoms, indicating that greater disease severity may exacerbate structural brain alterations [124].

An important consideration is whether the structural and functional brain alterations observed in patients with IBD are influenced by comorbid conditions, particularly disorders of gut–brain interaction (DGBIs). DGBIs encompass a range of GI disorders, with irritable bowel syndrome (IBS) being the most prevalent and clinically relevant in this context, as many IBD patients either meet criteria for IBS or exhibit IBS-like symptoms [125]. A recent meta-analysis reported that approximately 32.5% of IBD patients in remission experienced symptoms consistent with IBS [126]. Patients with IBS frequently display psychiatric

comorbidities and neuropsychological changes that resemble those seen in IBD, including abnormalities in brain regions and networks involved in salience detection, emotional arousal, central autonomic regulation, and executive and sensorimotor processing [127]. Meta-analytic comparisons of depression prevalence and severity between IBS and IBD populations indicate that while rates of depression are similar, IBD patients often experience more severe depressive and anxiety symptoms [128,129]. Moreover, Gracie et al. [130] found that IBD patients presenting with IBS symptoms had significantly higher Hospital Anxiety and Depression Scale (HADS) scores for anxiety and depression, as well as elevated somatization scores, compared with IBD patients without IBS-like symptoms, suggesting that overlapping gut–brain dysfunction may exacerbate psychiatric burden.

4. The Role of the GM and Its Metabolites in IBD and Psychiatric Disorders

The GBA underlies bidirectional communication between the CNS and the GI tract, mediated through neural, hormonal, metabolic, immune, and microbial pathways [27]. Alterations in GM composition, such as those observed in IBD, can influence brain function and behavior. Growing evidence suggests that dysregulation within the GBA contributes to the pathophysiology of IBD and psychiatric disorders individually, but also to their frequent comorbidity [30].

4.1. GM Alterations in IBD

Recent research has highlighted the role of the GM in modulating peripheral inflammation in IBD and also in influencing CNS function. IBD is commonly associated with reduced microbial diversity and an overrepresentation of potentially pathogenic taxa, including members of the families *Bacteroidaceae* and *Enterobacteriaceae*, as well as the genus *Fusobacterium*. In contrast, levels of beneficial commensal bacteria are frequently diminished, particularly those from the families *Lachnospiraceae*, *Clostridiaceae*, and *Ruminococcaceae*, as well as species of the genera *Bacteroides* and *Bifidobacterium* [131,132].

Dysbiosis in both CD and UC is characterized by reduced microbial diversity compared with a healthy GM, as well as by distinct compositional shifts across multiple taxonomic levels. At the phylum level, disease-associated patterns typically include decreased Bacillota and increased Pseudomonadota [133]. Notably, beneficial species such as *Bifidobacterium longum*, *Eubacterium rectale*, *Faecalibacterium prausnitzii*, and *Roseburia intestinalis* are markedly depleted in CD and UC, whereas potentially pathogenic bacteria, including *Bacteroides fragilis*, are enriched in abundance and growth rate [20]. Additional overrepresented taxa in IBD patients include *E. coli*, *Ruminococcus gnavus*, *Collinsella* spp., *Blautia* spp., *Fusobacterium* spp., and *Veillonella* spp. [134–142]. In contrast, reductions in genera such as *Akkermansia* and *Eubacterium* have also been reported [136,141], highlighting the dual pattern of loss of protective microorganisms and expansion of potentially harmful species in IBD-associated dysbiosis.

Several studies have reported distinct GM profiles between CD and UC [134,138,142]. In CD, reductions are commonly observed in the families *Christensenellaceae* and *Coriobacteriaceae*, as well as in genera including *Clostridium*, *Coprococcus*, *Faecalibacterium*, *Ruminococcus*, *Prevotella*, *Parabacteroides*, *Lachnospira*, and *Roseburia* [136,138–142]. In contrast, increased abundance has been reported for genera such as *Enterococcus*, *Klebsiella*, *Cetobacterium*, *Dialister*, *Actinomyces*, *Sutterella*, and *Actinobacillus*, as well as for species including *Enterocloster clostridioformis* (formerly *Clostridium clostridioforme*), *Bacteroides fragilis*, and *Ruminococcus torques* [134,136,138–141,143]. In UC, certain genera, including *Bifidobacterium*, *Clostridium*, *Bacillus*, *Peptostreptococcus*, and *Odoribacter*, typically present increased abundance [134,138,142,144,145], whereas *Faecalibacterium* and *Parabacteroides* tend to be

decreased [142,145]. These findings indicate disease-specific microbial signatures that may reflect differences in pathophysiology and gut-immune interactions between CD and UC.

Certain bacterial genera and species have been associated with disease activity in IBD and may hold potential for therapeutic intervention. Xu et al. [146] reported that *Roseburia intestinalis* abundance is significantly decreased in the gut of patients with UC during active disease but that it increases following remission. Supplementation with *R. intestinalis* has been shown to help restore gut microbial homeostasis, in part by promoting short-chain fatty acid (SCFA) production and supporting functional recovery of the GI tract. Recent evidence suggests that the dysbiotic alterations observed in the GM of CD and UC patients are linked to depressive symptoms and changes in neural activity, indicating that microbial imbalance may impact the GBA more broadly [147]. For instance, UC patients with comorbid depression exhibit reduced microbial diversity and abundance, as well as shifts in dominant taxa such as Bacillota, Pseudomonadota, and Clostridia, compared to UC patients without depression [148]. Similarly, *Phocaeicola* (formerly *Bacteroides*) *vulgatus* is less abundant in IBD patients experiencing depressive symptoms compared to those without [149]. In a DSS-induced colitis mouse model, administration of *P. vulgatus* resulted in lower disease activity scores, reduced weight loss, and longer colon length compared to untreated DSS mice. Notably, *P. vulgatus* also alleviated depression-like behaviors in both DSS-induced colitis and LPS-induced depression models [149]. Furthermore, in hyperlipidemic rats, *P. vulgatus* contributed to the degradation of complex carbohydrates, SCFA production, and improvement of lipid metabolic disorders, thereby supporting gut health and metabolic regulation [150].

Bacteriophages consist of viruses that specifically infect bacteria and play a pivotal role in maintaining the stability of microbial communities and in shaping GM composition. The most commonly studied groups include Caudovirales, Microviridae, crAssphages, and Gubaphages [151,152]. Several studies of the gut virome have reported a marked increase in viral abundance, predominantly bacteriophages, in patients with IBD [23,153]. Interestingly, this expansion in phage populations does not appear to correlate directly with shifts in bacterial composition [154,155]. In both UC and CD patients, elevated levels of Caudovirales have been observed in the intestinal mucosa compared to healthy controls. However, this is accompanied by reductions in viral diversity, evenness, and richness, affecting both Caudovirales and the virome [156,157]. On the other hand, some studies analyzing fecal samples have found no significant differences in the virome between CD patients and controls [136,158]. Methodological variations in virus particle enumeration likely contribute to these inconsistencies, highlighting the need for standardized approaches in gut virome research.

The gut mycobiome in IBD also exhibits dysbiosis, typically characterized by reduced fungal diversity and an increased Basidiomycota/Ascomycota ratio [159,160]. In both UC and CD patients, a decrease in *Saccharomyces cerevisiae* and an increase in several *Candida* species, including *C. albicans*, *C. tropicalis*, and *C. glabrata*, have been reported [161–163]. Additional alterations include increased abundance of the family *Cystofilobasidiaceae* and decreased abundance of genera such as *Leptosphaeria* and *Trichosporon* [163,164]. Interestingly, in pediatric IBD, *S. cerevisiae* appears to be more abundant, as well as other yeast species such as *Clavispora lusitaniae*, *C. utilis*, *C. albicans*, and *Kluyveromyces marxianus*, with higher levels correlating with greater disease severity [160].

4.2. Gut Microbiome Dysbiosis in Psychiatric Disorders

The GM has been increasingly recognized as a key regulator of psychiatric conditions, including anxiety and depression [31]. Preclinical evidence indicates that the absence of gut microbiota can attenuate depressive-like behaviors [165]. Furthermore, fecal microbiota

transplantation (FMT) from patients with MDD into microbiota-depleted animals has been shown to induce depression-like behavioral and physiological changes, providing strong support for a causal role of dysbiotic gut microbiota in the development of depressive symptoms [165–167]. Research has documented substantial alterations in gut microbial composition in individuals with depression. For instance, Naseribafrouei et al. [168] observed an increase in bacteria of the order Bacteroidales and a decrease in members of the *Lachnospiraceae* family. Jiang et al. [169] reported a negative correlation between fecal microbial diversity and the severity of MDD symptoms, identifying higher abundances of the genera *Gelria*, *Turicibacter*, *Anaerofilum*, *Paraprevotella*, *Holdemania*, and *Eggerthella*, whereas *Prevotella* and *Dialister* were diminished in depressed subjects. Similarly, Aizawa et al. [170] found reduced levels of *Bifidobacterium* and *Lactobacillus* in the GM of depressed individuals compared to controls. In socially defeated mouse models, decreases in *Dorea*, *Ruminococcus*, and *Akkermansia*, together with increases in *Parabacteroides*, *Prevotella*, and members of the phylum Actinomycetota, were reported [171]. Human cohort studies also corroborate these findings. Valles-Colomer et al. [172] identified an overall reduction in microbial load in depressed participants, classifying them into an enterotype characterized by lower abundances of *Faecalibacterium*, *Dialister*, and *Coprococcus*. More recently, Knuesel and Mohajeri [167] observed a marked reduction in GM diversity in depressed individuals, with increased representation of *Bifidobacteriaceae* and *Bacteroides*, and decreased levels of *Ruminococcaceae*, *Faecalibacterium*, and *Roseburia*.

Certain gut microorganisms have also been implicated in stress-induced anxiety and generalized anxiety disorder (GAD), which constitutes a condition associated with impairments in social and occupational functioning [173]. Jiang et al. [174] observed that individuals with GAD exhibited reduced abundances of *Faecalibacterium*, *E. rectale*, *Lachnospira*, *Butyricicoccus*, and *Sutterella*, which are microorganisms known for their role in producing SCFAs. The depletion of these SCFA-producing bacteria is considered a pivotal factor supporting the monoamine hypothesis in the context of both anxiety and depression [175].

4.3. Microbial Metabolites

SCFAs, including butyrate, acetate, and propionate, represent one of the most extensively studied classes of microbial metabolites. These compounds are generated through the fermentation of dietary fibers in the gut and act as important signaling molecules, influencing the epigenome and activating G-protein-coupled receptors such as free fatty acid receptor 2 (FFAR2) and free fatty acid receptor 3 (FFAR3) [176]. Through these pathways, SCFAs modulate diverse physiological processes, including glucagon-like peptide-1 (GLP-1) secretion, body weight regulation, and GI transit time. In addition, SCFAs impact histone deacetylase (HDAC) inhibition, gene expression, cellular proliferation, and immune function [177]. Butyrate, in particular, has been shown to exert protective effects against colitis by regulating regulatory T cells (Tregs) and enhancing macrophage antibacterial activity [178,179]. From a mechanistic perspective, butyrate stimulates intestinal gluconeogenesis (*IGN*) gene expression through a cAMP-dependent pathway, whereas propionate engages FFAR3-mediated signaling within a gut–brain neural circuit to activate *IGN* genes [180]. Moreover, butyrate serves as a primary energy source for colonocytes and enterocytes, while propionate is efficiently utilized for hepatic gluconeogenesis [181]. In line with these findings, Sun et al. [182] reported that oral administration of butyrate ameliorated colitis severity in DSS-treated mice by promoting IL-10 production from T cells, highlighting its potential therapeutic value in IBD. These results are consistent with earlier studies demonstrating reduced colonic inflammation and diminished neutrophil infiltration following butyrate treatment [183].

In addition to SCFAs, the GM plays a pivotal role in the production of tryptophan-derived metabolites, such as indole, 5-HT, and kynurenine (KYN), which have been shown to be altered during IBD [184]. The interactions between tryptophan metabolism, intestinal inflammation, and barrier function exert both local and systemic effects, including neurobehavioral manifestations commonly observed in depression [185]. It has been proposed that kynurenine pathway metabolites, which possess neuromodulatory properties, influence depressive symptoms by modulating glutamatergic NMDA receptor activity, a key regulator of neuroplasticity and cognitive function. Overactivation of NMDA receptors has been linked to impaired hippocampal neurogenesis and neuronal atrophy, mechanisms that have been shown to contribute to the pathophysiology of depression [186].

In a metabolomics investigation, Franzosa et al. [134] identified several molecular species that are enriched in IBD, including sphingolipids, carboximidic acids, bile acids, triterpenoids, lactate, and long-chain fatty acids. These compounds are implicated in various intestinal processes, including cell membrane integrity, fatty acid metabolism, and intracellular signaling pathways. Notably, polyunsaturated long-chain fatty acids (PUFAs), such as eicosatrienoic acid and docosapentaenoic acid, are elevated in the gut of IBD patients. Their increased levels may reduce microbial diversity due to inherent bactericidal activity, while also influencing immune modulation and inflammatory signaling [187]. Caprylic acid, which constitutes a medium-chain fatty acid, exhibits antibacterial and antiviral effects and can be generated in the GI tract through anaerobic fiber fermentation or derived from dietary intake [134]. Recent multi-omics analyses suggest that the GM and its metabolites may contribute to neuropsychiatric comorbidities in UC. Specifically, patients with UC experiencing anxiety or depression showed diminished microbial richness and diversity, accompanied by compositional shifts in gut taxa, compared to UC patients without such symptoms [188]. Corresponding alterations were also observed in the serum metabolome and proteome, including reductions in 2′-deoxy-D-ribose, 4-hydroxybenzoate, and L-pipecolic acid. Administration of these metabolites in a mouse model of colitis prevented the development of depression-like behaviors [188]. Similarly, p-hydroxyphenylacetic acid, which is the main metabolite of *Prevotella vulgatus*, demonstrated the ability to mitigate depressive symptoms in experimental colitis models [149].

4.4. The Role of the GM in IBD-Related Depression and Anxiety

From a clinical perspective, depressive episodes have been linked to impaired regulation of the HPA axis, which modulates the adaptive response to stress within the organism [189]. Abnormal HPA axis signaling is implicated in the development and progression of mood disorders, often manifesting as elevated cortisol levels and increased pro-inflammatory mediators, which contribute to a chronic inflammatory state [166]. Experimental research in animal models has further highlighted a strong connection between HPA axis responsiveness and GM composition. For instance, germ-free (GF) mice exhibit exaggerated corticosterone and adrenocorticotropic hormone responses to stress compared with conventionally raised, pathogen-free mice [190]. The absence of a commensal GM in GF mice is associated with an underdeveloped immune system and heightened sensitivity to environmental stressors [191]. Moreover, stress has been shown to compromise intestinal barrier integrity, facilitating bacterial translocation across the mucosa and enabling direct interactions with immune cells and neurons within the enteric nervous system (ENS) [192].

Several studies have explored the pathways linking the GM to the HPA axis [189,193]. One proposed mechanism suggests that dysbiosis within the GM may promote increased release of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α. This amplified cytokine signaling can, in turn, drive heightened activation of the HPA axis, potentially elevating the susceptibility to anxiety and depressive symptoms in patients with IBD [194,195].

Although evidence from rodent models underscores the bidirectional influence between the GM and HPA axis function, research in humans examining the role of HPA axis activity as a mediator between psychiatric disorders and GM alterations remain limited.

In terms of depression pathophysiology, several studies have reported alterations in GM composition [196,197], frequently observing an increased abundance of pro-inflammatory taxa, such as *Enterobacteriaceae* [169], as well as reduced levels of SCFA-producing bacteria, including *Faecalibacterium* [198], both of which have been linked to more severe depressive symptomatology. Qin et al. [199] identified several notable associations between IBD and specific GM changes that correlated with the presence of depressive symptoms. Specifically, depression was linked to altered abundances of *Desulfovibrionaceae*, *Ruminococcaceae*, *Clostridium*, and *Akkermansia*, as well as to shifts within the phyla Desulfobacterota and Myxococcota (formerly Deltaproteobacteria). In CD, higher depression scores were associated with reduced levels of *Lachnospiraceae*, *Eubacterium*, *Roseburia*, and *Ruminococcus*, as well as with increased *Bifidobacterium* abundance [200]. Conversely, in UC, elevated depressive symptom scores were associated with decreased prevalence of *Erysipelotrichaceae*, *Lachnospira*, *Blautia*, *Phascolarctobacterium*, and *Streptococcus*, as well as with higher levels of *Desulfovibrio* [200]. Notably, Scaldaferri et al. [201] reported that increased *Blautia* and *Streptococcus* abundances were most strongly correlated with depressive symptoms in IBD patients. A growing body of research has also documented an elevated prevalence of *Streptococcus* in individuals with depression [197,202], and this genus has been shown to produce 5-HT [203], implicating it in depression pathophysiology in the context of IBD. Furthermore, in UC, depressive symptoms have been associated with reduced levels of *Enterobacteriaceae* [201]. This family contributes substantially to SCFA production through carbohydrate fermentation, which is a process that stimulates 5-HT synthesis in enterochromaffin cells. Upon activation, these cells release 5-HT, which engages receptors on enteric neurons [204]. Therefore, reductions in *Enterobacteriaceae* may decrease 5-HT availability, potentially exacerbating depressive symptoms in the context of IBD [205,206]. However, given the conflicting findings in the literature, including reports of increased *Enterobacteriaceae* in MDD [196,207], further research is required to clarify the precise role of this bacterial family in depression pathophysiology.

Regarding anxiety symptoms, research has identified a relationship between decreased gut microbial alpha diversity and lower abundances of *Fusobacterium* with heightened anxiety severity in patients with UC [200,208]. Humbel et al. [200] further described multiple taxonomic shifts within the phyla Bacillota, Bacteroidota, and Pseudomonadota, noting that diminished representation of species within these groups correlated with more pronounced anxiety symptoms in individuals with IBD. Evidence also suggests that FMT may improve psychological well-being in patients with IBS by increasing beneficial Bacteroidota and by reducing potentially pathogenic *Enterobacteriaceae* [209]. In line with this, Scaldaferri et al. [201] reported that elevated *Enterobacteriaceae* abundance was linked to increased anxiety in IBD, a relationship also observed in patients with GAD [210]. More recently, Joo et al. [211] demonstrated positive associations between Enterobacterales and *Enterococcaceae* and the severity of anxiety and depressive symptoms in UC. Experimental administration of *Enterococcus mundtii*, which is a member of the *Enterococcaceae* family, was shown to decrease levels of the anti-depressive neuropeptide Y in the colon, plasma, and hippocampus of mice, an effect that corresponded with the emergence of anxiety- and depression-like behaviors [211].

4.5. Dietary Influence on IBD and Mental Health

Dietary factors play a pivotal role in shaping both physical and mental health. Consumption of a Western diet, which is high in fats and sugars, has been shown to negatively

impact GM composition, promoting the growth of microbial species linked to an increased risk of IBD [212–214]. The concept of "immunonutrition" encompasses the influence of dietary components on various aspects of the immune system and the GM [215]. Within the GI tract, nutrients can modulate mucosal barrier integrity, enhance cellular defense mechanisms, and regulate local inflammatory responses [216,217]. Maintaining a nutritionally balanced diet is thus essential for supporting a healthy GM, preserving intestinal barrier function, and promoting immune tolerance [218,219]. In contrast, diets high in refined grains, processed foods, and sugars (e.g., Western dietary patterns) are associated with reduced microbial diversity, which may contribute to increased intestinal permeability and chronic inflammation [220–222].

In individuals consuming a nutritionally balanced diet, rich in high-fiber vegetables, whole grains, and omega-3 fatty acids, intestinal homeostasis appears to be supported by the production of microbial metabolites, particularly SCFAs. These metabolites contribute to gut barrier integrity by providing energy to colonic epithelial cells and enhancing the activity of regulatory T cells [218,223–225]. SCFAs can be metabolized locally by colonocytes or absorbed into systemic circulation, where they interact with G protein-coupled receptors GPR41 and GPR43, promoting protective immune responses through epithelial cytokine and chemokine signaling [226]. Butyrate, in particular, serves as a key energy source for colonocytes and exhibits potent anti-inflammatory properties [227], while also demonstrating immunoregulatory, anti-obesity, antidiabetic, cardiovascular-protective, and neuroprotective effects [228]. SCFA regulation has been proposed as a mechanistic link between the GM and depression, highlighting the potential of GM modulation as a therapeutic strategy for mood disorders [169,229,230]. Multi-omics research has further identified specific bacterial species that exert positive effects on mental health, such as *Bacteroides uniformis*, *Roseburia inulinivorans*, *E. rectale*, and *F. prausnitzii* [231,232]. Indeed, these bacterial species support mental health via SCFA production and also by modulating amino acid metabolism, taurine levels, and cortisol pathways, all of which are closely connected to the pathophysiology of depression, anxiety, and related neuropsychiatric conditions [233–235]. Given the limitations of conventional pharmacotherapies and psychotherapies for psychiatric disorders, these insights underscore the potential of microbiota- and nutrient-based interventions within the framework of nutritional psychiatry as complementary strategies to support mental health [233,236].

An unhealthy diet has been shown to result in GM dysbiosis, which can subsequently impair intestinal barrier function, trigger systemic inflammation, disrupt glucose metabolism, and induce a state of chronic low-grade mucosal inflammation [221,237]. Recent research has highlighted the pivotal role of epithelial cell metabolism in regulating the GM, particularly in controlling overgrowth of *E. coli* [238]. Under physiological conditions, colonocytes primarily rely on butyrate as an energy source. Butyrate metabolism is associated with increased oxygen consumption, creating a hypoxic environment at the luminal surface that favors the growth of strict anaerobic bacteria from the phylum Bacillota [239]. In contrast, intestinal inflammation reduces the abundance of Bacillota, lowering butyrate production. In the absence of butyrate, colonocytes shift to glucose fermentation into lactate for energy, increasing intracellular oxygen levels. This rise in oxygen alters the local microbial environment, depleting strict anaerobes and promoting the expansion of facultative anaerobes such as pathogenic *E. coli*, which is a pattern commonly observed in the GM of patients with IBD [240,241]. In turn, diets rich in fiber and fermented foods have been proposed to support both physical and mental health [242], although clinical evidence for their efficacy specifically in IBD populations is still needed. Figure 1 presents the bidirectional communication between the brain–gut connectomes in IBD.

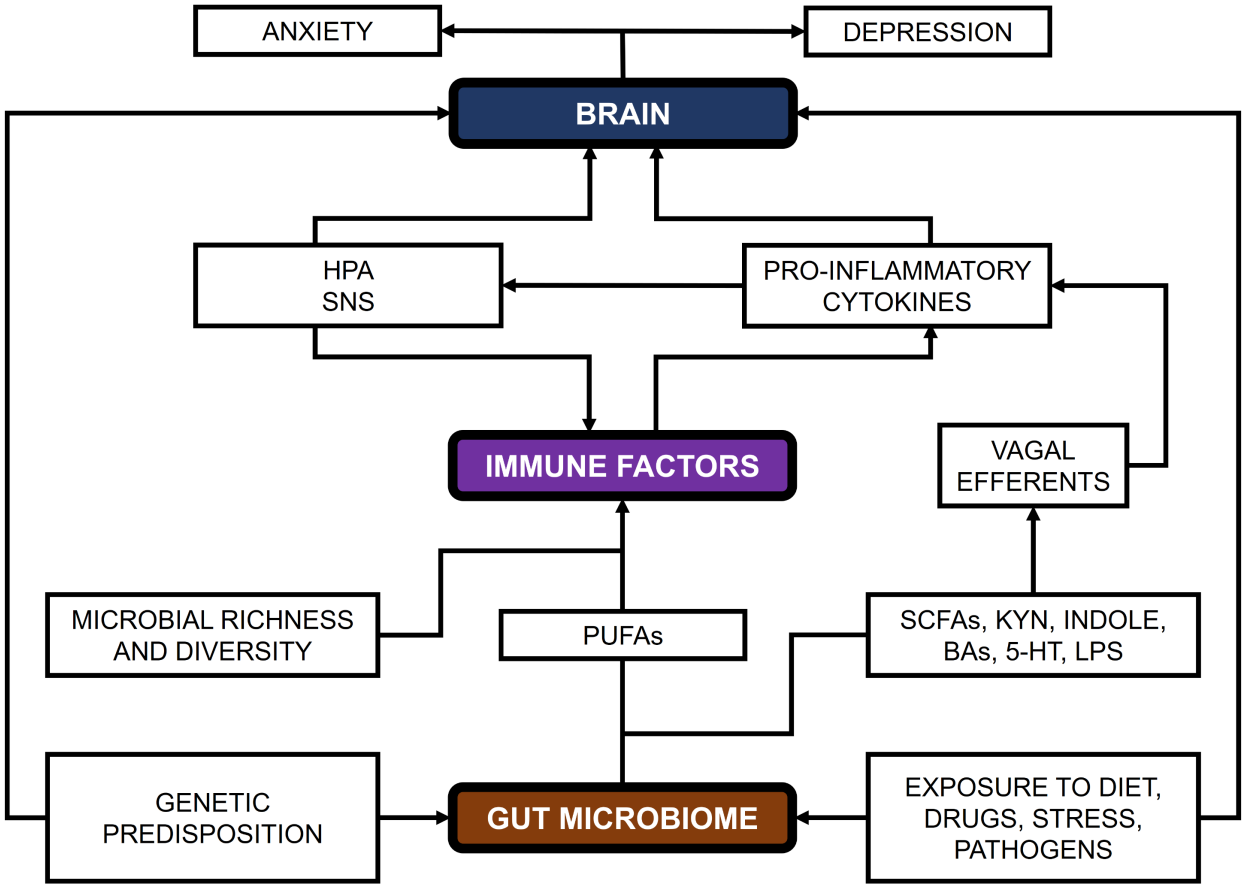

Figure 1. Bidirectional communication between the brain–gut connectomes in IBD. HPA: hypothalamic–pituitary–adrenal axis; SNS: sympathetic nervous system; SCFAs: short-chain fatty acids; PUFAs: polyunsaturated fatty acids; KYN: kynurenine; 5-HT: serotonin; LPS: lipopolysaccharides; BAs: bile acids.

5. Therapeutic Approaches for Depression and Anxiety in IBD

The coexistence of IBD with anxiety and depression has become a growing focus of research, leading to the exploration of effective treatment strategies for these comorbid conditions. Current therapeutic approaches primarily include psychological therapies, pharmacological interventions, and treatments aimed at modulating the GM. Furthermore, emerging evidence suggests that lifestyle interventions, such as dietary modifications and physical activity, may offer additional benefits in managing anxiety and depression associated with IBD [98].

5.1. Psychological Approaches

Currently, third-wave psychological therapies, which have evolved from traditional cognitive behavioral therapy (CBT), aim to enhance psychological well-being through approaches such as acceptance and commitment therapy (ACT), mindfulness-based interventions (MBI), and other techniques emphasizing metacognitive processes [243–245]. Accumulating evidence indicates that these therapies can effectively alleviate anxiety and depressive symptoms in individuals with IBD. Nevertheless, their impact on the pathophysiology or progression of the underlying disease remains a topic of ongoing investigation.

A meta-analysis evaluating CBT indicated that this intervention significantly decreased anxiety and depression scores while enhancing quality of life in patients with IBD [246]. In a randomized clinical trial (RCT), group-based CBT mitigated psychological symptoms and also led to reductions in the CD Activity Index and CRP levels [247]. Another RCT

assessed the COMPASS program, which constitutes a CBT-based intervention customized for chronic conditions, to determine its effectiveness in reducing psychological distress. Compared to a standard care support group, participants in the COMPASS intervention demonstrated a marked reduction in distress. Since the study population consisted of individuals with IBD, these findings suggest that such cognitive-behavioral strategies may alleviate anxiety and depressive symptoms in this patient group. However, it is important to note that COMPASS is not specifically designed for IBD [248]. Moreover, evidence indicates that CBT may have limited effectiveness in reducing anxiety or stress in patients in remission and that improvements in depressive symptoms are often transient [249].

In contrast, ACT appears to exert more robust effects. A RCT comparing ACT with CBT found that ACT significantly alleviated both anxiety and depressive symptoms, whereas CBT showed efficacy only for depression [250]. Another study comparing ACT with a psychoeducation control group reported a marked reduction in Depression Anxiety and Stress Scale scores in the ACT cohort [251]. Despite these promising results, the impact of ACT on anxiety and depression in patients with IBD has been inconsistent. For instance, an RCT involving 122 patients with quiescent or mildly active IBD demonstrated that ACT significantly improved depressive symptoms compared to standard care, but anxiety levels remained largely unchanged [252]. Conversely, a one-day ACT intervention for IBD patients led to a reduction in anxiety scores for 79% of participants, which decreased from a baseline of 6.9 to 4.3 at the three-month follow-up, while depression scores exhibited a non-significant downward trend [253]. Luo et al. [98] proposed that such inconsistencies might arise due to variations in intervention duration, disease activity, or assessment methodologies. Thus, these findings suggest that the effectiveness of ACT in addressing anxiety and depression may depend on study design and patient population characteristics.

Recent research into MBI remain relatively limited in both scope and rigor. A meta-analysis indicated that MBI can produce short-term reductions in CRP levels among patients with IBD. However, the effects on anxiety and depressive symptoms were not statistically significant [254]. On the other hand, a small-scale study suggested that virtual mindfulness-based stress reduction could lower scores on the Patient Health Questionnaire–Somatic, Anxiety, and Depressive Symptoms Scale from 11.2 to 6.4 while enhancing quality of life. Nevertheless, the small sample size of the study (N = 16) and its high attrition rate (only 7 participants finished the program) undermine the reliability of these findings [255]. Another recent meta-analysis reported that MBI confer lasting improvements in depressive symptoms and quality of life, although no significant benefits were observed for anxiety or physical disease outcomes [256].

In general terms, current evidence regarding the effectiveness of psychological interventions in improving outcomes for patients with IBD remains mixed. Measures commonly used to assess IBD status include both self-reported disease activity indices and objective biomarkers of inflammation. A meta-analysis of 28 RCTs reported that psychological interventions were associated with reductions in inflammatory markers, such as CRP and fecal calprotectin [257]. Conversely, a later meta-analysis incorporating 25 RCTs found that these interventions did not significantly affect disease activity indices in patients with quiescent IBD, nor did they lower the likelihood of relapse [258]. This discrepancy between findings may stem from the exclusion of studies that relied on patient-reported clinical measures. In line with this notion, a cohort study following 760 IBD patients for up to 6.5 years indicated that individuals experiencing active disease and psychological symptoms faced a heightened risk of disease progression [259]. Thus, if psychological interventions primarily alleviate anxiety and depressive symptoms without exerting a direct impact on the underlying IBD, managing these comorbidities may require supplementary strategies, including pharmacological treatment.

5.2. Pharmacological Approaches

Antidepressant drugs constitute therapeutic options for disorders involving the GBA, offering benefits that extend beyond mood regulation to include improvements in GI function [260]. These agents are well established in the management of depression, anxiety, and various chronic pain conditions. Although large-scale RCTs in patients with IBD are still lacking, available evidence suggests that selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs), particularly when combined with psychotherapeutic interventions, may alleviate symptoms of anxiety and depression in this population [261,262].

A number of clinical trials have examined the role of SSRIs in managing GI disturbances [263]. However, their efficacy in IBS remains a matter of debate, as findings across studies have been inconsistent. Research indicates that SSRIs confer certain therapeutic advantages for individuals with IBD. SSRIs effectively alleviate a range of depressive symptoms, including low mood, irritability, feelings of worthlessness, anxiety, and sleep disturbances [264]. Overall, SSRIs are regarded as well-tolerated pharmacologic agents. Nevertheless, as with many antidepressant classes, they have been linked to activation phenomena and, particularly at higher doses, to an increased risk of suicidal ideation [265].

SNRIs constitute a later generation of antidepressant agents that act by inhibiting presynaptic reuptake of both 5-HT and norepinephrine, thereby enhancing postsynaptic receptor activation [266]. This dual mechanism contributes to their therapeutic efficacy in treatment-resistant depression, anxiety disorders, and chronic pain syndromes. Their clinical benefits are well established, and their side-effect profile parallels that of SSRIs and TCAs, with most adverse events being mild in nature [264]. In a prospective RCT involving patients with IBD and comorbid anxiety or depression, venlafaxine, which is a prototypical SNRI, was shown to significantly lower HADS scores and also to reduce IBD activity indices and serum inflammatory markers over a six-month treatment period [267]. Similarly, a meta-analysis encompassing 13 studies and 884 participants found that antidepressant therapy not only yielded greater reductions in depressive and anxiety scores, but also improved disease activity outcomes compared with controls [268]. Moreover, a large-scale epidemiological study involving 403,665 individuals reported that a prior history of depression was associated with an elevated risk of developing IBD. Notably, this risk appeared to be attenuated among those receiving antidepressant treatment for depression [16].

Despite the well-recognized adverse effect profile associated with TCAs, evidence suggests that they may provide therapeutic benefit in the management of functional GI disorders. In a survey conducted in Australia examining antidepressant use among individuals with IBD, approximately one-third of respondents reported taking these agents, including TCAs [261]. In this context, the primary motivation for prescribing TCAs typically relates to comorbid depression or anxiety, but their use for somatic or GI symptoms remains relatively uncommon. Notably, a retrospective analysis found that high-dose TCA therapy for depression was linked to fewer disease flares, a reduced need for endoscopic evaluations, and decreased corticosteroid utilization [269]. Mirtazapine, classified as a noradrenergic and specific serotonergic antidepressant (NaSSA), exerts its pharmacological actions through multiple receptor pathways. Specifically, antagonizing postsynaptic 5-HT_2 and 5-HT_3 receptors, inhibiting presynaptic α_2-adrenergic receptors, and displaying strong H_1-histaminergic and moderate muscarinic receptor blockade. Among patients unable to tolerate SSRIs, mirtazapine has demonstrated treatment response rates between 50% and 73%. Recent research has indicated its potential utility in IBS, particularly in cases characterized by diarrhea and coexisting depressive or anxiety symptoms [270]. Preliminary findings further suggest that, in cases in which patients can tolerate common side effects

such as sedation and weight gain, mirtazapine exerts moderate antidepressant effects and may additionally alleviate nausea and vomiting [262].

Ustekinumab is a monoclonal antibody directed against interleukins 12 and 23 that has been introduced as an effective biologic therapy for IBD. Findings from two RCTs demonstrated that ustekinumab improved disease activity in patients with moderate-to-severe active CD and also significantly reduced anxiety and depressive symptoms [271,272]. Similarly, clinical research has shown that vedolizumab and anti–tumor necrosis factor (anti-TNF) agents, such as infliximab and adalimumab, can ameliorate both psychological distress and GI manifestations in individuals with CD and UC [17,273]. A meta-analysis further supported these findings, reporting significant reductions in depressive symptom scores following IBD-specific treatment in the absence of psychotropic medication, although improvements in anxiety did not reach statistical significance [274]. Overall, evidence indicates that biological and targeted therapies for IBD may exert beneficial effects on comorbid emotional disorders. However, the magnitude of improvement in depression and anxiety appears to vary across studies. Luo et al. [98] proposed that such discrepancies may arise from differences in study design, sample size, therapeutic regimen, or the complex pathophysiology underlying anxiety and depressive symptoms in IBD. Table 3 summarizes key studies evaluating therapeutic approaches for anxiety and depression among patients with IBD.

Table 3. Studies (2017–2024) on therapeutics for anxiety and depression in patients with IBD.

Study/Country	Treatment	Subjects	Effects on Depression	Effects on Anxiety
Psychotherapy				
Chappell et al., 2024 [255]/Canada	MBI/Multicenter single-arm	IBD patients	MBI: +	MBI: +
Ewais et al., 2019 [256]/Australia	MBI/Meta-analysis	IBD patients	MBI: +	MBI: –
Hou et al., 2017 [253]/USA	ACT/1-day workshop	IBD patients	ACT: –	ACT: +
Kalogeropoulou et al., 2025 [247]/Greece	CBT/Prospective RCT	IBD patients	CBT: +	CBT: +
Kok et al., 2023 [249]/UK	CBT, MBI, ACT/Practical guide	IBD patients	CBT: – MBI: + ACT: +	CBT: – MBI: – ACT: –
Naude et al., 2023 [254]/Australia and New Zealand	MBI/Meta-analysis	IBD patients	MBI: –	MBI: –
Naude et al., 2024 [250]/Australia and New Zealand	CBT, ACT/RCT	IBD patients	CBT: + ACT: +	CBT: – ACT: +
Romano et al., 2024 [251]/Australia and New Zealand	ACT/RCT	IBD patients	ACT: +	ACT: +
Wang et al., 2023 [246]/P.R. China	CBT/Meta-analysis	IBD patients	CBT: +	CBT: +
Wynne et al., 2019 [252]/Ireland	ACT/RCT	IBD patients	ACT: +	ACT: –
Pharmacotherapy				
Panés et al., 2023 [271]/ 12 European countries	Ustekinumab/Open-label multicenter RCT	CD patients	+	+
Stevens et al., 2017 [17]/USA	Vedolizumab and anti-TNF/Prospective cohort study	IBD patients	+	+
Zhang et al., 2018 [273]/P.R. China	Infliximab/Prospective cohort study	CD patients	+	+
Zhao et al., 2022 [274]/P.R. China	Standard medical therapy/Meta-analysis	IBD patients	+	–

CBT, cognitive behavioral therapy; MBI, mindfulness-based intervention; ACT, acceptance and commitment therapy; IBD, inflammatory bowel disease; CD, Crohn's disease; RCT, randomized controlled trial. Positive sign: improvement of symptoms. Negative sign: no improvement of symptoms, limited effectiveness, or results that are not statistically significant.

5.3. Microbiota-Targeted Approaches

Preclinical evidence has demonstrated the therapeutic potential of probiotics in alleviating colitis-related pathology and reducing anxiety-or depression-like behaviors in murine models of intestinal inflammation [275,276]. Despite these promising findings, human data remain comparatively scarce. Hassan et al. [277] summarized clinical trials investigating

probiotic use in IBD up to 2022, concluding that probiotic supplementation may attenuate IBD-associated depressive symptoms and enhance overall psychological well-being [277].

Administration of the *Bifidobacterium bifidum* strain G9-1 was shown to significantly decrease anxiety scores in patients with quiescent CD [278]. Although prebiotics and synbiotics have demonstrated beneficial effects on mood regulation and the reduction in anxiety and depression in other clinical contexts [279,280], their specific efficacy in individuals with comorbid IBD remains to be clearly defined. Interestingly, certain bacterial species typically regarded as probiotics, such as *Enterococcus faecium* and *Pediococcus acidilactici*, have been reported to exacerbate anxiety and depressive symptoms in IBD patients when excessive proliferation occurs, underscoring the importance of microbial balance [281].

Compared with probiotics and prebiotics, FMT represents a more intensive therapeutic approach, as it involves the transfer of an entire microbial community rather than isolated bacterial strains. Preclinical evidence has shown that fecal microbiota derived from patients with IBD and comorbid depression can induce anxiety- and depression-like behaviors when transplanted into mice. Notably, these behavioral alterations were reversed when animals subsequently received FMT from healthy donors [282]. Clinical research supports these preclinical findings. In a randomized trial involving 272 individuals with UC, repeated FMT administered via gastroscopy at three-week intervals using stool from sex-matched, healthy adolescent donors led to significant reductions in both anxiety and depression scores compared with placebo. Participants also exhibited improvements in GI symptoms, including diarrhea and abdominal discomfort, as well as lower scores on standardized self-rating scales for anxiety and depression [283]. Similarly, a smaller clinical investigation reported comparable antidepressant effects of FMT in patients with IBD [284]. Although large-scale RCTs remain limited, current evidence highlights the potential of FMT as a therapeutic strategy for addressing psychological comorbidities in IBD. These findings underscore the potential of the GM as a modifiable factor in the bidirectional relationship between intestinal inflammation and mood disorders.

6. Psychosocial Stressors and Microbiome Interactions in IBD

Living with IBD can be viewed as carrying a burden that causes the organism to betray the individual in the most private ways, with societal perceptions potentially exacerbating feelings of shame and devaluation. Patients with IBD commonly report a wide range of distressing and debilitating symptoms, with bowel urgency, diarrhea, incontinence, abdominal pain, and lack of energy constituting particularly burdensome physical complaints [8,285]. Moreover, psychological manifestations such as embarrassment, fear, anger, and worry further compound overall symptom distress and contribute substantially to perceived disease burden [8]. Within this context, stigma may intensify the physical and psychological burden of IBD by socially devaluing affected individuals, intersecting with other identity factors such as ethnicity or socioeconomic status, restricting access to care, and amplifying distress, thereby reinforcing both the perceived and actual impact of the disease [286].

Stigma has traditionally been conceptualized as a socially devalued attribute linked to a particular condition and often associated with reduced social status [287]. Corrigan and Watson [288] identify three interrelated elements in stigma: (i) stereotypes, which are oversimplified and generally negative societal beliefs that induce rapid judgments about certain individuals or groups; (ii) prejudice, referring to the adverse emotional responses triggered by these stereotypes; and (iii) discrimination, encompassing behaviors that lead to social exclusion or marginalization of those who are stigmatized. In turn, Pryor and Reeder [289] categorize stigma into four forms: (i) public stigma, encompassing societal attitudes and behaviors toward affected individuals; (ii) self-stigma, constituting

the internalization of these societal prejudices; (iii) stigma by association, consisting of the negative consequences experienced by those connected to stigmatized individuals; and (iv) structural stigma, which reflects institutional, cultural, and ideological mechanisms that sustain and reinforce stigmatized statuses. Building on the aforementioned, health-related stigma can be defined as a process in which individuals or groups experience, perceive, or anticipate social exclusion, rejection, blame, or devaluation stemming from unjustified negative social judgments linked to their identification with a specific health condition [286].

IBD is particularly susceptible to stigma due to its embarrassing symptoms and historical psychosomatic framing, with internalized stigma potentially exerting the greatest negative impact on physical, psychological, and self-management outcomes [290]. Negative disease perceptions and concerns about public reactions, including fear of bowel accidents, are common among patients and have been associated with poorer psychosocial adjustment [291]. This can be explained on the basis that IBD involves symptoms that are socially fraught, such as defecation and flatulence, which are frequently perceived as undesirable at a societal level [292]. Indeed, deeply ingrained social conventions toward feces often evoke feelings of disgust and revulsion [293,294]. In turn, incontinence-related symptoms, including fecal incontinence, are often experienced as shameful and stigmatizing, leading individuals to limit disclosure to healthcare providers and avoid social situations [295,296]. Moreover, GI flatus also provoke embarrassment and social discomfort due to their audible and olfactory effects, which cause individuals to suppress their natural expression [297]. These socially sensitive symptoms may trigger avoidance behaviors by others, such as reluctance to engage in close physical contact or share meals. Thus, despite being concealable, the unpredictable nature of IBD flares can produce visible, disruptive, and socially challenging manifestations, such as increased frequency and urgency to defecate, which interfere with daily activities and social participation. In this respect, societal norms demand complete control over bodily functions in adulthood, and lapses in such control can result in stigmatization, adversely impacting patient adaptation to the disease [298].

Stigma related to IBD can be complex, with individuals fluctuating along a continuum between feeling stigmatized and integrated, influenced by disease activity, social environment, and personal coping strategies [299,300]. Due to the largely invisible nature of IBD, individuals often face difficult decisions regarding self-disclosure, balancing anticipated negative social responses with the potential benefits of sharing their condition [300]. Disclosure of IBD constitutes a pivotal factor in mitigating stigma, with greater openness and knowledge about the disease associated with reduced social stigma, particularly among young adults [301]. However, dietary behaviors and GI symptoms, such as flatulence and fecal malodor, further contribute to perceived stigma and influence social participation, as patients often modify their diet to minimize embarrassing symptoms [302]. Importantly, young populations with IBD have reported bullying as a consequence of their stigmatized condition [299]. At the same time, young populations who experience bullying are more likely to develop IBS [303]. This reciprocal relationship highlights a troubling cycle, as bullying victimization has been linked to humiliation, which is an emotion characterized by the internalization of a devalued self-image [304]. Young individuals with IBD might be particularly vulnerable to this emotional dynamic, as the socially stigmatized aspects of their condition can intensify the degree to which they internalize negative perceptions of themselves. Moreover, humiliation has been associated with negative outcomes such as psychopathologies, feelings of helplessness, suicidal ideation, and avoidant tendencies [304]. In this context, avoidant coping strategies might mediate the relationship between self-blame attributions and psychological adjustment, with higher disease severity exacerbating maladaptive coping and poor psychological outcomes [305]. These mental health consequences

may indicate the presence of psychiatric comorbidities, which can be further compounded by the stigma related to mental illness, a factor that is often overlooked and can hinder recovery, discourage help-seeking, and restrict access to essential resources [306]. In turn, adolescence represents a critical period of vulnerability marked by increased curiosity and openness to novel experiences [307], which may lead some adolescents with IBD to engage in maladaptive coping strategies, such as the use of over-the-counter drugs (e.g., antidiarrheal medications, sedative antihistamines) or other substances to alleviate both the physical and psychosocial discomfort associated with their condition, potentially resulting in additional health complications [308,309]. These outcomes may be particularly pronounced in adolescents with IBD, as the complexity of pediatric-onset disease increases their vulnerability to adverse physical and mental health outcomes [310].

Discriminatory experiences have been increasingly recognized as potent psychosocial stressors that activate multiple physiological systems, including immune, cardiovascular, and metabolic pathways, thereby promoting a state of persistent inflammation and systemic dysregulation [311]. In addition, individuals reporting high levels of discrimination exhibit alterations in GM composition, including reduced abundance of beneficial taxa such as *Prevotella* and *Ruminococcaceae*, which are important producers of SCFAs that maintain gut barrier integrity and modulate immune homeostasis [312]. At the same time, high discrimination has been associated with increased microbial richness and significant shifts in beta diversity, indicating that stress-related environmental factors may drive compensatory restructuring within the microbial ecosystem. These GM alterations are accompanied by distinctive transcriptional profiles, particularly in genes linked to environmental sensing and metabolic pathways, which suggests functional consequences for host physiology [312]. Furthermore, chronic psychosocial stress may compromise intestinal barrier function, resulting in increased permeability that facilitates translocation of bacterial products and toxins into systemic circulation, thereby amplifying inflammatory responses [313,314].

Exposure to early-life stress (ELS) increases the risk of developing psychopathology later in life. However, the impact of ELS on the GM and its potential contribution to mental health outcomes remains incompletely understood [315]. In turn, although the precise role of the GM in shaping stress responses during early-life stages has not been fully elucidated, several studies have linked psychosocial stress to changes in the abundance of genera such as *Veillonella*, *Prevotella*, and *Coprococcus* in infants and adolescents [316,317]. Conversely, taxa including *Phascolarctobacterium* and *Anaerotruncus* tend to decrease in abundance under stress or psychopathological conditions, potentially reflecting the depletion of beneficial commensals associated with stress exposure [318,319]. The early establishment of microbial communities is pivotal for the concurrent development of the immune system and the maturation of the gut and its associated metabolic functions [320,321]. Disruptions in GM composition during this period can interfere with developmental programming, potentially resulting in long-term physiological alterations and increased susceptibility to disease [322]. Several early-life factors have been associated with IBD development, including prenatal exposure to antibiotics, maternal smoking, and breastfeeding practices [323,324]. Infants born to mothers with IBD exhibit increased abundance of members of the phylum Pseudomonadota and decreased bifidobacterial populations during the first three months of life [325]. However, the directionality of these associations remains unclear, as persistent inflammation in IBD patients may influence GM composition rather than dysbiosis being the primary causal factor [326]. Overall, these insights suggest that psychosocial experiences and early-life microbial exposures might simultaneously contribute to IBD risk and progression.

7. Discussion

Although the link between IBD and psychiatric disorders is increasingly recognized, the mechanisms underlying this association remain incompletely understood. A comprehensive understanding of the psychiatric consequences of IBD requires a holistic assessment of its psychosocial dimensions. Importantly, differences between CD and UC extend beyond their anatomical and pathological features to encompass distinct psychological experiences. In CD, the presence of transmural inflammation, strictures, and fistulas contributes to a disease course marked by uncertainty and chronicity, which are factors that can heighten stress levels and exacerbate psychiatric symptoms [327]. In contrast, UC, which is typically confined to the colon, often follows a more predictable trajectory, resulting in a different psychological burden [328]. These distinctions emphasize the necessity for individualized management strategies that address both the GI and psychosocial dimensions of IBD. The heterogeneity of these conditions complicates efforts to establish universal psychological profiles, as patient experiences and mental health outcomes vary widely across disease types and severities [329].

Evidence provides substantial support to the notion that chronic intestinal inflammation in IBD can induce alterations within the CNS, thereby contributing to the emergence of psychiatric symptoms. This association points to a biological foundation for the comorbidity between IBD and mental health disorders, suggesting that inflammatory processes may play a direct role in shaping neuropsychiatric outcomes. Nevertheless, additional studies are required to delineate the specific neuroinflammatory pathways involved and to determine how these mechanisms might be therapeutically modulated. In parallel, the persistent psychological stress associated with living with IBD can exacerbate psychiatric manifestations through HPA axis dysregulation. Recent research indicates that both chronic inflammation and stress-related neuroendocrine disturbances act synergistically, amplifying vulnerability to anxiety and depression in affected individuals [330]. This interplay highlights the importance of adopting an integrative framework that considers both biological and psychosocial contributors to psychiatric comorbidity. Moreover, psychological resilience and adaptive coping mechanisms constitute factors that may diminish the adverse neuropsychological effects of inflammation and represent promising targets for future therapeutic interventions.

Elucidating causal relationships between IBD and psychiatric comorbidities is complicated by substantial inter-individual variability. Anxiety and depression are the most frequently reported psychiatric disorders in IBD populations, with prevalence rates markedly exceeding those observed in the general population [55,62,65]. Less common, but still worthy of consideration, are conditions such as BD and schizophrenia [4,46,55]. This diversity in psychiatric presentations highlights the need for individualized approaches to understanding and managing mental health in IBD. In this context, research has underscored the significant role of genetic factors in the development of IBD. A recent review examining the genetic and epigenetic etiology of IBD as provided valuable insights into the key genes associated with the condition [331]. For instance, the *NOD2* gene has been recognized as a susceptibility factor for CD, with specific mutations linked to an increased risk of developing the condition. In addition, polymorphisms at the *IL23R* locus, particularly *rs11209026*, have been found to be associated with a reduced risk of CD, as well as with an elevated risk of UC in Caucasian populations. The *ATG16L1* gene, which plays a crucial role in autophagy, has also been implicated in susceptibility to CD. Furthermore, certain variants in the *CARD9* gene, including *rs10870077*, *rs10781499*, and *rs4077515*, have been associated with an increased risk of IBD, whereas other *CARD9* variants, such as *rs141992399* and *rs200735402*, have been shown to provide a protective effect against IBD. The *LRRK2* gene mutation has been linked to CD, where it results in heightened activation of intestinal

dendritic cells, leading to increased expression and release of pro-inflammatory molecules such as IL-2 and TNF-α. Notably, inhibition of *LRRK2* has been observed to reduce the production of these pro-inflammatory cytokines in CD patients. In turn, increased activation of the *STAT3* gene has been detected in intestinal epithelial cells in active CD, while the expression of the *TL1A* gene has been shown to correlate with levels of inflammation in IBD [331]. Research also highlights a notable overlap between IBD and psychiatric disorders, particularly anxiety and depression [332,333]. The genetic underpinnings of this correlation may be explained by two key factors: (i) the presence of shared genetic risk factors [334], with certain genetic variants potentially predisposing individuals to both IBD and psychiatric conditions, and (ii) inflammation [192,335], in which chronic inflammation among IBD patients has been shown to negatively affect brain function and mood regulation, potentially leading to the manifestation of psychiatric symptoms. Given that the precise nature of this correlation remains to be fully understood, the interaction between genetic predisposition, immune response, and mental health is an area of ongoing research.

A further challenge arises from the lack of standardized diagnostic criteria for psychiatric comorbidities in IBD. Although anxiety and depression are often assessed using self-report instruments, consensus on the most reliable and valid tools for evaluating psychiatric symptoms in the context of chronic GI disease is lacking. Developing and validating instruments specifically customized for IBD populations is pivotal to improve diagnostic precision and guide personalized interventions. In addition, self-report measures may inadequately capture the complexity of psychiatric symptoms in IBD, as overlapping somatic symptoms, such as fatigue and pain, are common to both GI disease and mood disorders [8,9,12]. Longitudinal studies that systematically monitor both GI and psychiatric symptom trajectories are essential to clarify temporal relationships and potential causative pathways. Such research can reveal whether psychiatric symptoms precede, coincide with, or follow IBD flares. Emerging tools in big data analytics and real-time symptom monitoring offer promising approaches to capture this temporal complexity [336]. Complementary advances in neuroimaging and biomarker identification may further elucidate the mechanistic links between IBD and mental health. For instance, functional MRI studies have demonstrated altered brain connectivity in IBD patients, particularly in networks implicated in mood regulation and stress response, providing compelling evidence of GBA involvement [337]. Nevertheless, trends regarding IBD and mental health may differ by age, with adolescents and older individuals potentially experiencing distinct psychiatric impacts, and gender differences adding further complexity to the clinical landscape. Thus, addressing the aforementioned challenges will require a multidisciplinary approach. In this respect, emerging research is shaping the study of IBD-related psychopathology. Integrating routine psychological screening into standard clinical care could facilitate early identification of at-risk patients, enabling timely intervention. Furthermore, future investigations should focus on establishing standardized diagnostic frameworks and evidence-based therapeutic approaches for psychiatric disorders in the context of IBD. By elucidating the multifaceted interactions between intestinal inflammation and mental health, clinicians and researchers will be able to improve both physical and psychological outcomes for patients. The evolving research landscape offers promising opportunities to deepen our understanding of the complex interplay between IBD and psychopathology, potentially informing more precise and effective clinical management strategies. Figure 2 presents traditional and emerging research areas in IBD psychopathology.

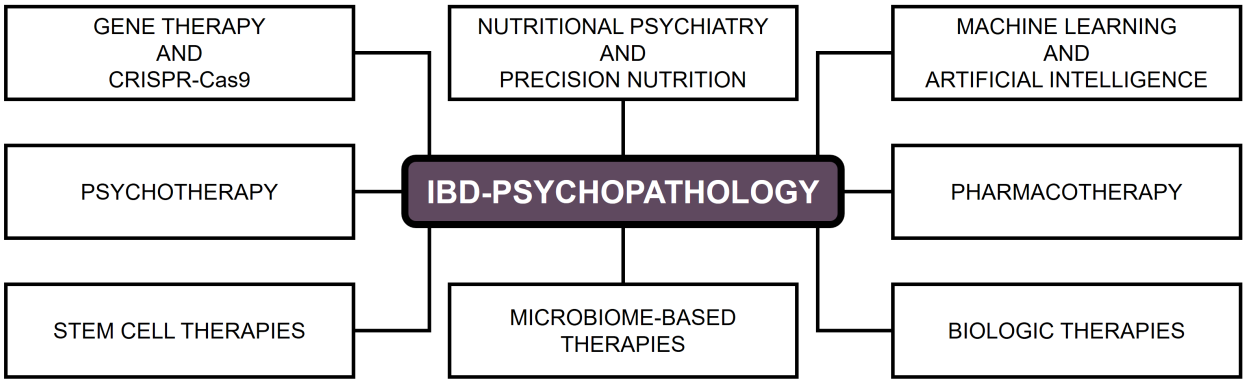

Figure 2. Traditional and emerging research areas in IBD psychopathology.

To fully realize the therapeutic potential of emerging interventions in IBD, rigorous RCTs involving larger and more diverse patient populations are essential. Among these interventions, GM modulators, including probiotics and FMT, have shown considerable promise in infection prevention and neuroprotective effects. In this context, psychobiotics, defined as probiotics, prebiotics, and synbiotics that confer health benefits to individuals with psychiatric disorders, have demonstrated promising potential efficacy across various psychiatric conditions, particularly in the management of stress, anxiety, and depression [338,339]. Nevertheless, as research in this field progresses, there is a growing need for further studies to elucidate their underlying mechanisms of action, identify the most effective bacterial strains, and establish optimal treatment parameters. Thus, it is plausible to assert that the integration of microbiome-based therapies into routine clinical practice is still in its early stages, highlighting the need for further research to establish their safety and effectiveness. A deeper understanding of the differences between CD and UC is also pivotal for interpreting therapeutic responses. For instance, FMT has demonstrated efficacy in multiple RCTs for UC, but comparable benefits have not been observed in CD [340,341]. Future research should therefore focus on elucidating the mechanisms underlying these divergent responses to microbiome-based interventions across IBD subtypes, which could inform more precise and effective treatment strategies.

The exploration of nutritional psychiatry and nutritional psychology is critical for identifying dietary patterns and specific nutrients that may facilitate the alleviation of the mental health burden associated with IBD [236,329]. Other pathologies, such as obesity and type 2 diabetes mellitus, also involve significant metabolic disruptions, with evidence suggesting that altered GM and its metabolites (e.g., SCFAs) play a crucial role in modulating overall health through mechanisms involving the GBA [342,343]. Dietary habits exert a profound influence on GM composition, which in turn modulates inflammatory processes and impacts mental well-being. Integrating nutritional strategies into IBD management offers the potential for a personalized strategy addressing both GI and psychological dimensions of the disease [344]. Individual variability in response to dietary and microbiome-targeted interventions highlights the necessity of such customized approaches. Advances in microbiome research have revealed that genetic, environmental, and lifestyle factors contribute to differential responses to dietary modulation. For instance, certain individuals may experience marked improvements in gut health and psychological outcomes following probiotic supplementation [345], whereas others may exhibit limited response due to differences in baseline GM composition or genetic predispositions [346,347]. In addition, the increasing use of complementary and alternative medicine (e.g., herbal products) among elderly IBD patients highlights the need for careful consideration of potential drug-herb interactions, which may lead to adverse effects due to polypharmacy and the presence of comorbidities in this population [348]. The intake of probiotics is also increasing in popularity. However,

it is crucial to consider their safety, particularly in vulnerable populations, due to concerns about potential adverse effects, drug interactions, and long-term safety, which require further research and monitoring [349]. Similarly, other microbial therapeutic tools, such as FMT, also require caution. In this respect, adverse events associated with FMT can be influenced by factors such as stool bank practices, delivery routes, and the success of donor microbial engraftment [350]. In turn, the long-term consequences of donor microbial engraftment may include a range of health issues, such as increased susceptibility to infections, obesity, immune-mediated disorders, and even IBD [350]. Precision nutrition, which involves customizing dietary recommendations based on personal biomarkers, microbiome profiles, and metabolic phenotyping, holds promise for becoming an integral component of IBD clinical practice [351]. The adoption of these individualized strategies by healthcare providers may enhance understanding of the complex interactions between diet, the GM, and mental health, ultimately facilitating the development of more effective, targeted interventions for patients with IBD [352].

CBT and MBI have been shown to effectively alleviate psychological distress in patients with IBD [353]. These therapeutic approaches can be complemented by targeted dietary strategies aimed at reducing inflammation and supporting gut health. For instance, mindfulness-based eating practices may be incorporated into nutritional interventions to encourage healthier food choices and mitigate stress. Similarly, cognitive and behavioral techniques can help patients to manage food-related anxiety that may exacerbate GI symptoms [354]. Future research should explore the synergistic potential of combining psychological therapies with nutrition-based interventions, assessing their integrated impact on both GI and mental health outcomes. Such an approach could optimize overall patient well-being, potentially reducing the need for separate treatments for the GI and psychological aspects of IBD.

Anti-tumor necrosis factor-alpha (anti-TNF-α) therapy, which constitutes a key approach for the management of IBD, has also been associated with improvements in mental health. Research has reported significant reductions in anxiety and depressive symptoms following anti-TNF-α treatment, effects that are likely mediated by decreased systemic inflammation and improved disease control [355]. These findings highlight the dual potential of anti-TNF-α therapy in addressing both the GI and psychological dimensions of IBD. Nevertheless, the long-term impact of these treatments on mental health outcomes remains incompletely understood, and inter-individual variability in response requires further investigation to clarify sustained benefits and optimize patient care.

Precision medicine offers significant promise for advancing the management of psychiatric comorbidities in IBD. Progress in genomics and biomarker research may enable the early identification of patients at heightened risk for developing mental health complications [356]. For instance, genetic studies have highlighted polymorphisms in inflammatory pathway genes, including IL-1β and TNF-α, as contributors both to IBD severity and susceptibility to depression [357]. By customizing interventions according to the genetic and microbiome profile of an individual, clinicians may deliver more precise and effective treatments. In addition, the integration of advanced technologies, such as machine learning and artificial intelligence (AI), further enhances this precision approach. AI-powered analysis of large-scale datasets, such as electronic health records and patient-reported outcomes, can reveal novel patterns and predictors of psychiatric comorbidities [358]. Such data-driven strategies may also inform the selection of optimal therapeutic interventions and facilitate real-time monitoring of disease progression, ultimately supporting more personalized and effective patient care.

Although the present narrative review provides a comprehensive synthesis of the influence of the GBA on the relationship between IBD and psychiatric disorders, including

interventions targeting IBD-related psychiatric comorbidities, several limitations should be acknowledged. First, the inherent heterogeneity of IBD, encompassing diverse phenotypes, variable disease severity, and differential treatment responses, poses challenges for generalizing findings. Second, the lack of standardized assessment tools for psychiatric symptoms across studies introduces variability in reported outcomes, complicating comparisons and synthesis. Third, intervention studies often face limitations related to small sample sizes, heterogeneous populations, and differences in study design, while the scarcity of robust longitudinal and interventional research further restricts the ability to extrapolate findings across CD and UC subtypes. Finally, as a narrative approach, this review is subject to potential selection bias, lacks formal risk-of-bias evaluation, and does not include quantitative synthesis, all of which may limit the generalizability of the conclusions.

8. Conclusions

There is a bidirectional relationship between IBD and psychiatric conditions, particularly anxiety and depression, which arises from a complex interplay of genetic susceptibility, GBA dysregulation, and neuroimmune processes. Disturbances in GM composition represent a core mechanism underlying IBD psychiatric comorbidities, although a substantial body of the current knowledge is derived from preclinical models. Consequently, there is a need for large-scale RCTs to confirm the translational relevance of these findings in human populations. As personalized medicine continues to advance, integrating genomic information, microbiome profiling, and lifestyle factors may enable more individualized management strategies that address both the physical and psychological complexities of IBD. Nevertheless, challenges such as disease heterogeneity, variability in psychiatric symptom presentation, and the lack of standardized diagnostic tools remain as significant barriers. Ongoing interdisciplinary collaboration and rigorous research will be essential for developing customized interventions that effectively target both GI and mental health outcomes. In essence, the future of IBD-psychopathology research is characterized by both substantial promise and considerable challenges. Innovations in microbiome science, nutritional psychiatry, collaborative care, and precision medicine provide options to improve the lives of patients affected by these comorbid conditions. Realizing this potential will require sustained investment in multidisciplinary research and the establishment of standardized clinical protocols to guide integrated care.

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Abbreviations

The following abbreviations are used in this manuscript:

ACT	Acceptance and commitment therapy
AI	Artificial intelligence
ASD	Autism spectrum disorders

BBB	Blood–brain barrier
CBT	Cognitive behavioral therapy
CD	Crohn's disease
CI	95% Confidence interval
CNS	Central nervous system
CRP	C-reactive protein
DEGs	Differentially expressed genes
DGBIs	Disorders of gut–brain interaction
DSS	Dextran sulfate sodium
ENS	Enteric nervous system
FFAR2	Free fatty acid receptor 2
FFAR3	Free fatty acid receptor 3
fMRI	Functional magnetic resonance imaging
FMT	Fecal microbiota transplantation
GAD	General anxiety disorder
GBA	Gut–brain axis
GF	Germ-free
GLP-1	Glucagon-like peptide-1
GM	Gut microbiome
GMMs	Gut microbiota modulators
GI	Gastrointestinal
GWAS	Genome-wide association studies
HDAC	Histone deacetylase
HPA	Hypothalamic–pituitary–adrenal
5-HT	Serotonin
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
KYN	Kynurenine
MBI	Mindfulness-based intervention
MDD	Major depressive disorder
MR	Mendelian randomization
OR	Odds ratio
PUFAs	Polyunsaturated long-chain fatty acids
PVT	Paraventricular thalamic nucleus
RCT	Randomized clinical trial
SCFAs	Short-chain fatty acids
SNPs	Single nucleotide polymorphisms
SNRIs	Serotonin and norepinephrine reuptake inhibitors
SSRIs	Serotonin reuptake inhibitors
TCAs	Tricyclic antidepressants
UC	Ulcerative colitis

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