

## **The Relationship Between Affective Disorders and Pain: Focusing on the Functional Gastrointestinal Disorders such as Irritable Bowel Syndrome**

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### **Abstract**

Affective disorders and pain could exert an important relationship with digestive manifestations, especially those related to irritable bowel syndrome (IBS). Also, this relationship could be a result of different mechanisms, as here we are discussing some possible pathways between affective disorders, pain and IBS including gut-brain axis, pain, stress, genetics, micro biome, and the oxidative stress status.

**Keywords:** irritable bowel syndrome (IBS) , affective and pain disorders , gut-brain axis, genetics

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### **Introduction**

Irritable bowel syndrome (IBS) is a common disorder that affects the digestive system especially large intestine, with no specific treatment affecting 11% of the global population; its symptoms are varied and including cramping, bloating, abdominal pain, diarrhea, constipation. IBS has been linked to some psychiatric disorders including anxiety, and depression [1, 2]

### **General aspects, digestive manifestation, and affective disorders**

In point of fact, there is a link between digestive manifestation and psychiatric disorders, as observed in many studies, a three population-based prospective study, found that gastrointestinal disorders occur and mood and anxiety occur later [3, 4 ,5] depressive and anxiety syndromes were the most recurrent in German patients with gastroenterology and hepatology diseases and authors recommended enhancing of psychosomatic basic care in these patients. [6] Patients with bipolar disorders are more likely to have peptic ulcer diseases [7], in a case-control study female bipolar patients with high HADS depression score exhibit more GI symptoms [8], in a community study dyspepsia was associated with a generalized anxiety disorder and major depressive disorder [9] and also with stress [10], in a population-based study peptic ulcer diseases was correlated with mental health problems including depression, and suicidal ideation [11] and also anxiety disorders [12], in cross-sectional study patients with IBD

were more likely to have BD than patients without IBD [13] also chronic abdominal pain syndromes were linked to increase the risk of suicidal behaviors [14]

### **IBS in affective and pain disorders**

Functional imaging studies on patients with IBS show a significant difference when they compared to healthy controls in certain areas of the brain involved in the regulation of affective and sensory processes [15, 16] A study by Cristina Stasi et al analyzed sub threshold psychiatric symptomatology in 135 patients with FGD, where (40.0%) patients had irritable bowel syndrome, they observed that obsessive-compulsive spectrum was correlated with the presence of functional constipation and irritable bowel syndrome, also they conformed to other studies that show the high presence of psychiatric disorders among patients with FGD especially IBS Patients [17, 18, 19, 20], bipolar disorder was higher in IBS patients than in controls. [21, 22, 23] , a strong association between symptoms of IBS and symptoms of anxiety and depression was observed in a cross-sectional study, investigate the prevalence of IBS symptoms, and factors associated with gastrointestinal symptoms in patients with recurrent depressive disorder [24], A review on some case-control studies , reported an association between anxiety and depressive disorders in both ulcerative colitis (UC) and IBS patients compared to healthy controls [25] , While symptoms of anxiety disorders or somatization disorders present with irritable bowel syndrome and functional dyspepsia in 40–50% of patients with neurotic and behavioral disorders suffer from functional gastrointestinal symptoms [26] IBS patients can exhibit or can suffer from a psychiatric symptoms higher than non IBS patients[27] another study demonstrated that abdominal pain is associated with depression and anxiety not only In IBS patients but also in healthy people with abdominal pain [28] patients with both panic disorder and IBS show a more a higher anticipatory anxiety scores than patients without IBS [29] In a prospective, 6-month follow-up study, somatization disorder was associated with psychiatric and IBS symptoms [30]. Patients with a panic disorder had more IBS than controls, while also the treatment of their panic disorder reduces their gastrointestinal symptoms. [31]. catastrophizing and somatization were the most important psychological factors associated with IBS severity among 286 IBS patients [32] GI symptoms have been associated with sexual abuse [33, 34] while also early life stress may increase risk of IBS as mentioned in a systematic review [35] and a population-based cohort study [36], a large-scale population-based study, reported that stress and depression linked to many digestive diseases especially FD and IBS, also it may cause gastric cancer [37]. In an epidemiological population based study of women , IBS was associated with anxiety and mood disorders suggesting that IBS may has psychosomatic aspect [38] a nationwide Population-based cohort study found that within 1 year of IBS

diagnosis there is a highest risk for bipolar disorder , anxiety disorder , sleep disorder and depressive disorder however the risk remains statistically significant for more than 5 years since diagnosis [22] , chronic abdominal pain syndromes was linked to increase the risk of suicidal behaviors [14] take into account that chronic pain is a risk factor for suicidality or suicidal behaviors [39] , Patients with irritable bowel syndrome have an increasing in suicidal ideation over IBD Patients although this study contain some limitations but to our knowledge there is no study else addressed this topic [40] , although Guthrie et al reported a study addressed this topic but his study contain several limitations, as the IBS patients were unresponsive to medical therapy , and no control group [41] , a cross-sectional study on a large cohort of IBS patients with and without symptoms of abdominal bloating and healthy controls reported that IBS patients with symptoms of abdominal bloating have psychological distress, particularly somatization and depression [42] also these findings with also addressed in children [43]. patients with severe IBS and severe GI symptoms exhibit more of psychiatric features [44]. Back pain, headaches, and high blood pressure were observed in IBS patients [45, 46], take into account that chronic back pain was associated as a risk factor for major depression disorder [47] and also low back pain was associated with depression [48] IBS is associated with chronic pain [49] and chronic pain is associated with depression [50] several studies linked fibromyalgia to IBS [51,52, 53] while headaches especially migraine is associated with gastrointestinal disorders [54, 55] suggesting that gut micro biome plays a role in these association [56] what is more that several studies found IBS and migraine have a relationship [57, 58 ,59] also gastrointestinal disorders was higher in patients with rheumatoid arthritis than general population [60] ,rheumatoid arthritis especially psoriatic arthritis and osteoarthritis considered to be a higher risk factor for IBS [61] . there is small growing evidence support a role of oxidative stress in IBS [62, 63, 64, 65] given the fact that oxidative stress has a role in psychiatric disorders [66, 67] and affective disorders [68, 69] including depression [70, 71] and anxiety [72] and bipolar [73]

### **The relationship between IBS genes and affective disorders genes - the possible genetics bridge between IBS and affective disorders**

Nerve growth factor gene (NGF) gene has shown to play a role in IBS especially IBS-D[74, 75] and it is also linked to anxiety and depression [76], While some SNPs in genes play a role in IBS pathology like Brain-derived neurotrophic factor (BDNF) has shown to play a role in IBS especially IBS-D [77, 78] and it is linked to affective disorders [79] Catechol-O-methyltransferase (COMT) gene has also a role in IBS [80] and is linked to anxiety and depression [81, 82], Mu Opiate Receptor gene OPRM1 its linked to IBS [83], and also to pain perception, serotonin-transporter-linked polymorphic region (5-HTTLPR ) has

linked to IBS especially IBS-C [84, 85] and it is linked to depression, anxiety [86, 87].

### **Microbiome and IBS**

There is growing evidence that micro biome has a role in psychiatric disease and mental health [88], while gut-brain axis also has been known to play a role in several gastrointestinal and psychiatric disorders [89] a new term was emerged “gut-brain communication and behavior” [90, 91], A gut-brain axis can modulate affective behavior via interacting with immune [92] Studies also observed that gut micro biome are capable of inducing pain and inflammation [93, 94] Micro biome has a role in modulating the behavior including anxiety as experimental results on mice indicated [95, 96, 97]. Kennedy, Paul J., et al was the first one who named IBS as a micro biome-gut-brain axis disorder [98] probiotics can be used to treat IBS and mood disorders as reviewed in [99] a gram-positive bacteria, *Lactobacillus acidophilus* is cable to function as analgesic in the gut like morphine, [100]. Probiotic therapy composed of *B infantis* 35624 that is cable of relieve many symptoms of IBS as observed in 77 IBS patients [101] and 362 women with IBS [102], in pilot study of placebo-controlled trial, Probiotic *B. longum* NC3001 reduces depression and improved quality of life in IBS patients [103], *B. longum* NCC3001 also was cable to normalize anxiety-like behavior in mouse [104], a fermented dairy product containing *B. lactis* DN-173 010 can reduce abdominal distension and improved bloating as reported in a clinical trial on females suffering from IBS with constipation [105] *B infantis* 35624 also can reduce visceral pain as reported experimentally in mice [106] and in rats [107, 108], probiotic bacteria found to help children with IBS as reviewed in [109] but not only IBS, also anxiety and depressive symptoms as reported in a systematic review of randomized controlled trials [110] a decrease in anxiety symptoms among Patients with chronic fatigue syndrome (CFS) after receiving probiotic bacteria *Lactobacillus casei* strain Shirota (LcS) in pilot study of randomized, double-blind, placebo-controlled trial [111] fecal micro biota transplantation (FMT) may help patients with functional gastrointestinal disorders [112, 113], fecal micro biome transplantation (FMT) for ten patients was an effective treatment for IBS [114] a randomized, double-blind, placebo-controlled study on 165 patients found also that FMT is an effective treatment for IBS [115] and also (FMT) for IBS patients can reduce symptoms for 70 % of patients [116]

### **The possible micro biome bridge between IBS and affective disorders**

A decreasing in Bifidobacteria and increasing in Enterobacteriaceae were observed in patients with IBS [117] Enterobacteriaceae was higher also in patients with major depressive disorder [118] and depressive BD patients [119]

also IBS patients had increasing in Veillonella and Lactobacillus [120] while increasing in Veillonella were observed in patients with bipolar disorder [121] and Lactobacillus were higher in patients with first-episode psychosis [122] also Lactobacillus were increased in BD individuals with metabolic syndrome [119] . increasing in Firmicutes:Bacteroidetes ratio in IBS patients [123] while also increasing Firmicutes:Bacteroidetes ratio were observed in patients with autism spectrum disorders [124] take into account that autism spectrum disorders is associated with depression [125] , increasing in Firmicutes were observed in patients with major depressive disorder [126] Alistipes were associated with the of frequently recurrent abdominal pain in children with IBS [127] , Alistipes also were higher in patients with depression [118, 128] and in patients with bipolar depression [129] Proteobacteria were higher in the micro biome of children with IBS [127]

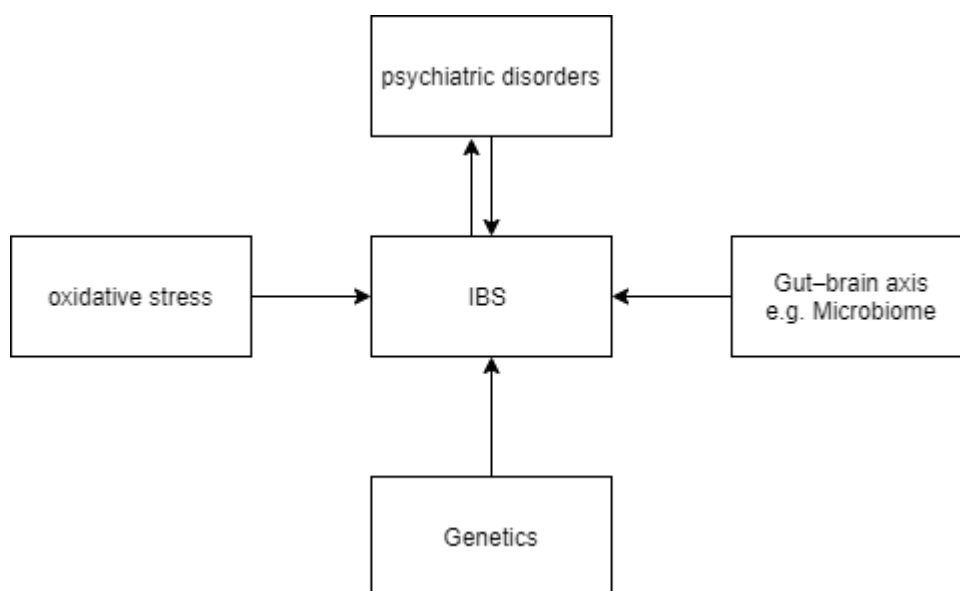
### **Psychiatric treatments for IBS**

In two Systematic review and meta-Analysis of randomized controlled trials investigate the role of antidepressants and some psychological therapies in IBS found that these treatment are effective [130, 131] and also other article [132] take the advantage that antidepressants can be used to treatment chronic pain [133] In a longitudinal assessment of IBS patients received paroxetine , improvement in their psychiatric and gastrointestinal symptom was observed [44] although that paroxetine did not show a significant difference in Primary outcome over placebo , but offered some benefit over placebo on secondary outcome as reported in a double-blind, randomized, placebo-controlled trial [134] , In another double-blind, placebo-controlled trial paroxetine provide an improvement of well-being [134] , cognitive behavioral therapy for Functional gastrointestinal disorders could be help the patients with symptoms of functional gastrointestinal disorders (FGIDs) as reviewed in [135] CBT therapy for IBS was not only form nowadays but also was long ago [136] CBT therapy and psychological interventions maybe useful in the treatment of IBS [137, 138, 130, 139, 140] while also gut-directed hypnotherapy was beneficial in IBS patients [141, 142, 143 , 144] .an increasing in the tolerance to rectal distension after psychological treatment and reduction in depression was reported in patients with severe IBS [145] decreasing in anxiety was associated with decreasing in abdominal pain-related pediatric functional gastrointestinal disorders [146] Interestingly, preliminary data supporting the benefit of yoga therapy in IBS [147,148,149] and also in abdominal pain-related functional gastrointestinal disorders in children [150] given the fact that yoga therapy is an effective complementary treatment in psychiatric disorders [151] including depression and anxiety [152, 153] Also It is worth noting that there are standard screening questions for identifying any psychiatric symptoms associated with gastrointestinal disease in a proposed

framework named "gastrointestinal (GI) distress ", made by BM Spiegel and his colleagues, based on asking some questions to patients, an approach can be used to evaluate maladaptive cognitions and emotions, associated with physical symptoms of gastrointestinal disease while the GI cognitions were focusing on the locus of control, catastrophizing, anticipatory concerns, and embarrassment/stigma, and GI emotions were divided into visceral anxiety, depression, and devitalization [154]

### Conclusion

In the light of all mentioned above, it seems that there is a bidirectional pathway between psychiatric disorders and gastrointestinal disorders especially IBS the crosstalk between them may be regulated through different mechanisms in the disease etiology, including gut-brain axis, pain, stress, genetics, micro biome, and even the oxidative stress statues. Finally, gastroenterologists should aware of the psychiatric symptoms of their patients also psychiatrists should aware of the gastrointestinal symptoms of their patients and both should treat these symptoms. microbiome based treatment could be used as a novel efficient treatment for these symptoms especially for IBS patients, psychiatric medicines such as antidepressants are recommended also in IBS, as originally suggested in Figure 1.



**Fig. 1. Irritable bowel syndrome and its possible etiology**

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