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Review Article

# Insight into Improved IBS Clinical Outcomes Using a Combination of Quantitative and Qualitative Research Methods to Better Understand Visceral Hypersensitivity and Treatments Addressing it

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## Abstract

IBS is a functional gut disorder with abdominal pain and discomfort, bloating, urgency, irregular bowel habits, and increased sensation to bowel contents, the latter called visceral hypersensitivity. IBS treatments are historically unrewarding and unsuccessful for both the patients and providers. Quantitative research has provided a better understanding of the pathological etiology of visceral hypersensitivity and its role in abdominal pain. Qualitative research highlights the emotional struggles of patients coping with IBS and the impact on their life and daily routines. This article spotlights using a combination of quantitative and qualitative research methods to better understand visceral hypersensitivity and treatments addressing it for improved clinical outcomes.

**Keywords:** IBS; Visceral Hypersensitivity; NGF; CRF; Stress; Cognitive Therapy

## Introduction

IBS, Irritable Bowel Syndrome, is a Rome IV functional bowel disorder [1] which clinically presents as abdominal pain and discomfort, bloating, irregular bowel habits, negative endoscopy studies with intact gut lining, commonly coined "absence of an organic cause" [2,3], and increased sensitivity to bowel contents called "visceral hypersensitivity" [4] declare up to 40% of IBS patients with visceral hypersensitivity "exhibit enhanced sensitivity to colonic distension, which is noticeable through their reduced threshold for pain, increased intensity of sensations and/or exaggerated viscerosomatic referral in response to colonic distension" which has become accepted as an etiological source of abdominal pain, bloating, and urgency in the IBS population [5,6].

The Rome Foundation is a non-profit organization involved in the development and advances of functional gastrointestinal disorders supporting the field of Disorders of Gut Brain Interactions (DGBI) [1].

- Motility disturbances
- Visceral hypersensitivity
- Altered mucosal and immune function
- Altered gut microbiota
- Altered Central Nervous System processing.

The Rome VI criteria for IBS is as follows [7]

### C1. Irritable bowel syndrome

### Diagnostic criteria*

IBS under the Rome IV criteria recognizes 4 subtypes clinically correlating to the tendency of bowel habits; IBS-C (primarily con-

stipation), IBS-D (primarily diarrhea), IBS-M (mixed and alternating between either constipation or diarrhea), and IBS-U (meet the criteria but do not follow a trend of C, D, or M).

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two or more of the following criteria

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool

## Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

The IBS worldwide prevalence in 2019 was approximately 10-15% averaging 3 million physician visits annually, and furthermore, is considered a "valued market" [8] for the US upwards of 1.5 billion with an estimated growth rate of 10% over the next 8 years [8,9] Over the past decade, IBS and its common visceral hypersensitivity have been exploited with a better understanding of the pathological mechanism of action driving the increased sensitivity and its relation to abdominal pain [5,6].

The enhanced scientific viewpoint of visceral hypersensitivity and disruptions of the gut-brain neurohormonal signaling has allowed for significant changes to the IBS treatment approach with improved clinical outcomes [6]; rewarding for both the patient [5] and the treating clinician [10] each individually tainted with feelings of frustration and lack of effective therapy [11].

The opposing research methodologies, Quantitative and Qualitative [12], when analyzed or conducted together can enhance improved understandings of both disease expression (quantitative) and disease experience (qualitative); with the latter being a relatively newer research design. Regarding qualitative studies, there are only a handful of publications which assess the patient perspective of living with IBS and the commonly experienced visceral hypersensitivity [11] On the contrary, over the past two decades the science has evolved around a better understanding of the gut-brain vagal nerve bidirectional crosstalk through the enteroendocrine synapses and its clinical correlation to the IBS-perceived visceral hypersensitivity [2,3,13,14] In support of a mixed study design, my goal is to highlight benefits of each.

Quantitative research paradigms can tell us about the disease. These types of studies use surveys such as cross-sectional studies, or questionnaires, interventional or experimental human or animal studies, and typically applies statistics [12]. Applying this to IBS visceral hypersensitivity, we learn molecular pathological mechanism of action and correlated underlying etiologies of the disease. Understanding the source directs treatment to focus around it. Advances in mechanistically understanding the phenomenon of visceral hypersensitivity and its increased perception of bowel contents has helped create therapeutic strategies aimed to reverse the aberrant sensations back to basal unperceived physiological levels by addressing the actual source(s) of it.

Qualitative research paradigms use interviews and face-to-face sessions without interventions to gain an understanding of the "experience" and humanistic side of research models and disease [12]. In studies of IBS, it emphasizes the personal struggle and emotional distraught of people dealing with symptoms of bowel disorders and how it negatively impacts their quality of life and daily routines. Alternatively, these studies also have highlighted physician distress and frustration that surrounds an inability to positively influence patient outcomes and recurrence in IBS patient populations.

Utilization of the Mixed Method takes characteristics and attributes of each and combines them into one study [12]. An example would be using cross-sectional study with a symptom survey questionnaire as the quantitative portion to recruit a subject group. Of the subjects, upon acceptance into the study agree to participate in an interview with open-ended questions about the topic to gain insight on how the topic influences the patient. The combination may assist in developing better understandings of disease from physicians and improved therapeutic outcomes that address multifaceted levels of healing, beyond the physical/biological underlying pathological etiology.

Visceral hypersensitivity is a hallmark of IBS sufferers and scientific research has exploited its pathogenesis through quantitative human and animal studies while qualitative research has deepened the empathetic requirement for improved therapeutic strategies. Quantitative advancements connect disruptions in the gut-brain signaling and identify specific molecular components allowing for advancements in therapies focused on restoring gut-brain crosstalk through cognitive therapy techniques and with greater clinical outcomes.

Highlighting several monumental quantitative studies affords an excellent example of their profound attribute to the enhanced understanding of disrupted gut barrier, aberrant neurohormonal communications, and immune dysregulation as key drivers of visceral hypersensitivity. In contrast, evaluating remarkable qualitative studies reveals the desire to better understand a-day-in-the-life-of IBS sufferers to provide a platform of necessary change in patient-centered care.

## Quantitative study designs - nerve growth factor (NGF), stress and visceral hypersensitivity

Xu., *et al.* [3] explored the clinical correlation between IBS-D symptoms and IBS-related quality of life measures with abnormal expression of mast cell-derived NGF and its relationship to visceral hypersensitivity. They recruited a total of 38 IBS-D and 20 healthy controls, between the ages of 26-30 with BMI range of 21-22. The subjects began with clinical and psychological assessments including questionnaires addressing anxiety, depression, quality of life, visceral hypersensitivity, sleep, and coping skills. Fasting venous blood was collected for assessment of intestinal permeability and baseline markers. Following an evacuating enema, a colonoscopy and biopsy was performed at the rectosigmoid junction. Lastly, they underwent a visceral hypersensitivity test with rectal balloon distention. Several positive associations were present in the IBS-D vs control group. The perceived visceral hypersensitivity correlated to worse clinical and psychological survey results (anxiety, depression, sleep, negative coping, visceral hypersensitivity), disrupted gut barrier with increased permeability, and increased colonic mucosa expression of NGF mRNA protein but not serum NGF. In both groups the colonoscopy was for mucosal immune cell infiltration, epithelial damage, and parasites consistent with IBS's negative diagnostic histological assessments. However, they reported increased mucosal mast cell counts found during colonoscopy in the IBS group. Additionally, there was quantifiable increased perceived visceral hypersensitivity in the IBS group demonstrated as decreased tolerance to rectal balloon distention. The group concluded symptom severity clinically correlated with the presence of mucosal NGF mRNA and NGF protein expression noted as byproducts of mast cell degranulation alongside mast cell histamine. Their serum tests also confirmed increased histamine and confirmed disrupted gut barrier in the IBS group. This study demonstrated colonic increased pain signaling pathways and hyperalgesia response of the colonic sensory fibers orchestrating proof of a dysregulated afferent response as an underlying etiology of visceral hypersensitivity, while also supporting the current understanding of impaired gut barrier, higher rates of anxiety and depression, and lower quality of life in the IBS patient population.

These findings are in line with original work from Dothel., *et al*. [2] who successfully investigated the presence of IBS increased nerve fiber density and release of NGF, termed NGF-sprouting. They provided support of NGF-induced neuroplastic changes attributed to a dual effect of NGF stimulating nerve fiber growth and pain stimulation which has become known to be a neurotrophic factor-induced source of visceral hypersensitivity. Their team confirmed through proximal descending colon biopsy of 10 human subjects with IBS-D or IBS-M an average of 57% increase in nerve density and increased expression of NGF as well as the NGF-stimulating effect on its preferred receptor NTRK1 expressed constitutively on nerve fibers but also mast cells. Their research postulated the increased NGF to be a source of mast cell hyperplasia in IBS. "In conclusion, our results suggest that an abnormal mucosal milieu and neuroimmune interactions play a role in the pathophysiology of intestinal dysfunction and pain transmission of IBS patients." [2].

In an alternative pathogenesis model of etiological visceral hypersensitivity, Botschuijver., *et al*. [13] conducted a study comparing the mycobiome for fungal commensals or opportunistic overgrowth in IBS vs healthy controls. They included Rome III criteria of IBS diagnosis, anxiety and depression prevalence, dietary food intake questionnaire, and comparison of stool sample assessing commensal fungal population and species differences. They additionally conducted a rat-model of visceral hypersensitivity with rectal inflation which utilized stress-induced visceral hypersensitivity. They confirmed a difference in mycobiome of healthy subject's vs IBS with a significantly higher prevalence in hypersensitive IBS patients of the 2 fungal species, Saccharomyces cerevisiae and Candida albicans. The rat model was able to induce visceral hypersensitivity in a rat stress model which was prevented by pretreatment of 2 different fungicides which were equally successful. They also elucidated the role of the C-type lectin receptor Dectin-1 which recognizes fungal expressed beta-glucans on their outer cell wall and confirmed treatment with high dose soluble beta-glucans could prevent stress-induced visceral hypersensitivity. This study confirmed a functional etiological role of fungal gut commensal prevalence, fungal stimulation of gut immune cells, and protective roles of fungicides. Additionally, they evaluated the ability of fun-

gal species to activate mast cells and confirmed Dectin-1 mast cells who recognize fungal species then respond with histamine release, in support of prior studies of mast cell involvement in visceral hypersensitivity.

Another interesting etiological perspective of visceral hypersensitivity [13] is the involvement of peripheral corticotropin releasing factor (CRF), a peptide involved in the stress response. CRF release and receptors are primarily located in the central nervous system hypothalamic brain centers [15], however they were discovered to exist peripherally in the intestinal ileum and colon [13]. It has been well-documented that IBS clinically correlates with stress [16] however appreciating the clinical implications of intestinal release of CRF further supports the pathological role of stress in IBS and stress management and cognitive therapy as treatments. The intestinal CRF induces mast cell degranulation, known to be involved in NGF and multiple visceral hypersensitivity mast cell models [2,3]. Intestinal CRF additionally influences ileal and colonic motility impairing regularity of bowel habits and increases mucosal permeability quantified and observed in IBS visceral hypersensitivity populations [3].

Further exploiting stress in IBS and the intestinal CRF, the HPA-SAS in digestion is vital to understand. Stress negatively influences digestive activity through the HPA-Axis, hypothalamic-pituitary-adrenal, and its induced SAS, sympatho-adrenal-system [17].

Optimal digestive function is an interplay of meal-time acetylcholine dominance regulating secretions, motility, and intestinal blood flow orchestrated through the autonomic parasympathetic nervous system which is intimately integrated with the enteric nervous system of the intestinal mucosa together sustaining the "rest and digest" through acetylcholine-secreting plexus and Vagus nerve. Additionally, the enteroendocrine cells of the intestine are also responding to local signals of distention, chemical irritation, immune generated cytokines and inflammatory molecules, microbial byproducts, as well as taking part in the communication from bidirectional gut-brain crosstalk of neurotransmitters, neurohormones, and neuropeptides [18,19].

Stress disrupts the balance by allowing excessive mealtime amounts of the autonomic antagonistic sympathetic secretions of the catecholamines epinephrine and norepinephrine. Their presence, especially during mealtime, has a dose-response inhibitory effect where a strong enough surge can completely inhibit digestive secretions and motility [19]. Stress has been diagnostically implicated as an important pathological etiology in IBS onset, exacerbations, and remission [20]. Stress and inflammation each activate the HPA axis; hypothalamus releases CRF stimulating the pituitary to release its adrenocorticotropin hormone (ACTH) which stimulates the adrenal gland to release its Cortisol [15,17,19] although intestinal CRF release is now also known to occur [3,15]. The Cortisol through a paracrine fashion has an almost immediate effect on the neighboring adrenergic sympathetic neighbor in the adrenal medulla which responds with a release of sympathetic catecholamines, the SAS component of the HPA-SAS stress- response. Guilliams explains [19], through activation of the HPA axis, the "*hypothalamus consolidates all of these* (circadian, appetite, temperature, blood glucose, blood volume, and external threat) *internal and external threat assessments*." Gastrointestinal inflammation including inflammatory eicosanoid PGE2, and inflammatory cytokines IL-1 and TNF among others also induce an HPA axis over-activity and stress-response, resulting in higher levels of catecholamines [17]. This basic mechanistic understanding allows for appreciation of the gut-brain-adrenal connection and further exemplifies the importance of intestinal CRH overactivity in IBS patients and an etiological factor of IBS visceral hypersensitivity [13,15]. Progressions in therapy have begun to address these physiological components with improved clinical outcomes using cognitive therapy, hypnosis, and stress management in the IBS population, along with dietary changes [21].

## Qualitative study designs - personal experiences and improved clinical outcomes

Spot-lighting the importance of qualitative research in IBS establishes the emotional trauma and decreased quality of life of IBS patients through interviews and focus groups to gain insight into their daily struggles.

Harkness., *et al.* [10] conducted a qualitative study to address the perspectives of IBS-treating physicians with a goal from interviews to answer why there was a resistance of medical doctors to refer IBS patients for psychological referrals for treatment. The participating physicians all expressed frustration of poor clinical outcomes and low patient compliance for office visits. There was also a pattern of attitude that IBS was a diagnosis of exclusion, manageable in-office. Through face-to face interviewing the authors

concluded most general practitioners recognized its existence and assumed a psychosocial issue dictating bowel movements, but also felt the poor return for patient follow-up visits was part of them accepting their disease and "living with it".

Frandemark., *et al*. [22] conducted a qualitative study interviewing IBS sufferers to examine work life experiences and coping mechanisms for symptomatic days at work and amount of IBS driven sick days. They interviewed twenty-four individuals with a take-away of work-life revolving around the persistent potential threat of symptoms forcing individuals to develop routines and purposeful activity avoidances. There was also a high amount of stress if there were unforeseen disruptions of routines. Their study pairs nicely to gain insight on IBS sufferer's experience and mirrors a qualitative study two decades earlier [11] documenting low quality of life but also social isolation from IBS.

Cognitive behavioral gut-brain targeted treatment has gained popularity with improved symptom outcomes as well as self-help workbooks and apps [5,6]. Current treatment models developed around the growing acceptance of the gut-brain connection use hypnosis and cognitive therapy as key attributes to improving visceral hypersensitivity [23,24].

Qualitative studies can assess and evolve such therapies. For example, an ongoing mixed methods feasibility study [25] was designed to compare outcomes between high intensity psychotherapist interventions consisting of 60-minutes therapy sessions multiple days a week vs a combination of low-intensity 30-minute treatment sessions once a week paired with self-help educational tools, however outcomes of the study have not yet been published.

Utilizing qualitative research to improve clinical outcomes is an excellent use of this unique humanizing style of research. Maddux., *et al.* [26] conducted a remarkable mixed model study for improving IBD, Inflammatory Bowel Disease, patient transitions as they approach the age-limit with their pediatric gastroenterologist physician. It was occupationally accepted an elevated level of anxiety and distress existed within the population of the transitioning patients and their family. The outcome goal was to improve the transition with new established guidelines following data they obtained from the study. The team of authors used a quantitative cross-sectional survey to recruit local gastroenterologists into their study. Once they had all participating GI doctors, they conducted a 2-tier qualitative study. The doctors participated in a round table while patients were interviewed who had recently gone through the transition in their early adulthood. The mixed study successfully implemented updated guidelines for both pediatric and adult gastroenterologists to educate and initiate transitional steps several years prior to the actual referral, successfully addressing the problem of poor patient experiences through the transitional period.

## Conclusion

Xu., *et al*. [3] and Dothel., *et al.* [2] confirmed the dual involvement of mast cell degranulation of histamine and nerve growth factor (NGF) involvement in visceral hypersensitivity. Botschuijver., *et al*. [13] exposed an alternative mast cell mechanism of action paired with a fungal dysbiosis as pathologies in development of visceral hypersensitivity. Additionally, Xu., *et al*. [3] and Botschuijver., *et al.* [13] validated the physiological role of stress in IBS disruptions of the gut barrier and intestinal release and response to stress induced peptides.

In summary of demonstrating quantitative research in IBS visceral hypersensitivity, experimental and investigative studies have aided in demonstrating NGF as a key driver and is secreted by sensory fibers and mast cells negatively influencing pain pathways and colonic mucosa responses. Furthermore, there is a CRF physiological basis of stress-induced onset and exacerbations in IBS, and a fungal dysbiosis. Each acting as a synergistic contributor to disruptions of the gut-brain communication, gut and mucosal permeability, and dysregulated immune response acting collectively as a repertoire of drivers of visceral hypersensitivity. Understanding disease expression from its pathological mechanism of action allows therapies to address and aim to reverse the core of the molecular pathogenesis. This is nicely demonstrated in IBS patients, where lifestyle and diet are helpful and necessary components of treatment, however the addition of utilizing cognitive therapies to restore the parasympathetic balance and rewire the bidirectional gut-brain-immune crosstalk with better clinical outcomes and disease regression. The use of qualitative research allows analysis of outcomes and provides direction of therapy to continually adapt for patient-centered care and improved clinical outcomes by listening to the patients and providers perspectives. The ultimate combination of pathogenesis and treatment for it. In support of a mixed study design, it is the author's opinion there is value in not only scientifically searching for disease etiology but also the impact of disease on patient experience and quality of life.

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