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Psychiatric Comorbidities in Irritable Bowel Syndrome (IBS)

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Additional information is available at the end of the chapter

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Abstract

FA lot of research has pointed out that irritable bowel syndrome (IBS) is a multifactorial illness involving visceral hypersensitivity, alteration of communication between the enteric nervous system (ENS) and central nervous system (CNS), increased intestinal permeability, minimal intestinal inflammation, and altered intestinal microflora. Psychological, social, and genetic factors appear to be important in the development of IBS symptomatology through several mechanisms. This chapter addresses the relationships between irritable bowel syndrome (IBS) and psychiatric comorbidities. The aim of this chapter is to provide an overview of explanatory hypothesis and to describe a variety of approaches which integrate the vast research data about IBS and psychiatric comorbidities, including genetic, brain imaging, and neuropsychological findings. The section of this chapter which overlooks the psychotropic treatment reviews the comparative efficacy of various drugs.

Keywords: irritable bowel syndrome, neuroimaging, psychiatric comorbidities, psychosocial factors

1. Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal (GI) disorder that has been reported to be associated with increased use of health-care resources and impaired quality of life.

Over the last two decades, it is becoming increasingly clear that many factors are involved in IBS, and they interact in very complex ways, which have not been yet elucidated.

The biopsychosocial model has been developed to explain the IBS pathogenesis better. According to this model, the gastrointestinal function is modulated via brain-gut axis by psychosocial factors. Particular attention is given to stress, emotion, and psychological factors in the IBS pathogenesis.

Emerging data reveals the interaction between psychiatric disorders and IBS, which suggests that this association should not be ignored when developing strategies for screening and treatment. The simultaneous presence of a mental disorder and IBS worsen the prognosis of both diseases involved to a significantly greater extent.

It is very important to understand better how social and psychological factors influence biological processes both in IBS and psychiatric conditions. Several mechanisms have been proposed to explain this association. In this chapter, we highlight data from a wide range of research including genetic, neurotransmitter, and brain imaging studies.

Stressful life events can lead to the activation of hypothalamic-pituitary-adrenal (HPA) axis. Neurotransmitters including serotonin, norepinephrine, and corticotropin-releasing factor change the motility and the perception in the gut. Brain regions necessary for pain processing and pain and emotional regulation may be involved. The psychological burden of a chronic relapsing illness can increase the maladaptive behaviors and negative emotions and decrease the coping abilities. A better understanding of these processes will be crucial for developing more useful treatments.

Although pharmacological treatments have proven efficacy in IBS, the illness remains chronic with the symptomatic and functional problems only partially influenced for most patients.

A lot of papers have documented improved clinical prognosis in IBS through psychological and pharmacologic interventions. Despite these promising data, the evidence is still limited by underpowered sample sizes.

With this growing awareness of the importance of psychosocial factors in IBS care, medical professionals experience an increased need for accessible background information and practical guidelines for diagnosis and management of psychiatric comorbidities.

Over the last two decades, it is becoming increasingly clear that many factors are involved in IBS and they interact in very complex ways, which have not been yet elucidated.

2. Psychosocial factors linked to IBS

The biopsychosocial model aims to integrate the multidimensional mechanisms to understand how IBS can be developed under such multiple interactions. The most important characteristic of this model is the bidirectional causality: the psychosocial factors influence the brain and the gut, and the gut interacts with the brain via the autonomic nervous system and the hypo-thalamic-pituitary-adrenal (HPA) axis [1]. The principal psychological and social factors that have been reported to contribute to the onset, the severity, and the evolution of IBS are presented in **Table 1**.

Sociological factors	– Parental beliefs and behaviors
	– Illness behavior
	– Learning through positive reinforcement or reward and modeling
	– Adverse life events (sexual, emotional, physical abuse)
	– Chronic life stress
	– Social support
	– Culture (cultural beliefs, norms)
Psychological factors	– Anxiety, depression
	– Anger
	– Cognitive-affective processes: gastrointestinal anxiety, hypervigilance, and attentional bias, catastrophizing, alexithymia
	– Coping mechanisms

Table 1. Psychological and sociological factors involved in IBS.

- Parental beliefs and behaviors. It is accepted that there is a familial aggregation of IBS. Studies demonstrated that not only the genetic factors could explain why IBS tends to cluster in families, but the development of gastrointestinal symptoms could also be explained by reinforcement and modeling of gastrointestinal illness behavior by parents [2].

- Positive reinforcement of illness behavior. Children whose parents reinforce sickness behavior (through parental protective behaviors) report more severe pain and more school absences than other children. Studies of childhood learning have also suggested that social learning through modeling processes (children observing and learning to exhibit the behaviors they witness) may also contribute to the intergenerational transmission of GI illness behavior and play a significant role in development and maintenance of IBS symptoms [3–5].

- Various types of early adverse life events (EALs) are associated with the development of IBS, in particular sexual, emotional, and physical abuse [6]. The relationship between abuse and severity of gastrointestinal symptoms and poorer health-related quality of life (HRQOL) seems to be partially mediated by concomitant mood disturbances [7]. Studies have shown that other types of EALs have been associated with an increased vulnerability toward developing IBS (parental death, divorce, or separation) [8]. A substantial body of evidence suggests that epigenetic mechanisms play a major role in the causal link between EALs and IBS. Findings from animal models and human studies highlighted the long-term effects of exposure to stress in early life through changes in gene expression [9]. Furthermore, prospective studies have demonstrated that chronic life stress is the most significant predictor of IBS symptom severity over 16 months. Stress has a marked impact on mucosal

immune activation, intestinal sensitivity, permeability, secretion, and motility and through various mechanisms can affect the IBS treatment outcomes [10–12].

- Social support is related to many aspects of IBS. It was shown that social support is reduced in chronic illnesses. The association between the quality of social support and the severity of IBS symptoms was mostly investigated. Perceived adequacy of social support appears to have a positive influence on pain possibly through a reduction in stress levels [13]. In contrast, negative social relationship correlates with increased symptom severity.

- Culture. The impact of culture on the perception and description of IBS symptoms is already known. It was emphasized that cultural beliefs, norms, and behaviors should be taken into account when evaluating the IBS presentation and management of the symptoms. Cultural norms could shape the acceptability of expressing symptomatology and the willingness to seek health-care assistance.

- Gastrointestinal-specific anxiety (GSA) represents "the cognitive, affective, and behavioral response stemming from fear of gastrointestinal symptoms, and the context in which these visceral symptoms occur" indicating awareness of and concern about gastrointestinal sensations. It has been suggested that GSA may be more relevant than general anxiety for symptom severity and health outcome and represents a key predictor of IBS diagnosis. Moreover, GSA was found to be associated with the mental component of quality of life, suggesting that GSA is an important endpoint for different interventions [14].

- Hypervigilance. IBS patients selectively attend to gastrointestinal sensations compared to healthy individuals. Some researchers indicated that visceral hypersensitivity is linked with the hypervigilance toward visceral sensations and a tendency to label them negatively [15]. Hypervigilance may reflect poor coping with gastrointestinal-specific anxiety.

- Attentional bias. Studies indicate that attentional bias toward gastrointestinal sensations is exaggerated and could represent a potential factor in IBS development and maintenance. Researchers reported that focusing attention on bodily sensations leads to increased physical symptom complaints and illness behavior.

- Catastrophizing has been defined as a psychological construct characterized by the tendency to have a distorted negative view of health problems and amplify the threat of symptoms. Cross-sectional studies have found that catastrophizing in IBS is associated with increased pain, increased health-care utilization, and increased disability [16].

- Alexithymia is a multidimensional construct defined as an inability in experiencing, expressing, and describing emotions in a verbal manner. Alexithymia can be conceptualized as a deficit in cognitive processing and emotional regulations. IBS patients present higher levels of alexithymia than general population. Also, studies suggest that alexithymia, a stable trait, could be a stronger predictor of IBS severity than GSA, thus implying that impaired affective awareness may weigh in the clinical presentation of IBS [17].

- Anger represents a negative emotional state that has several dimensions: anger experience, anger expression, and anger control. Inhibited anger expression is associated with depression, pain interference, and the frequency of pain behaviors. There are results that higher

levels of trait anger characterize IBS patients when compared to healthy population, and this may be associated with clinical manifestations [18]. Other studies demonstrated that IBS patients appear to have higher levels of anger than a group of patients with organic bowel diseases.

• Coping mechanisms. Studies have begun to focus on the coping mechanisms because these factors influence treatment options, patients' expectations, and treatment outcome. Coping represents the cognitive and behavioral efforts to deal (reduce or tolerate) with a perceived stressful situation. As mentioned above, the coping can influence the outcome of the illness. Therefore the quality of a coping strategy should be evaluated according to with its effect on the outcome. Lazarus has defined two categories of coping from the cognitive perspective: problem focused and emotion focused [19].

Problem-focused strategies strive for resolving the stressful situation or event or altering the source of the stress. It includes strategies such as:

– Problem solving (managing external aspects of the stressor)

– Seeking information or support in handling the situation (instrumental support)

– Accepting responsibility

– Removing oneself from a stressful situation

Emotion-focused coping represents the efforts to regulate the emotions associated with the situation. It involves strategies as:

– Positive reappraisal

– Distancing

– Escape-avoidance

– Seeking social support

Studies showed that in cases of chronic illnesses, the effects of coping are not influenced by the type of problem, or emotion-focus strategies are used but rather if active or avoidant methods are employed. Moreover, in IBS patients, it seems that the presence or absence of depression and/or anxiety influences how they cope with illness. Maladaptive coping and visceral sensitivity appear to be significantly associated with psychological distress, illness perception directly affecting the maladaptive coping.

Phillips et al. evaluated the role of psychosocial factors in predicting the belonging to IBS group and severity of IBS symptoms [20]. They found that four coping strategies (active coping, instrumental support, self-blame, and positive reframing) were best predictors of IBS.

Coping seems to be a relevant factor in mediating the adverse impact of IBS symptomatology on daily activities. Patients' quality of life could be impaired by the lack of adequate social support and by lower coping abilities acquired through social learning during childhood. Also, the impact of IBS symptoms on HRQOL impairment is mediated by dysfunctional attitudes and avoidant-oriented coping. Inefficient coping strategies represent important treatment

targets for cognitive-behavioral therapy (CBT) because coping styles are modulated by the use of cognitive abilities [21].

3. Genes and IBS

As discussed before, IBS is a chronic disease characterized by familial clustering. In the recent years, the hypothesis of a genetic contribution to the development of IBS has gained some support [22].

It was postulated that IBS is a multifactorial, polygenic complex disorder. A candidate gene study evaluates a specific polymorphism or set of polymorphisms. Until now, approximately 60 candidate genes were investigated to determine whether specific genetic variants may be associated with IBS. Until now the data sustaining the genetic hypothesis are scarce, and some results have not been replicated.

Many epidemiological studies reported psychiatric comorbidities, and also reported higher rates of these comorbidities than in the general population. Different pathways could be affected in the subgroup of IBS patients with psychiatric comorbidities. Recent studies tried to evaluate if the IBS and mental disorders share common genetic pathways (primary cortico-tropin-releasing system and serotoninergic pathway).

Data are sustaining that HPA axis and serotoninergic system are likely to be involved in the genetic susceptibility to major depressive disorder, but currently, there is no clinical evidence for a common gene in IBS and major depression.

Eight genes involved in psychiatric disorders were investigated with mixed results:

1. FKBP5 gene (the gene encoding FK506-binding protein 51) is located on the short arm of chromosome 5; some variants were associated with stress reactivity and post-traumatic stress disorder (PTSD) risk.

2. Catechol-O-methyltransferase (COMT) gene: COMT Val158Met was related to IBS with constipation. The same variant was associated with obsessive-compulsive disorder (OCD), panic disorder (PD), and cognitive performance.

3. Opioid receptor Mu 1 (OPRM1) gene: diseases related to this gene include opioid dependence, pain sensitivity, and social sensitivity. OPRM1 118AG variant was associated with IBS-mixed and IBS-diarrhea (IBS-D).

4. Brain-derived neurotrophic factor (BDNF) gene: psychiatric diseases related to this gene include schizophrenia, anorexia and bulimia nervosa, PTSD, and mood disorders. BDNF Val166Met was associated with IBS with psychiatric comorbidities.

5. Neuropeptide Y (NPY) gene is implicated in stress response

6. Ankyrin repeat and kinase domain containing 1 (ANKK1) gene: it was associated with impulse control disorders and alexithymia.

7. Dopamine receptor D2 (DRD2) gene: it seems to have a role in cocaine dependence.

8. Fatty acid amide hydrolase (FAAH) gene also has a role in substance dependence.

A recent study found preliminary evidence that IBS patients with comorbid anxiety or depression are more likely to present functional variant alleles of serotonin transporters than IBS patients without psychiatric comorbidities.

Maybe the new technological advances in genomic studies will make it possible to identify common and rare variants on genomic deoxyribonucleic acid (DNA) [23]. Until now, based on candidate gene studies, it appears that there may be a different molecular basis for IBS with comorbid anxiety versus IBS without comorbid anxiety. Thus the role of environmental factor contributors to IBS development should not be underestimated.

4. Psychiatric comorbidity in IBS

Many studies reported an increased frequency of psychiatric comorbidities (diagnosis and symptoms) among patients with IBS. It has been estimated that IBS patients have high rates of psychiatric comorbidities (50 %–90 %). There are multiple factors involved in the determination of this comorbidity. The latest disease models of IBS encompass the overlap of brain circuits involved in emotion regulation, autonomic responses, and pain modulation as the most important features.

Clinical reports indicate that the relationship between IBS and psychiatric illnesses is bidirectional between the gastrointestinal tract and the brain, through various pathways (neural, neuroimmune, and neuroendocrine). Among mental disorders, mood disorders, anxiety disorders, and somatoform disorders have been the most frequently diagnosed conditions [24]. The complexity of the underlying pathophysiological processes is not completely understood. The hypothesis linking cognitive and emotional areas in the central nervous system (CNS) with the autonomic nervous system (ANS) and the enteric system (ENS) had a significant contribution to the understanding of the pathogenesis of IBS.

The increased comorbidity among IBS and psychiatric disorders is well established. Even though data refers to patients seen in tertiary gastroenterology centers, recent data pointed out that psychiatric comorbidity is also present in primary care.

Another important aspect that should be emphasized is that the majority of the study results are based on the administration of self-report screening instruments rather than a psychiatric interview. The screening tools only assess the probability of a psychiatric diagnosis, but further investigations are necessary. Moreover, studies of a causal relationship between IBS and psychiatric comorbidities are still limited in number and provide contradictory data.

Some authors argued that the data are applying only to those patients who have sought treatment and are not applicable to the non-consulters. Others suggested that could be a subset of patients with IBS characterized by high psychiatric comorbidity. Nevertheless, there is some evidence supporting the biological association between IBS and mental disorders.

Approximately 50 % of patients with a psychiatric disorder develop the disease before the GI symptoms became manifest, and psychiatric symptoms appear to develop at the same time in a majority of the remaining 50 %.

Many studies pointed out that worry-rumination can influence the brain-gut axis. Moreover, it has been identified as one fundamental factor that mediates the high co-occurrence of the two most frequent psychiatric comorbidities in IBS patients (anxiety and depression) [25].

It is noteworthy that the patients with severe IBS and comorbid psychiatric disorders have been found to have a higher impairment in HRQOL, elevated symptom burden, increased functional disability, and increased health-care costs.

4.1. Mood disorders and IBS

Many studies have investigated the prevalence of depression among IBS patients, but the results are vastly variable, ranging from high to much lower rates. There are also studies showing that patients with major depressive disorders present gastrointestinal symptoms.

Relevant findings from a large-scale population-based study suggest that depression and stress are independent risk factors for IBS. In this study, the incidence rate of IBS was higher in the patients with mild depression than in those with severe depression.

Several authors reported that IBS is associated with suicidality. The findings of one study indicate that 4 % of IBS patients who sought help from primary care, 16 % from secondary care, and 38 % from tertiary care endorsed suicidal ideation determined primary by the gastrointestinal symptoms. A systematic review indicated that IBS patients were two to four times more likely to recognize a history of suicidal behavior, even in the absence of depression.

A study conducted by Guthrie et al. revealed three definite groups of IBS patients [26]:

– Distressed high utilizers: characterized by multiple psychosocial comorbidities, increase levels of health-care utilization, high frequency of sexual abuse, and low pain thresholds to rectal balloon distension; the patients from this group reported suicidal ideation and self-harm history.

– Distressed low utilizers: marked by high psychiatric comorbidity, low physician consultations, low frequency of sexual abuse, and low pain threshold.

– Tolerant low utilizers: characterized by low rates of psychiatric comorbidities, low levels of consultations, and high pain thresholds.

It should be taken into account that an increase in suicidal ideation is not entirely explained by the symptom intensity and the presence of anxiety or depressive comorbidity. Therefore, IBS patients, especially distressed high utilizers, should be assessed for suicidality [27].

4.2. Anxiety disorders and IBS

As mentioned earlier, there is a higher prevalence of anxiety disorders among IBS patients than in the general population (47 % versus 26 %). According to the available literature, the

most prevalent anxiety disorders among patients with IBS are generalized anxiety disorder (GAD) and panic disorder (PD). Some studies suggest that mixed IBS (IBS-M) patients are more likely to present higher scores for anxiety, especially in comparison with IBS with constipation (IBS-C) [25].

It must be noted that recent studies suggest that the strong association between GAD morbidity and IBS observed in tertiary centers was not a consequence of increased help-seeking behavior.

PD and IBS share common characteristics such as gastrointestinal symptoms, anticipatory anxiety, and avoidant behavior because of fear of symptoms. Based on results of different studies, it appears that the presence of IBS is associated with greater severity of agoraphobia, anticipatory anxiety, and panic attacks in PD patients. Moreover, patients with IBS reported having high scores of anxiety sensitivity, as the PD patients. Further information on IBS and PD came from a review emphasizing that the experience of feeling uncontrollable somatic symptoms, very common in IBS, could be a stimulating component for PD in patients with subclinical PD symptoms [28].

4.3. Somatoform disorders and IBS

IBS is considered a functional disorder, and it is congruent with the definition of somatoform disorders. The Diagnostic and Statistical Manual for Mental Disorders (DSM-4-TR) and the International Classification of Diseases (ICD) classify physical symptoms that cannot be medically explained together with persistent requests for medical investigations in a separate somatoform category. In the DSM-5 this category was renamed as "somatic symptoms disorder" (SSD) and redefined; there is no longer a demand for lack of "medical" explanation of symptoms. It means that this diagnosis could be a primary diagnosis (somatic symptoms may be medically unexplained) or could be a secondary diagnosis in patients who have an organic illness. The documented prevalence rates of somatoform disorders among IBS patients vary from 15 % to 48 % [29].

5. Neuroimaging in IBS

Studies using structural and functional techniques in IBS patients showed abnormalities that were associated with:

- Visceral hypersensitivity

- Impairment of affective processes involved in visceral pain modulation

- Alteration of descending pain inhibitory pathways

Data obtained from brain imaging studies in IBS demonstrated physiological differences that distinguish patients with IBS from a healthy population. The results obtained have varied maybe because of different study designs or due to the heterogeneity of study populations [30, 31].

5.1. Structural neuroimaging

Nowadays, structural approaches are provided mainly by diffusion tensor imaging (DTI) and by structural magnetic resonance imaging (sMRI). The studies focus on structural connectivity.

IBS patients with chronic pain have regional cortical thickness (CT) alterations in comparison with healthy controls. CT represents the results of neural reorganization of pain circuits and regions associated with sensorial processing.

IBS patients present decreased gray matter density in prefrontal and parietal regions and in emotional circuits. Ellingson et al. demonstrated in a study using DTI that IBS patients have microstructural changes in areas involved in the cortical pain modulatory areas and cortico-thalamic modulation. The anterior insula and basal ganglia (BS) have a prominent role in the integration of sensory and non-sensory information.

Another study demonstrated that IBS patients showed lower cortical thickness (CT) in the interoceptive association cortex (aINS) in the right hemisphere than in healthy controls.

The anterior insular subregion has multiple roles:

- Integration of food-related (olfaction and taste), interoceptive, emotional, and cognitive functions

- Provides output to autonomic and pain modulation systems

- Plays a key role in prediction, error processing, and self-awareness of sensations

In the relationship with these roles, insular regions seem to be involved in psychopathology. As already highlighted, patients with IBS have an abnormal processing of visceral pain in this area as a result of the dysfunctional inhibition of the pain in cortical areas. Patients reporting higher levels of pain intensity associated with their IBS symptoms presented an important CT in the bilateral orbitofrontal cortex (OFC). Also, it was observed that disease duration and pain intensity were correlated with CT in the dorsolateral prefrontal cortex (DLPFC) and OFC, bilaterally.

Other studies reported CT in the anterior midcingulate cortex (aMCC), ventrolateral prefrontal cortex (vlPFC), and thalamus. The structural changes of gray matter density in the periaqueductal gray (PAG) region may be a reflection of the compromised descending modulation of pain.

Blankstein evidenced increased gray matter density in the hypothalamus of the IBS patients.

Depression and anxiety have a well-established role in the modulation of pain. It was suggested that the decreased gray matter density in the anterior/medial thalamus in patients with IBS could be related to the clinical levels of anxiety or depression.

Interestingly, some authors suggested that structural changes in the primary interoceptive cortex, as well as in the attentional and emotional network, could represent endophenotypes of IBS.

5.2. Functional neuroimaging

Functional approaches are provided by single-positron emission computerized tomography (SPECT), positron emission tomography (PET), resting-state magnetic resonance (MRI) and functional magnetic resonance (fMRI), magnetic resonance spectroscopy (MRS), near-infrared spectroscopic imaging (NIRSI), and magnetoencephalography (MEG).

A recent meta-analysis of research on cortical responses to rectal distension suggests the conclusion that brain responses to rectal distension are different in IBS patients and healthy controls. IBS patients showed greater activation in brain regions involved in emotional processing, cognitive modulation, and interoceptive analysis.

Using the functional neuroimaging techniques in IBS patients, it was identified the hyperactivity of the amygdala (an essential component in the emotional arousal network). The amygdala network is involved in processing visceral input in relation to emotional stimuli, modulation of sensorial information, and emotional regulation.

Another area that exhibited functional alteration during experimental pain in IBS patients is represented by the basal ganglia (BG). The data obtained are consistent with the reduction of the dendritic density in cortico-basal ganglia-thalamic-cortical circuits involved in modulation of pain. Moreover, hypersensitive IBS patients present more DLPFC activation than normo-sensitive patients.

The results obtained in studies using neuroimaging techniques sustain the hypothesis that IBS have a biological substrate, but the same changes could be noticed in other chronic disorders. Furthermore, psychosocial factors (early-life trauma, catastrophizing, anxiety, and depression) have had a substantial impact on the neuroimaging correlations of IBS. An association was noticed (either positive or negative) between the level of psychopathology and neuroimaging findings, thus emphasizing the relevance of psychological factors in IBS determinism [32–34].

6. Neuropsychological findings in IBS

Stress induces changes in HPA axis functioning with neurobiological and cognitive consequences. The brain-gut axis appears to have a major importance of cognitive performance. The psychiatric comorbidity has also impact in the neurocognitive functioning [15, 35].

In general, normal cognitive functioning was reported in IBS, but some researchers demonstrated subtle cognitive deficits that remained after the correction for psychiatric comorbidity.

6.1. Attention and IBS

Attention is a behavioral and cognitive process involving the selection of sensory information to optimize current behavioral responses to specific stimuli relevant for the organism.

Researchers suggest that IBS patients have specific abnormalities in attentional network functioning. IBS patients present attentional biases for pain words. Attentional alterations are associated with increased pain report and illness behavior.

6.2. Memory and IBS

Currently, there are data suggesting impairment in visuospatial memory in patients with IBS. The researchers found that IBS patients displayed poorer performance in hippocampal-mediated visuospatial tasks than non-IBS controls. They made twice to three times as many errors on the visuospatial test as the healthy control group. It was suggested that visuospatial memory dysfunction could represent a common component of IBS [36].

6.3. Executive function and IBS

Cognitive flexibility in IBS patients was evaluated with Wisconsin Card Sorting Test (WCST). Recent researches have shown that IBS patients present latent impairments in the cognitive flexibility. The biological substrate for those findings seems to be the modified activity of the DLPFC, hippocampus, and insula. Also, the altered connectivity between the DLPFC and pre-supplementary motor area appears to be involved [37].

7. Psychopharmacology of IBS

Treatment of IBS could be classified in pharmacologic and non-pharmacological strategies. The choice of therapy depends on types of symptoms and their severity and frequency. It is clear that many aspects of IBS may be linked to psychosocial stressors and psychiatric comorbidities. More recent research emphasized that the psychotropic drugs can play a major role in the treatment of IBS patients [38].

7.1. Antidepressants

IBS is characterized by abnormalities in visceral sensations and dysregulation of central pain perception. Thus, the antidepressants represent a treatment option in patients with moderate and severe symptoms. The antidepressants were found to be efficacious for abdominal pain but have no effect on bowel habit. Moreover, their tolerance may represent a problem. Currently, antidepressants are used as a second-line therapy. The beneficial effects of antidepressants could be the results of influence in central pain threshold (an increase of threshold). Other mechanisms of action are represented by the anticholinergic effects (influence on gastrointestinal motility and secretion) and by reducing the pain sensitivity of peripheral nerves [39].

7.1.1. Tricyclics antidepressants (TCA)

Most recent research supports the use of TCAs in IBS treatment. The effects of several TCAs including clomipramine, nortriptyline, and imipramine were investigated in IBS patients. The results showed that the required dose of TCAs is lower than that used to treat patients with depression. TCAs are effective in IBS-D due to the prolongment of whole-gut transit times. A systematic review of 11 randomized controlled trials RCTs comparing TCAs and placebo revealed that the benefit attributable to TCA therapy relative to placebo was 12.5 %. The

numbers needed to treat (NNT) were four, equal or superior to other pharmacological agents (like motility agents and probiotics). The TCAs slow gut-transit time and could be used in diarrhea-predominant IBS.

7.1.2. Selective serotonin reuptake inhibitors (SSRIs)

Efficacy of SSRIs in the treatment of IBS was evaluated in seven randomized trials comparing SSRIs with placebo. The SSRIs studied were fluoxetine, paroxetine, and citalopram. One small open trial demonstrated the efficacy of paroxetine on abdominal pain. A common limitation of all the studies is represented by the short duration of the study (12 weeks) and the small sample size. The relative risks (RR) in the treatment of IBS symptoms were 0.62, but significant heterogeneity characterized the studies. The SSRIs decrease orocecal transit and would be of greater benefit in constipation-predominant IBS. According to Cochrane database of systematic reviews, SSRIs are prescribed at dosages standard for treating psychiatric disorders and should be used as a third-line treatment.

7.1.3. Serotonin-noradrenaline reuptake inhibitors (SNRIs)

Both serotonin and norepinephrine have a role in visceral motility and visceral sensation. It was noticed that low-dose SNRIs (duloxetine and venlafaxine) seem to be more efficacious than SSRIs. One study performed on healthy volunteers showed that venlafaxine reduced pain sensation ratings in response to grade distensions but did not have a significant impact on the colonic transit. SNRIs are promising, but more studies need to be done.

7.2. Atypical antipsychotics

Quetiapine may help patients with IBS by decreasing the anxiety and ameliorating sleep disturbances. It also augments the effect of antidepressants and provides an independent analgesic effect [40].

7.3. Anticonvulsants

Preliminary data from animal models provides evidence suggesting that the γ-aminobutyric acidergic (GABA) agents (gabapentin) and $\alpha2\delta$ ligand (pregabalin) may also be efficient in reducing central sensitization in hyperalgesia [41]. Gabapentin has more recently been used in the treatment of chronic pain. Pregabalin has been shown to be more potent than gabapentin. In patients with IBS, both gabapentin and pregabalin have been shown to reduce rectal sensitivity to balloon distension, but currently, there are no results published from clinical trials examining the efficacy of $\alpha2\delta$ ligands on symptoms in IBS patients.

7.4. Anxiolytic agents

The rationale for the use of anxiolytic drugs for the treatment of IBS likely came from the observation that the majority of patients also present of comorbid anxiety. Buspirone, an azapirone, is an anti-anxiolytic nonbenzodiazepine drug. It is a partial serotonin 1A (5-HT1A) receptor agonist used to augment the effects of antidepressants. The effects on gastrointestinal

motility are represented by the reduction of funding tone and the delay of emptying. Also, a relaxation effect on the rectal tone was observed [42].

8. Conclusions

There is a general agreement that a global assessment of IBS patient should be done. The significant overlap between IBS and mental disorders should encourage the clinicians to evaluate for comorbid psychiatric disorders routinely. It is very important to recognize the linkage between psychiatric diagnoses and IBS because these comorbid conditions are characterized by increased symptom burden and additive functional impairment. Thus, successful management of patients with IBS requires careful attention to all psychosocial factors involved.

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