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Sex- and Gender-Related Differences in Common Functional Gastroenterologic Disorders

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Abstract

Functional gastrointestinal (GI) disorders (FGIDs) result from central and peripheral mechanisms, cause chronic remitting-relapsing symptoms, and are associated with comorbid conditions and impaired quality of life. This article reviews sex- and gender-based differences in the prevalence, pathophysiologic factors, clinical characteristics, and management of functional dyspepsia (FD) and irritable bowel syndrome (IBS) that together affect approximately 1 in 4 people in the United States. These conditions are more common in women. Among IBS patients, women are more likely to have severe symptoms and coexistent anxiety or depression; constipation or bloating, and diarrhea are more common respectively in women and men, perhaps partly because defecatory disorders, which cause constipation, are more common in women. Current concepts suggest that biological disturbances (eg, persistent mucosal inflammation after acute gastroenteritis) interact with other environmental factors (eg, abuse) and psychological stressors, which influence brain and gut to alter GI tract motility and/or sensation, thereby causing symptoms. By comparison to a considerable understanding of sex-based differences in the pathogenesis of visceral hypersensitivity in animal models, we know less about the contribution of these differences to FGID in humans. Slow gastric emptying and colon transit are more common in healthy women than men, but effects of gonadal hormones on colon transit are less important than in rodents. While increased visceral sensation partly explains symptoms, effects of sex on visceral sensation, colonic permeability, and the gut microbiome are less prominent in humans than rodents. Whether sex or gender affects response to medications or behavioral therapy in FD or IBS is unclear because most patients in these studies are women.

Introduction

Roughly one-third of the adult population has 1 or more symptoms (eg, dyspepsia, constipation, diarrhea, chronic abdominal pain, or fecal incontinence).[1] Accounting for a

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majority of gastroenterology consultations, these patients often have chronic remitting-relapsing symptoms, comorbid conditions (eg, fibromyalgia, anxiety, depression), and impaired quality of life (QOL) and use considerable health care resources.[2] Initially, these conditions were defined as symptoms, in the absence of an organic explanation (eg, inflammatory bowel disease, peptic ulcer or celiac disease, ischemic bowel disease) for the same by routine laboratory, endoscopy, and imaging studies.[3] Currently, these conditions, broadly termed *functional gastrointestinal disorders* (FGIDs), are conceptualized as disorders of gut functions, especially gastrointestinal (GI) tract motility and sensation. Some tests may show generally subtle abnormalities (eg, microscopic inflammation, altered gut microbiota) in some patients. Psychosocial conditions and stressors contribute to the development, perception, and management of FGIDs.

This review covers the 2 most common FGIDs: functional dyspepsia (FD) and irritable bowel syndrome (IBS) (Figure 1). Other FGIDs that are less prevalent but more common in women (eg, chronic abdominal pain and pelvic pain), are not considered herein because the differences between men and women are poorly understood.[3, 4] Nor do we consider GI tract motility disorders that are characterized by more pronounced enteric neuronal injury in the stomach (ie, gastroparesis), small intestine (ie, chronic intestinal pseudo-obstruction), or colon (ie, slow transit constipation and megacolon). Geared to practitioners, this review discusses the effects of sex (the biologic differences between men and women) and gender (ie social constructs and behavior) on FD and IBS. Similar to other disorders accompanied by chronic pain, such as fibromyalgia, migraine, and rheumatoid arthritis,[5] (Figure 1) FD and IBS are more common in women than men. The pathophysiologic factors, clinical characteristics, and, to a lesser extent, response to therapy also differ between women and men (Table 1). This review highlights the differences between the sexes in humans and animal studies (Table 2).

Prevalence

Among 5,931 community adults in the United States, the United Kingdom, and Canada, the overall questionnaire-based prevalence of dyspepsia in 2018 showed a women to men ratio of 11:7.[6] For adults older than 65 years, the prevalence was similar in men and women. Absent endoscopy, approximately 15% of these patients may have an organic explanation for their symptoms, such as peptic ulcer disease or erosive esophagitis.[7] A meta-analysis of 55 studies showed that FD developed in 25% of women and 22% of men.[8]

In a systematic review of global, population-based studies that evaluated the *prevalence* of IBS, the disease was more common in women (14%) than men (9%) (odds ratio [OR], 1.67 [95% CI, 1.53–1.82]).[9] In tertiary centers, the female to male ratio is generally higher, (eg, 3:1).[10] In a systematic review of population-based studies dealing with the *incidence* of IBS, female sex was a risk factor in 19 of 31 studies, most of which were from the West.[11] In the other 12 studies, of which 6 were from Taiwan, sex was not a risk factor for incident IBS.

GI Tract Symptoms

A meta-analysis of clinic-based studies of IBS found that constipation and diarrhea symptoms are respectively more common in women and men as follows: constipation predominant (women, 40%; men, 21%; OR, 2.38; 95% CI, 1.45–3.92) and diarrhea predominant (women, 31%; men, 50%; OR, 0.45; 95% CI, 0.32–0.65).[9] The proportion with mixed IBS (ie, constipation and diarrhea) did not show a statistically significant difference between men and women. Selected symptoms—notably, bloating and/or abdominal distention—are more common and severe for women than men.[2, 9, 12, 13] Women also are more likely to report harder stools, greater total somatic symptom burden, less sense of coping, general anxiety and GI tract–specific anxiety, and impaired QOL.[12] Other characteristics were not different between men and women: depression, pain, stool frequency, effect on daily life, dissatisfaction with bowel habit, and extracolonic symptoms.[12]

The National Health and Nutrition Examination Survey defines *chronic diarrhea* as a predominance of mushy or watery stools but does not consider abdominal pain; hence, it characterizes functional diarrhea but not IBS–diarrhea type (IBS-D), which includes abdominal pain and loose stools.[14] Approximately 6.6% of the US population had chronic diarrhea, defined as a predominance of mushy or watery stools. Adjusted for several other important variables (ie, ethnicity, education, depression, body mass index, and higher dietary carbohydrate intake), the prevalence of chronic diarrhea was greater (OR, 1.68; 95% CI, 1.28–2.21) in women (7.8%; 95% CI, 6.9%−8.8%) than men (5.4%; 95% CI, 4.3%−6.6%).[14] Microscopic colitis causes diarrhea and is more common in women than men; it may partially explain the greater prevalence of chronic diarrhea in women than men.[15, 16]

Pelvic floor dysfunction (ie, defecatory disorders [DDs]) and endometriosis cause constipation and are more common in women than men. This distribution may explain at least partly the greater prevalence of IBS–constipation type (IBS-C) in women than men. Social norms for women equate thinness with attractiveness, which may at least partly explain why bloating is more common and bloating is a source of physical discomfort and psychological distress for women.[17] A 2016 publication cited, “For many women, the sensation of being overweight, with or without an increase in the size of their abdomen, may evoke worry and shame about their body and therefore about themselves”.[18] The physical and psychological distress caused by abdominal discomfort, together with the perception that their pain is minimized or trivialized by health care professionals, may prompt women to become more hypervigilant to any sign of pain or discomfort.

Sex-related differences in the prevalence of upper gastrointestinal symptoms seem smaller than corresponding differences in lower gastrointestinal symptoms. A population-based telephone survey of 21,128 adults from Olmsted County, Minnesota, showed that 26% of women and 20% of men reported early satiety and 12% of women and 7% of men had nausea.{Camilleri, 2005 #5586} The proportion of men and women is comparable with patients who have epigastric pain syndrome or postprandial distress syndrome, or both. {Aziz, 2018 #5835}

Extra–GI Tract Symptoms

Anxiety and Depression

FD is associated with major anxiety (OR, 2.56; 95% CI, 1.06–6.19) [19] and depression (OR, 2.28; 95% CI, 2.02–3.81).[20] Compared with healthy control patients, IBS patients were roughly 3-fold more likely to have anxiety,[21] which was more common in women (47.8% [95% CI, 36–59.6]) than men (31.5% [95% CI, 15.3–47.7]). To a lesser extent, depressive symptoms also were more common in women (35.1% [95% CI: 23–47.3]) than men (25.9% [95% CI: 11.9–9.9]). Perhaps, the greater anxiety and depression of women alter central pain processing and predispose to more severe GI tract symptoms in women. Indeed, anxiety and depression in women are associated with more severe GI and non-GI somatic symptoms and a lower QOL.[22] Among patients with acute gastroenteritis, self-reported anxiety and depression were each associated with a 2-fold increased risk of IBS.[23] Among community residents, persons with anxiety and/or depression were at increased risk for incident FD, FGID, or IBS; conversely, persons with FGID at baseline were at increased risk for anxiety and/or depression several years later.[24, 25] These outcomes are not different in men compared with women. Together, these studies support a bidirectional relationship between anxiety and/or depression and the FGIDs. For women with IBS-C, the severity of anxiety was associated with abdominal discomfort and abdominal pain but not with abdominal bloating. For men with IBS-C, the severity of anxiety did not show a statistically significant association with abdominal bloating, discomfort, or pain.[26]

Fibromyalgia

More prevalent in women than men, fibromyalgia affects 26% to 65% of patients with IBS, [27, 28] and 32% to 70% of fibromyalgia patients have IBS.[27, 29] Among patients with fibromyalgia, IBS was less prevalent in men than women.[30] Menstruating and postmenopausal women with IBS had significantly higher somatic symptom scores (eg, backache, headache, joint pain and muscle pain) than men with IBS.[31] However, the risk of IBS is not different between men and women with fibromyalgia.[32] In contrast, the association between FD and fibromyalgia is poorly characterized.

Other Conditions and QOL

The prevalence of sexual dysfunction (43%) is similar for men and women with FGIDs.[33] A higher proportion of women (35%) than men (32%) with overactive bladder have concurrent IBS.[34] A small proportion of patients with FGID, and more often women than men, have a history of [35] or an ongoing [36] eating disorder. Among patients with FD or IBS, physical and mental QOL is poorer for women than men [12, 37–39]. These differences were limited to selected domains of IBSQoL (ie, emotional, energy, physical functioning, food, and sexual); mental health, sleep, social role, or physical role were not different between men and women with IBS.[12] In population-based surveys, differences in sociodemographic and socioeconomic status partly explain lower health-related QoL scores in United States women than men.[40] Further studies should compare sex-related differences in health-related QoL in the overall population and people with IBS.

Pathogenesis and Pathophysiologic Characteristics

The biopsychosocial model integrates the contribution—and complex interaction—of psychosocial stressors, environmental factors, and diet to the pathogenesis of IBS and FD (Figure 2). These factors affect the GI tract neuromuscular apparatus, microbiota, and/or mucosal epithelial barrier, the central nervous system, and/or the interactions between the big and little brain, resulting in altered GI tract motility and/or sensation.

GI Tract Sensorimotor Dysfunctions

While the symptoms of FD and IBS *define* them, patients also have GI tract sensorimotor dysfunctions, which are associated with the presence and severity of selected symptoms. In the largest series of FD patients (N=560) so far, 37%, 37%, and 23% of patients had gastric hypersensitivity, impaired gastric accommodation, and delayed gastric emptying, respectively.[41] Among 407 IBS patients from 3 medical centers, 81% had 1 or more GI tract–related disturbances, including allodynia, hyperalgesia, accelerated or delayed oroanal transit, anxiety, and depression.[10] In that study, the number of pathophysiologic abnormalities was associated with the symptom severity but not with the patient's sex.

GI Tract Transit

Gastric emptying and colonic transit are slower and the intraindividual variation of colonic transit is greater for healthy women than men.[42] Female sex is an independent risk factor for delayed gastric emptying for patients with FD.[43]

In studies of adult female rats, higher hormone levels during proestrus-estrus in nonpregnant rats and in pregnant rats are accompanied by slower colonic transit and vice versa.[44] Progesterone (P4) relaxes circular smooth muscle strips and reduces fecal output in rats with diarrhea.[45] In contrast to rats, variations in colonic transit across the menstrual cycle in humans are not statistically significant.[42] Among women with slow-transit constipation, results of small studies have been suggestive that in vitro colonic contractile response to G protein–independent agonists (eg, acetylcholine, cholecystokinin) is impaired because of the downregulation of G proteins that mediate contraction (eg, Gq/11 protein).[46] In addition, G proteins that mediate relaxation are upregulated, which may predispose to colonic relaxation. Both these changes in Gq/11 and Gs proteins are associated with overexpression of P4 receptors in the colon, perhaps rendering its muscle cells more sensitive to physiologic P4 concentrations. They can be induced by pretreating normal colonic muscle cells with P4 for 4 hours. However, among 49 healthy postmenopausal women, P4 (400 mg daily for 7 days) *accelerated* colonic transit.[47]

The effects of estrogen on gastrointestinal motility are mediated by the, predominantly nuclear, α and β receptors and the more recently described 7-transmembrane G-protein coupled estrogen receptors (GPER), which are located in the myenteric plexus throughout the gastrointestinal tract including the colon.[48–50] While nuclear:cytoplasmic ratio of ER-α ισ greater in male than female mice, the distribution of ER-β and GPER is similar in male and female mice.[48] Stimulation of GPER elicits a response within seconds to minutes. By contrast, the responses to stimulation of ER-α and ER-β, which initiate transcription and

translation, are delayed in onset and prolonged in duration. G-1, which is a selective GPER agonist, and 17β-estradiol, which also binds to ER-α and ER-β, inhibit colonic response to electric field stimulation motility in mice and humans.[50] Both agonists also inhibited *in vivo* colonic motility in mice. By contrast, treatment with micronized estradiol for 7 days induced lose stools but did not affect colonic transit in healthy people.[47] To our knowledge, the physiologic effects of estrogen on colonic motility in humans have not been investigated (eg with a selective estrogen receptor disruptor or modulator). In most but not all animal models, stimulation of GPER increases visceral sensitivity.[48]

Current etiologic concepts implicate slow colon transit to a loss of colonic nerves and interstitial cells of Cajal.[51, 52] More investigation is necessary to determine the contribution of gonadal hormones to slower colon transit in women and men and to slow transit constipation.

Visceral Sensation

Studies have shown that sex hormones affect pain processing in humans.[53–55] Visceral pain is often regarded as more unpleasant and is more difficult to localize than somatic pain.[56] Visceral hypersensitivity consists of 2 components: allodynia, in which an innocuous stimulus is perceived as painful, and hyperalgesia, defined as a more intense perception of a painful stimulus. [10] Patients with visceral hypersensitivity have more severe IBS symptoms. [10, 57] A majority of patients in these studies were women.

Among IBS patients, bowel symptoms and rectal sensation are more intense during menses than during the follicular, luteal, or premenstrual phase.[58] Other, small studies suggest that bowel symptoms are worse during menses than other phases of the menstrual cycle for women with IBS.[59] The UK General Practice Research Database indicated that postmenopausal women who were being or had been treated with hormone replacement had increased risk of IBS compared with nonusers.[60] However, the data are conflicting on the perception of esophageal, duodenal, and rectal distention of male and female healthy persons vs patients with FGIDs.[18] This inconsistency is likely due to differences in the patients' IBS types, rectal distention techniques, ovarian hormone and receptor levels, and levels of stress among study participants. In particular, few studies controlled for the menstrual phase, which, as explained above,[58] affects rectal sensation in IBS patients. A wide range of menstrual cycle phases, different definitions of the same phase, and lack of cycle phase confirmation by hormone measures limit the understanding of the relationship between menstrual cycle and pain outside the GI tract.[53, 54, 61]

Plasma hormone measurements allow for a more refined assessment of the relationship between gonadal hormones and sensation.[62] Assessments of somatic sensation (ie, pinprick pain sensitivity, incision-induced pain, and pinprick hyperalgesia) were significantly correlated with plasma P4 and follicle-stimulating hormone and negatively correlated with testosterone in humans. By contrast, few studies have evaluated the relationship between sex, gender, and visceral (gastrointestinal) sensation using such refined techniques. While plasma luteinizing hormone levels were significantly lower in male IBS patients than control patients,[63] the differences between male IBS patients and healthy male patients were small. Among IBS patients, rectal sensory thresholds inversely correlated with serum testosterone

levels, a result that is counterintuitive since plasma testosterone is protective against somatic pain.[62]

Assessment of cortical activation or regional changes in cerebral blood flow with functional magnetic resonance imaging or positron emission tomography, respectively, provide insights into the central processing of visceral pain.[56] These studies assessed cortical activation at rest and during balloon distention, cortical thickness, and functional connectivity. The spinal and vagal afferents from the GI tract indirectly project to the thalamus, insula, amygdala, prefrontal cortex, primary somatosensory cortex, secondary somatosensory cortex, and cingulate cortices, including the anterior cingulate cortex.[56] The somatosensory cortices, the lateral pain system, serve to encode the intensity and location of visceral pain. The cingulate cortex, or the medial pain system, is implicated in the emotional interpretation of the stimulus—specifically, the affective-motivational aspect (pain unpleasantness and related anxiety) and the cognitive-evaluative aspect (anticipation and attention of pain). The insula serves to process of the affective dimension of pain, integrate it with emotional information, and inform the amygdala, hypothalamus, and periaqueductal gray. The amygdala is critical to affective dimension, especially fear, and painful sensation. Together with the periaqueductal gray, the amygdala has a key role in the descending modulation of pain. These studies have uncovered the following salient sex-based differences in the central processing of pain.

1. At rest, the female brain allocates greater resources to interoceptive awareness (ie, to stimuli originating in the body), whereas the male brain relies more on cognitive function.[64]
2. The patterns of central activation during rectal distention and the differences between healthy men and women differ among studies.[65–67]
3. The largest study of IBS patients, comprising 42 patients, observed greater activation of the ventromedial prefrontal cortex, right anterior cingulate cortex, and left amygdala in women and greater activation of the right dorsolateral prefrontal cortex, insula, and dorsal pons and periaqueductal gray in men (Figure 1).[68] These findings suggest greater activation of the affective and autonomic regions in women and greater activation of regions belonging to a corticolimbic pain inhibition system in men. Similar differences were observed in the anticipation of distention.
4. Connectivity analysis of the same data suggested that differences in the effective connectivity of emotional arousal circuitry, rather than visceral afferent processing circuitry, underpin the differences between men and women.[69]
5. The right pregenual anterior cingulate cortices are thinner but the bilateral anterior insula is thicker in women than healthy men.[70] Another study of healthy volunteers found that increased visceral sensitivity to rectal distension correlates with decreased gray matter volume in the brain’s pain processing regions—thalamus, insula, cingulate cortex, ventrolateral and orbitofrontal prefrontal cortices, amygdala, and basal ganglia.[71]

6. These sex-related differences are detailed elsewhere.[72] One exception [68] is the small studies with 15 or fewer IBS patients.[73] Many studies enrolled only men or only women. Another recent study observed that “the published literature on sex differences in brain activation by visceral stimuli is still sparse and somewhat contradictory. Although many reviews emphasized the importance of considering sex-related differences, no conclusive studies have been performed”.[74]

In rodents, the effects of sex hormones on visceral sensation have been studied through investigation of changes during the estrus cycle and after ovariectomy followed by replacement of estrogen and progesterone.[18] The estrus cycle is shorter (4–6 days) and changes in plasma estrogen and P4 levels are smaller in rodents than in humans. The variations in visceral sensation during the estrus cycle are subtle and differ among studies. Estrogen has pro- and antinociceptive effects. When considered together, these observations suggest that sex steroids do not contribute substantially to visceral hypersensitivity in patients with IBS.

Acute Gastroenteritis

Acute gastroenteritis is the most important risk factor for IBS and, to a lesser extent, FD in children [75] and adults.[76] After infectious enteritis, IBS symptoms occur in 10.1% (95% CI, 7.2–14.1) at 12 months and 14.5% (95% CI, 7.7–25.5) at more than 12 months.[76, 77] Since 1 in 6 persons, or a total of 48 million people, in the United States have acute infectious gastroenteritis every year, postinfectious IBS probably accounts for a substantial proportion of new cases of IBS.

Female sex, younger age, psychological distress during or before acute gastroenteritis, and more severe acute enteritis are risk factors for postinfectious IBS.[77] Unknown is whether female sex is an independent risk factor for postinfectious IBS after correction for other risk factors, especially psychosocial stressors. Only 2 studies included psychosocial stressors in the multivariate analysis. In those 2 studies, sex was not a risk factor for development of IBS.[78, 79]

The mechanism(s) that predispose to a greater rate of developing postinfectious IBS after acute gastroenteritis are unclear. Compared with male IBS patients, female IBS patients had more gastrointestinal mucosal mast cells, which were correlated with the severity of GI tract symptoms, but fewer CD3+ and CD8+ T cells.[80] Perhaps these differences are at least partly explained by sex-related differences in the immunologic profile that are mediated by sex hormones, contributions of X chromosome genes, and environmental factors. Indeed, women have a greater prevalence of various autoimmune diseases, including Sjögren syndrome, scleroderma, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis.[81] Another possible mechanism is that acute diarrhea is more likely to increase rectal sensitivity, which is a feature of IBS, in women than men.[82].

The relationship between sex and the risk of postinfectious FD is unclear. The sex distribution of patients with postinfectious and unspecified-onset FD is comparable [83] or different.[84] A meta-analysis of risk factors for postinfectious FD did not study sex.[85] Some but not all studies have observed duodenal mucosal inflammation in FD.[86, 87]

In summary, whether female sex is an independent risk factor for developing postinfectious IBS and FD is unknown. The mechanisms by which female sex may predispose to development of these diseases after acute gastroenteritis are poorly understood.

Psychosocial Stressors

Psychosocial stressors include environmental factors and psychological distress (ie, mood disorders, anxiety, somatization, and cognitive-affective processes) that influence the brain and the gut and are associated with FGIDs. Environmental factors include social constructs and behavior, parenteral anxiety, depression, somatization, and adverse early life experiences (ie, physical, sexual, and emotional abuse), which are all strongly associated with abdominal symptoms.[88] Gender-related social or societal expectations such as standards for attractiveness, norms for women's caretaking role in relationships, and sanctions against anger expression by women can impair health and well-being.[18] Among IBS patients, women described shame because they were not living up to gender norm expectations for women in the domains of relationships (taking care of others at the expense of their own needs), attractiveness (because of bloating), and lack of desire to engage in sex.[89] Men were more concerned about the effect of IBS symptoms on paid employment and sense of control. Although men also were embarrassed by IBS symptoms, "they had a more relaxed attitude to feces and passing wind" than women.[93] During health care visits, women risked being trivialized and men risked being overlooked because IBS may be regarded as a health concern for women.

During childhood, children whose mothers reinforce illness behavior have more severe stomach aches and more school absences than other children.[88] More common in persons with IBS than healthy control persons, physical punishment, emotional abuse, and sexual abuse, which often coexist, are related to the severity and clinical outcomes of FGIDs. They may lead to increase health care seeking, which might explain the greater prevalence of abuse in tertiary care than primary care. In a large community-based study from Sweden, the prevalence of childhood and adulthood abuse was more common in women who had FGID (45%) than women in the control group without GI tract symptoms (16%).[90] In contrast, the corresponding prevalence was not different in men with FGID (29%) vs without it (24%). Likewise, at a tertiary center, the prevalence of abuse was greater among female IBS patients than control patients compared with male patients vs control patients.[91] In meta-analyses, a history of sexual abuse has been associated with FGIDs, nonspecific chronic pain, chronic pelvic pain, and psychogenic seizures but not with fibromyalgia or headache.[92] Yet, most of these studies were conducted with adult female participants. The extent to which gender affects the relationship between stressful events, abuse, and IBS is unknown.

In contrast, studies of animals suggest that the effects of early life stress (ELS) on visceral sensation are modified by sex and gender. ELS, and especially unpredictable stress, induced visceral hypersensitivity during colonic distention in female but not male rats.[93] This phenomenon may be partly mediated by epigenetic changes associated with chronic prenatal stress [94] and neonate-maternal stress [95] that cause visceral hypersensitivity.[94, 96] Chronic prenatal stress induced visceral hypersensitivity that was markedly greater in female than male rats. It was attributed to increased H3 acetylation and expression of spinal cord brain-

derived neurotrophic factor (BDNF) in female but not male offspring.[94] Of interest, abnormal activation occurred to the amygdala, which regulates visceral sensitivity, after ELS, and in IBS patients; gender differences have not been evaluated.[93, 97]

ELS increased the expression of corticotrophin-releasing factor (CRF) and glucocorticoid receptors in the amygdala, which modulate nociception and stress, in female but not male rats.[93] This sex-based interaction may be at least partly explained by estrogen. This hormone preferentially binds to the CRF promotor region and increases CRF expression, increasing visceral hypersensitivity.[93] In adult rats, the ELS-induced visceral hypersensitivity can be reversed through elimination of estrogen cycling and restored with reintroduction of estrogen.[98]

Effects of Stress

Stress activates the hypothalamic-pituitary-adrenal (HPA) axis. The cortisol response to mental stressors is greater in healthy men than healthy women.[99] In response to psychosocial stress, the adrenocorticotropic hormone (ACTH) response was greater in men than in women regardless of their menstrual cycle,[100] and the salivary cortisol response to ACTH was comparable in men and women in the luteal phase.[99, 100] In both groups, the response was greater than in women during the follicular phase.[99, 100]

Mediators of stress probably participate in the pathophysiologic characteristics and persistence of chronic pain. Supportive of this concept, hydrocortisone increased the sensitivity for visceral (ie, during rectal distention) but not somatic pain in women vs men.[101] However, ratings for pain and unpleasantness were unaffected by hydrocortisone. These findings suggest that cortisol primarily affects visceral sensory-discriminatory aspects, or pain sensitivity, rather than cognitive-evaluative or affective pain components (ie, ratings of intensity and unpleasantness) for healthy persons.

Among IBS patients, the autonomic response (ie, increased sympathetic and decreased parasympathetic activity) to rectosigmoid distension was more pronounced in men than women.[102] Unclear is whether the exaggerated autonomic response in men, which was not correlated with the severity of daily symptoms or rectal sensory thresholds, contributed to and/or was a consequence of abdominal discomfort. One large study compared sex differences in responses to CRF and ACTH among healthy control patients and patients with IBS.[103] Compared with sex-matched healthy controls, the CRF-induced ACTH release and the ACTH-evoked cortisol response was *increased* in male IBS patients and *decreased* in women with IBS.[103] The mRNA expression of glucocorticoid receptors in peripheral blood mononuclear cells was less in men but not in female IBS patients vs control patients and was correlated inversely with the severity of IBS symptoms. Whether the reduced mRNA expression of glucocorticoid receptors is a cause or a consequence of activation of the HPA axis is unknown.

Stress-induced visceral hypersensitivity is more pronounced in female rats than male rats, blocked by ovariectomy, and increased by orchiectomy.[104] Altered expression of glutaminergic receptors and BDNF may explain the opposing effects of estrogen and testosterone on stress-induced visceral hypersensitivity.[104] In summary, intravenous

hydrocortisone increased rectal sensitivity in healthy women. The CRF-induced ACTH release and the ACTH-evoked cortisol response were *increased* for male IBS patients and *decreased* for women with IBS. In contrast to animal models, no data confirm that the gonadal hormones influence the response to stress or stress-induced visceral sensitivity for healthy people or those with IBS.

Serotoninergic Pathways and the Brain-Gut Axis

Mechanical and chemical stimuli release serotonin from enteric neurons and mucosal enterochromaffin cells. Serotonin initiates motor reflexes and visceral sensation. Sex-related differences in GI tract serotoninergic pathways and the brain-gut axis may contribute to differences among the sexes in IBS. Some [105, 106] but not all [107] studies suggest that the colonic mucosal expression of serotonin transporter (SERT), which terminates serotonergic signaling, is reduced in IBS patients. Reduced SERT expression could predispose to higher serotonin levels and hence to faster colonic transit and greater visceral pain. However, the correlations between mucosal SERT expression, transit, and sensation have not been assessed in humans. Increased colonic extracellular serotonin in female SERT knockout rats is associated with visceral hypersensitivity and hyperexcitability of colon projecting sensory neurons.[108] Postprandial plasma serotonin levels were higher in female IBS patients with elevated progesterone and estrogen levels compared with IBS patients with low hormone levels.[109] Serotonin turnover is reduced in female IBS patients and elevated serotonin levels may be due to defects in uptake or metabolism.[109] In summary, IBS is associated with serotoninergic disturbances, the functional importance of which is unclear.

Intestinal Permeability, Foods, and the Microbiome

Conceptually, increased intestinal permeability in IBS may reflect the sustained immune and inflammatory response that is characteristic of postinfectious IBS and/or long-term intermittent psychological stress, which in male Fischer rats activates release of proinflammatory cytokines to alter tight junction proteins and increase gut permeability.[110] Although some patients with postinfectious IBS have increased small intestine permeability, this parameter is not useful for discriminating between healthy control patients and patients with IBS-C or IBS-D.[111] Acute psychological stress increased intestinal permeability through corticotropin-releasing hormone and mast cell–dependent mechanism studies in animals and healthy people.[112] In that study of 23 healthy volunteers, the effects of acute psychological stress were comparable among men and women. Larger studies are necessary because estrogen *reduces* colonic permeability through estrogen receptor β and the upregulation of tight junction proteins in ovariectomized rats.[113]

Certain foods cause GI tract symptoms either directly or after microbiome-induced fermentation of carbohydrates to short-chain fatty acids [114] or metabolism with bile acids.[115] Moreover, the diet can modify the gut microbiome. Although the gut microbiome differs between IBS patients and control patients, no specific microbial signature is associated with IBS.[116] In addition, sex hormones can alter the gut microbiome in selected mice strains, [117,118] yet no evidence shows sex-specific differences in the fecal or colonic mucosal microbiome in IBS.

Genetic Alterations Associated With FGIDs

Family and twin studies suggest there is a heritable component to IBS.[119, 120] In a sample of 45,750 Swedish twins, investigators saw no evidence of sex differences in heritability of IBS.[121] Subsequently, a multinational study observed a significant association between chromosome 9q31.2 (single-nucleotide polymorphism rs10512344) and women with IBS-C in some countries.[122] Intriguingly, this locus is also associated with other conditions and traits (eg, voice breaking in males, body mass index, breast and prostate cancer; GWAS catalog www.ebi.ac.uk/gwas/) are influenced by hormonal stimuli and sex hormones. Further studies are necessary to understand the specific gene(s) at this locus that predispose to IBS, possibly via biological mechanisms that are regulated by sex hormones.

Reporting of Pain, Interpersonal Connections, and Health Care–Seeking Behavior

Men manage their pain through self-distraction and problem-focused challenges, whereas women resort to emotion-focused tactics, catastrophizing, positive self-statements, and social support.[123] Expression of pain is socially more acceptable among women,[124] whereas men show increased pain tolerance and greater resistance in reporting pain.[125] These differences may at least partly explain why women with IBS are more likely to seek health care than men with IBS.[126, 127]

Since women attach more importance to interpersonal relationships than men,[128] perhaps female IBS patients might regard their relationships as more problematic (eg, higher levels of interpersonal problems) than men with IBS. To the contrary, among IBS patients, men reported more interpersonal difficulties (ie, less support from others and more interpersonal problems involving hostile-dominant behaviors) than women with IBS.[129] These interpersonal difficulties may influence the estimation of IBS symptoms by physicians, especially among men, and may undermine the quality of the physician-patient relationship.

Conditions That Are Much More Frequent or Occur in Women Only

Defecatory Disorders

Resulting from impaired coordination between rectal propulsive force and relaxation of the anal sphincter and pelvic floor muscles, DDs are a common cause of constipation and are more common in women than men in both clinical practice and the community. Because symptoms of a DD are similar to functional constipation and IBS-C, this condition is overlooked unless anorectal tests are performed. Functional constipation, IBS-C, and DDs are more common among women than men.[130] The age-adjusted incidences per 100 000 person-years for women and men are 31.8 (95% CI, 27.4–36.1) and 6.6 (95%CI, 4.4–8.9), respectively.

Endometriosis

Up to 80% of women who present with chronic pelvic pain (defined as noncyclic lower abdominal pain lasting at least 6 months) have endometriosis.[3] The typical presenting symptoms include perimenstrual lower abdominal pain and dyspareunia; dysuria, urinary urgency, hematuria are other symptoms. Patients also may have pelvic floor dysfunction with symptoms of a DD. The diagnosis is confirmed with laparoscopy-guided biopsy.

Effect of Sex on Response to Treatment of Functional GI Tract Disorders

Perhaps reflective of the predominance of female patients in clinical practice, most patients enrolled in the pharmacologic and behavioral trials of FD and IBS were, by chance or design, women (Table 3). Hence, our understanding of the efficacy of several drugs and potential sex-based differences in the response to treatment are limited and possibly are biased. For example, on the basis of early drug trials conducted in the United States (alosetron) and Japan (ramosetron), investigators inferred that the serotonin ($5\text{-}HT_3$) receptor antagonists ondansetron and ramosetron were more effective for patients with IBS-D, respectively, for women and men.[131] Thereafter, ramosetron was shown to be effective for women with IBS-D—but at one-half the dose for men.[131] Likewise, alosetron delayed colonic transit to a greater extent for women than men.[132] For the other drug treatments and for behavioral therapy, differences in efficacy have not been assessed or observed for men compared with women. Some drugs are approved only for women (eg, alosetron for IBS-D). Although with limited data, other drugs (eg, lubiprostone) are approved for use in men and women for chronic idiopathic constipation but only in women for IBS-C.

Conclusions

Several sex- and gender-related differences exist in the prevalence and clinical features, pathophysiologic characteristics, and management of FD and IBS for women compared with men. The understanding of sex-based differences in the pathogenesis of FGIDs lags behind the understanding of these mechanisms in animals. Additional research into the gaps detailed in the tables not only will provide more insight into the differences between the sexes but more broadly will enhance the understanding of FGIDs, especially the mechanism(s) by which adverse early life experiences predispose to IBS, sex-based differences in the evolution of acute gastroenteritis to postinfectious IBS, the contribution of sex steroids to normal and disordered gastrointestinal sensorimotor functions, and sex-related differences in the response to treatment in these diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACTH	adrenocorticotropic hormone
BDNF	brain-derived neurotrophic factor
CRF	corticotropin-releasing factor
DD	defecatory disorder

ELS	early life stress
FGID	functional gastrointestinal disorder
FD	functional dyspepsia
GI	gastrointestinal
HPA	hypothalamic-pituitary-adrenal
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome–constipation type
IBS-D	irritable bowel syndrome–diarrhea type
OR	odds ratio
P4	progesterone
QOL	quality of life
SERT	serotonin transporter

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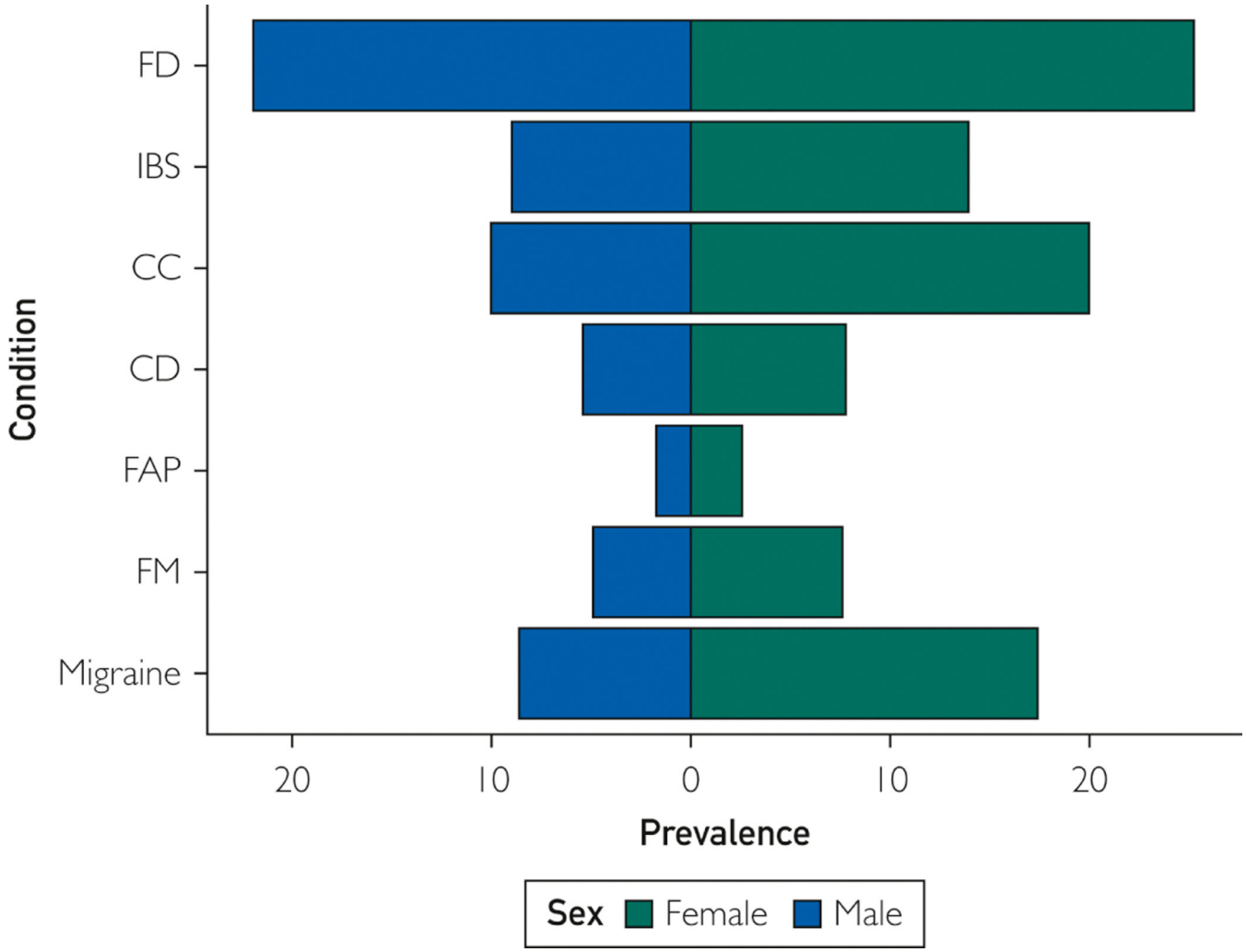

Figure 1.

Prevalence of Common Functional Gastrointestinal Tract and Somatic Disorders of Men and Women. Values are approximate and are derived from individual population-based studies or systematic reviews. For chronic constipation, the estimate is derived from the average prevalence (16%) and the female to male ratio (1.5:1) in systematic reviews and with the assumption that the female to male ratio is 1:1 in the general population.

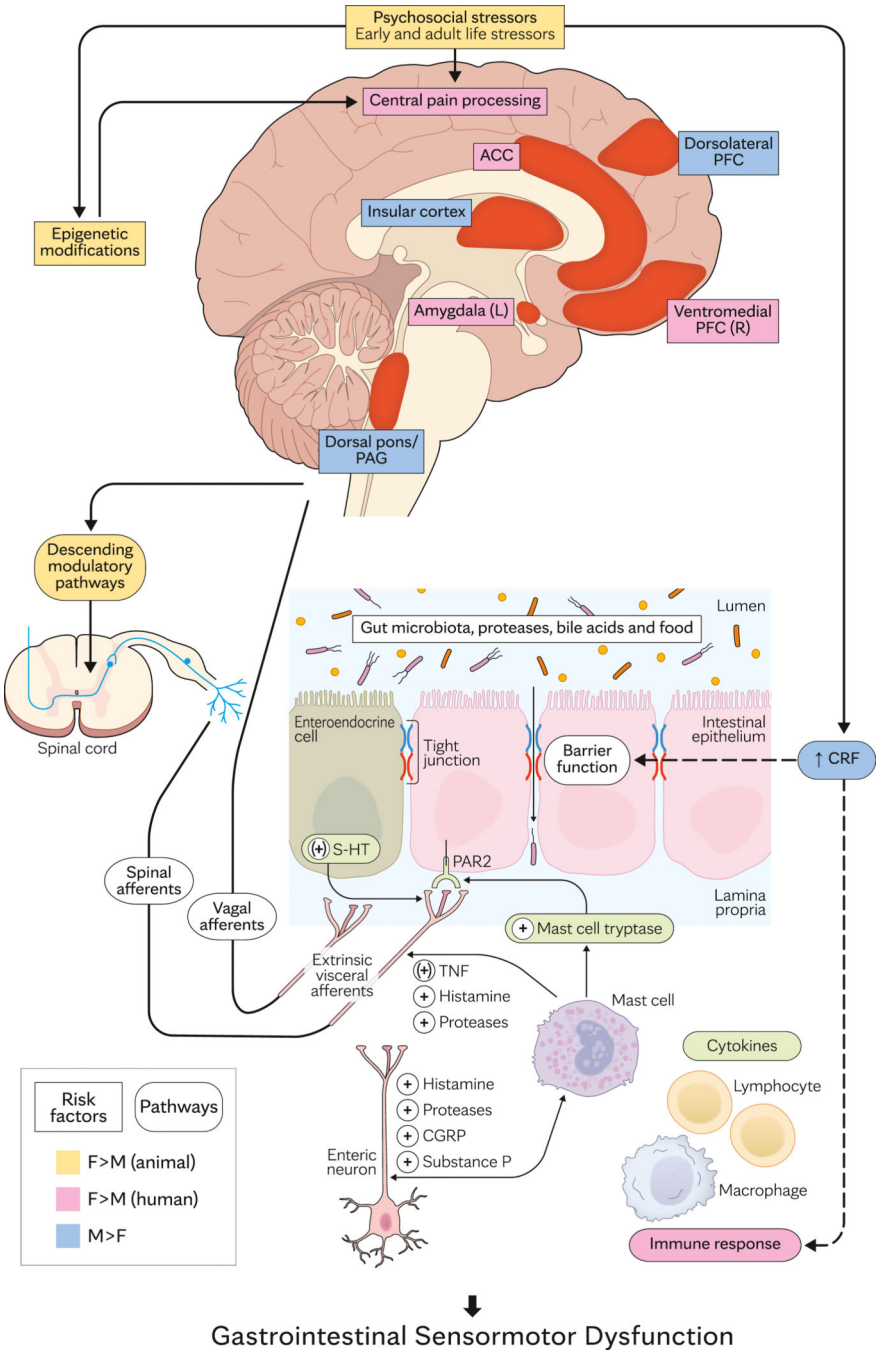

Figure 2.

Sex- and Gender-Based Differences in the Pathogenesis of Common Functional GI Tract Disorders. Peripheral disturbances (ie, postinfectious irritable bowel syndrome) and central factors (eg, psychological stressors) cause GI tract sensory and motor dysfunctions that contribute to symptoms. The peripheral mechanisms include triggers (eg, postinfectious inflammation, bile acids) that stimulate enterochromaffin cells, may change mucosal permeability, and activate immune mechanisms to stimulate afferent nerves. Central sensitization may result from this peripheral sensitization and/or reduced descending

inhibition, which normally gates visceral sensation in the spinal cord. Sex-related differences in activation of brain centers and mechanisms are shown in colors. Difference between male and female sexes in humans are shown in blue and dark pink; corresponding differences only observed in animal models are shown in olive. ACC indicates anterior cingulate cortex; CGRP = calcitonin gene-related peptide; CRF = corticotropin-releasing factor; 5-HT = serotonin; GDNF = glial cell line–derived neurotrophic factor; GI = gastrointestinal; HPA = hypothalamic-pituitary-adrenal; IFNγ = interferon gamma; L = left; PAG = periaqueductal gray; PAR2 = proteinase-activated receptor 2; PFC = prefrontal cortex; R = right; TNF, tumor necrosis factor.

Table 1.

Key Concepts About Sex- and Gender-Based Differences in FGID

Characteristic	Key Concept
Prevalence	FD, IBS, and chronic diarrhea are more common in women than men
Nature of GI tract symptoms	In FD, the M:F ratio is comparable in patients with epigastric pain syndrome and/or postprandial distress syndrome. Among IBS patients, constipation and diarrhea are more common in women and men, respectively. Bloating is more common in women
Variation in GI tract symptoms during menses	Women with IBS have more severe symptoms during menses
Extra–GI tract symptoms	
Anxiety and depression	Anxiety and to a lesser extent depression are more common in female than male IBS patients. Severity of anxiety correlates with some IBS symptoms in women but not men
Gender roles/social factors	Among IBS patients, women described shame because they were not living up to the gender norm expectations in domains of relationships and attractiveness. Expression of pain is socially more acceptable among women than men
Pathophysiologic characteristics	
Postinfectious IBS	Women are at increased risk for postinfectious IBS after acute gastroenteritis
GI tract motility	Gastric emptying and colon transit are slower in healthy women than men
GI tract sensation	Sex-based differences in the perception of GI tract distention in healthy people and patients with FGIDs are unclear
Central processing of GI tract sensation	Small studies suggest that during rectal distension, greater activation of affective and autonomic regions occurs in women and greater activation of regions belonging to a corticolimbic pain inhibition system occurs in men
Early life stress	Associated with increased risk of IBS; effects of sex and gender on this association are unknown
Acute stress	In a pharmacologic model (ie, intravenous hydrocortisone), acute stress increased rectal sensation of distention in women but not men
Gut microbiome and permeability	No evidence for sex-specific alterations in fecal or colonic mucosal microbiome in FGID
Gut inflammation	In IBS, colonic mucosal biopsies have more mast cells but fewer CD3+ and CD8+ T cells for women than men
HPA axis and autonomic responses	Men have greater HPA axis and sympathetic responses to stress than women
Serotonergic pathways	Higher postprandial plasma serotonin levels in female than male IBS patients and with elevated progesterone and estrogen levels compared with IBS patients with low hormone levels

Abbreviations: FGID = functional gastrointestinal disorder; GI = gastrointestinal; HPA = hypothalamic-pituitary-adrenal; IBS = irritable bowel syndrome; M:F = male to female; FD = nonulcer dyspepsia.

Table 2.

Comparison of Sex-Related Differences in the Pathogenesis of Functional GI Tract Disorders, From Animal and Human Studies

Sex-Related Differences

Characteristic	Animal Studies	Human Studies
Visceral sensation in health	Greater in female than male rodents [18]	Unclear[18]
Effects of early life stress on visceral sensation	Increased perception of colonic distention in female but not male rats [93], in part through epigenetic mechanisms	Unknown
Stress-induced visceral hypersensitivity	More pronounced in female than male rodents; increased by estradiol and blocked by testosterone [104]	Hydrocortisone increased rectal sensation in healthy women but not men [101]
GI tract motility and transit	In rats, higher hormone levels were accompanied with slower colonic transit [44]. Progesterone relaxes circular smooth muscle strips and reduced fecal output in rats with diarrhea [45]	Slower gastric emptying and colon transit in healthy women than men[42]. Among women, variations in colonic transit during menstrual cycle were not significant [42]. Progesterone accelerated colonic transit in postmenopausal healthy women [47]
Intestinal permeability	Estrogen-reduced colonic permeability in ovariectomized rats [113]	Increased psychological stress in healthy people; effects were not different between men and women [112]
Intestinal microbiome	Sex hormones selectively modified gut microbiome [117, 118]	No evidence of sex-related differences for fecal or colonic mucosal microbiome in IBS

Abbreviations: GI = gastrointestinal; IBS = irritable bowel syndrome;

[a]Sex-related differences in the characteristic.

Table 3.

Relationship Among Sex, Gender, and Treatment Efficacy for Commonly Used Pharmacologic and Behavioral Therapies for FD and IBS in the United States

Therapy	Men and/or Women	Differences in Efficacy Between Men and Women[a]
Pharmacologic		
IBS-D		
Alosetron (5-HT_3 receptor antagonist)	In large trials, 81% women [133]	Retards small bowel and colonic transit to greater extent in women than men [132]. Approved for use in women only, under a restricted marketing program
Ondansetron	Approximately 75% women [134]	Not assessed
Ramosetron	Men [135] and women [131]	In women, effective dose was one-half that in men
Bile acid sequestrant colesevelam	Approximately 92% women [136]	Not assessed
Loperamide (μ-opioid receptor agonist)	Men and women [137, 138]	Not assessed
Eluxadoline (μ- and κ-opioid receptor agonist)	Two-thirds women [145.]	Approved for use, no significant differences between men and women
IBS-C and chronic constipation		
Fiber	Meta-analysis of 6 RCTs in chronic idiopathic constipation [139]; 65%−100% women. An RCT had 78% women [140]	Not assessed
PEG	85% women [141]	None
Laxatives: prucalopride, lubiprostone, and linaclotide	Meta-analysis; predominantly women [142]	Not assessed
Stimulant and nonstimulant laxatives	Systematic review; sex distribution not provided [143]	Not assessed
Bisacodyl	75% women [144]	Not assessed
Prucalopride	Review of all trials. In the 3 pivotal trials, 85% women. Later, another trial enrolled 100% men [145]	Efficacious in men and women
Guanylate cyclase-C agonists (linaclotide and plecanatide)	Systematic review [146]; most were women	Not assessed
Tegaserod (5-HT_4 agonist)	Systematic review [133]; 83%−100% women in all but 1 study, which had 100% men[147]	More extensively evaluated, hence approved for IBS-C in women; limited data suggest that it has more efficacy in men [133]
FD		
Helicobacter pylori eradication therapy	Men and women [148]; distribution varied among studies	Not assessed
PPI therapy	Men and women [149]; distribution varied among studies	Not assessed
Amitriptyline	75% women [150]	No significant differences between men and women
Prokinetics	Men and women [151, 152]; distribution varied among studies	Not assessed
Behavioral		
CBT	Women only [153]	

Therapy	Men and/or Women	Differences in Efficacy Between Men and Women[a]
Pharmacologic		
CBT	Approximately 80% women [154, 155]	Gender did not affect response to CBT of IBS patients [154]; not assessed in second study [151]
Hypnotherapy	Men and women, variable response, 62%–87% women [156]	Not assessed

Abbreviations: CBT = cognitive behavioral therapy; 5-HT = serotonin; IBS = irritable bowel syndrome; IBS-C = irritable bowel syndrome–constipation type; IBS-D, irritable bowel syndrome–diarrhea type; PEG = polyethylene glycol; PPI = proton pump inhibitor; RCT, randomized controlled trial.