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Review

The gastrointestinal symptoms present in patients with postural tachycardia syndrome: A review of the literature and overview of treatment☆

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ABSTRACT

Orthostatic intolerance, including postural tachycardia syndrome, is often associated with gastrointestinal symptoms. In the vast majority of the cases, the gastrointestinal symptoms are not secondary to the orthostatic disorder, but rather just a comorbid condition. This concept is critical, since treatment aimed at the orthostatic condition will not improve the gastrointestinal symptoms. Only when the gastrointestinal symptoms develop in the upright position and improve or resolve in the supine position, they may be related to the orthostatic stress.

The most common symptoms associated with orthostatic intolerance include nausea, dyspepsia, bloating and constipation. The majority of subjects do not have gastroparesis. The chapter discusses available treatments of these conditions.

1. Introduction: what comorbidities are part of postural tachycardia syndrome (POTS)?

Postural tachycardia syndrome (POTS) as well as orthostatic intolerance (OI) is associated with gastrointestinal (GI) symptoms, such as nausea, epigastric discomfort, sometimes vomiting (Ojha et al., 2011; Antiel et al., 2008; Safder et al., 2009). OI is defined as difficulties tolerating the upright position due to symptoms, that resolve or improve drastically when in the supine position (Stewart et al., 2018). POTS is defined as having daily symptoms of chronic OI with an excessive tachycardia of > 40 bpm in the first 10 min of upright tilt, without a significant drop in the blood pressure. In this chapter, we will use the term OI when symptoms worsen or develop in the upright position. POTS is one of the disorders included in chronic OI (Stewart et al., 2018).

Our understanding of the association of orthostatic disorders with GI issues has recently evolved. On the one hand, POTS is comorbid with many other syndromes, such migraine headaches, fibromyalgia, chronic fatigue, nausea, sleep disorders, abdominal pain, etc. (Ojha et al., 2011) On the other hand, some symptoms develop mainly in the upright position. It is critical to conceptually differentiate these two categories of associations: co-morbid disorders without an orthostatic mechanism (e.g. chronic idiopathic nausea) and symptoms secondary to the orthostatic changes that primarily occur in the upright position and improve when the person is supine (e.g. upright nausea). The symptoms that develop while standing and resolve when supine are part of the orthostatic disorder per se, while the symptoms that are present irrespective of body position are simply comorbid conditions and do not constitute an intrinsic manifestation of the POTS syndrome or the orthostatic disorder. Such conditions will typically occur with or without OI. The importance of this differentiation lies in the choice of treatment strategy.

To investigate this concept, we compared the co-morbid conditions in patients with chronic overlapping pain condition with and without POTS. We found that the comorbidities present in subjects with POTS and those without POTS were not significantly different. These comorbidities included fatigue, sleep complaints, dizziness, syncope, migraines, chronic nausea, fibromyalgia and joint hypermobility. Given that all the comorbidities were similar, we concluded that POTS was not the driver of the comorbidities (Chelimsky et al., 2015). Similar findings were described by Antiel et al., 2008. This concept is critical. Many patients and physicians attribute all the comorbid conditions to POTS or OI leading to disappointment when either the patient has no POTS on autonomic testing (which were ordered in an attempt to explain these symptoms) or concerned that the comorbid symptoms did not improve with treatment aimed at the orthostatic challenge.

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2. Upper gastrointestinal symptoms reproduced during an orthostatic challenge in OI: which symptoms and why

Such symptoms are defined by replication during the upright position and resolution or significantly improvement once supine. A few elegant studies have shown the relationship of the orthostatic challenge and gastrointestinal symptoms. The gastrointestinal symptoms that often occur during HUT include nausea and abdominal pain (Fortunato et al., 2011; Fortunato et al., 2014; Sullivan et al., 2005). Moak et al. performed 24-h antroduodenal manometry studies in pediatric patients with OI and GI symptoms and tilted the subjects during the antroduodenal motility study. The vast majority of the patients reproduced the GI symptoms during tilt, suggesting that the symptoms were related to the orthostatic challenge. Furthermore, the head up tilt (HUT) induced abnormalities in antroduodenal motility in 68% of the subjects, with neurogenic intestinal dysmotility, antral hypomotility, visceral hyperalgesia, and regurgitation or a combination of these findings (Moak et al., 2016). Sullivan et al. (2005) and later Fortunato et al. (2011) documented that nausea replicated during HUT often improves with volume expansion with fludrocortisone. Other symptoms and complaints which also improved with this treatment, including dizziness, abdominal pain, flushing, and missing school (Fortunato et al., 2014).

Why the orthostatic challenge induces symptoms in subject with OI is still unclear. Some studies have shown change in the electrical activity of the stomach while upright. Safder et al. also described that the electric activity of the stomach worsens during HUT in subjects with POTS, with a decrease in the normal 3 cpm, increase in the bradygastria, tachygastria and gastric arrythmia but not in those without POTS (Safder et al., 2010). Subjects with POTS also have more abnormalities in the gastric electrical activity while supine. Even within the POTS group, the subjects with gastrointestinal symptoms have differences in the electrical activity when compared to those with POTS and no GI symptoms (Fortunato et al., 2014; Seligman et al., 2013). Whether gastric dysrhythmias improve with fludrocortisone remains to be seen.

Abnormal electrical activity in some patients with POTS could be explained in part by a more generalized alteration in overall autonomic modulation. Cardiovagal modulation, as measured by heart rate variability (HRV), particularly the high frequency band (hfHRV), provides a broader measure of autonomic modulation. hfHRV drops in healthy subjects with standing. However, pediatric subjects with functional gastrointestinal disorders and chronic overlapping pain conditions have much lower cardiovagal modulation than healthy control subjects both supine and upright (unpublished data). Similarly, adults with irritable bowel syndrome have also decreased vagal modulation, although the reports are only in the supine position (Liu et al., 2013). However, the presence or absence of POTS does not seem to influence this general finding in chronic overlapping pain conditions with functional GI disorders (unpublished data), suggesting that lower vagal modulation may be associated more with chronic pain disorders rather than with POTS subjects. Of particular interest, cardiovagal modulation improved in adults with gastroparesis after treatment with gastric electrical stimulation as shown by a decrease in the low-frequency/high-frequency ratio (baseline 1.4 ± 0.1 vs. follow-up 1.1 ± 0.07, P = 0.1) (Stocker et al., 2016). To the best of our knowledge, no study has evaluated HRV simultaneously with electrogastrography to determine the relationship between gastric and cardiovagal modulations.

Another possible explanation may be a redistribution of the splanchnic blood flow in the upright position in patients with POTS. In orthostatic hypotension, which is a different condition from POTS, in the post-prandial state during head-up tilt, the mesenteric artery flow decreases (Fujimura et al., 1997). Interestingly, subjects with normal-flow POTS have mesenteric hyperemia rather than decreased flow when in the upright position, questioning the role of splanchnic perfusion in the pathophysiology of symptoms (Stewart et al., 2011).

Although not common, intracranial hypotension, which is caused by low cerebrospinal fluid pressure, can present with an orthostatic headache, nausea and vomiting. Therefore, it is important to assess for other possible causes of nausea replicated in the upright position (Michali-Stolarska et al., 2017).

3. POTS and gastroparesis

Despite the high prevalence of nausea in subjects with POTS, only 9–18% show delayed gastric emptying; the majority has normal gastric emptying (34–64%) or accelerated gastric emptying (27–48%) (Loavenbruck et al., 2015; Park et al., 2013). Interestingly, the symptoms of delayed gastric emptying and accelerated gastric emptying are very similar. Patients with fast gastric emptying may complain of nausea, feeling faint, bloating followed by diarrhea, feeling lethargic, usually within the first 3 h after a meal. The symptoms are related to a drop in serum glucose due to dumping. This can be evaluated with an extended glucose tolerance test, which will show an appropriate increase in glucose followed by a drop in serum glucose between 150 and 300 min after the glucose load. These subjects will often respond to a change in diet, “grazing” small amounts of food throughout the day (Middleton and Balan, 2012). At least in children, the velocity of gastric emptying in teens with and without POTS did not differ (Antiel et al., 2008).

The relationship of delayed gastric emptying and POTS is only an association. Given that is impossible to perform a gastric emptying during a tilt, all the reports just describe the results of a supine scanning during gastric emptying test with the presence or absence of POTS evaluated at a different time. This could be evaluated by utilizing a wireless motility capsule that can assess gastric emptying (see below).

In some cases of delayed gastric emptying in subjects with POTS, an autonomic neuropathy was present (Loavenbruck et al., 2015). A few studies report more gastrointestinal symptoms in patients who have neuropathic POTS vs non-neuropathic POTS, suggesting that the neuropathy present in these patients may involve gastrointestinal innervation (Gibbons et al., 2013; Al-Shekhlee et al., 2005).

4. Symptoms that may be present in patients with POTS and OI, but are not reproduced or exacerbated in the upright position

Some gastrointestinal symptoms are associated with POTS or OI, but are NOT produced by the orthostatic challenge. Many subjects with OI including POTS complain of constipation, diarrhea, abdominal pain or discomfort with may be suggestive of irritable bowel syndrome, chronic nausea, bloating and swallowing difficulties (Ojha et al., 2011; Deb et al., 2015). These symptoms will probably not improve with treatment aimed at the orthostatic challenge.

Given the frequent overlap of OI and GI symptoms, even if not related to the OI, it is important for the practitioners to understand the basic management of the most common symptoms such as: nausea, abdominal pain, constipation, and bloating. All the medications and treatments described in this chapter are used off label. It is critical to emphasize that prior to treatment, organic causes need to be ruled out. This may require endoscopies, laboratory studies or imaging.

4.1. Nausea

Nausea is typically defined as a subjective, unpleasant sensation that often precedes vomiting, but may occur in isolation and on a chronic basis. It is defined as chronic idiopathic nausea when no cause is identified. This feeling can be perceived in different locations, like in the epigastric area, back of the throat, or in head (Stern et al., 2011). When trying to understand the causes of nausea in patients with OI, it is critical to determine when the nausea occurs (Fig. 1). For example, is it present in the morning before getting up from bed or during the night? Does it happen when the person stands up and is associated with dizziness? Is it only related to migraines or headaches with photo or phonophobia? Does it happen only after eating or is it related to

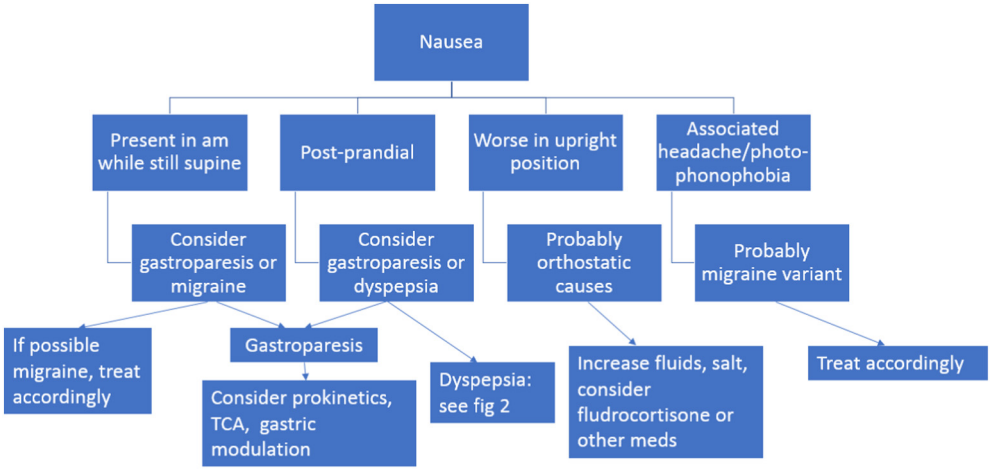

Fig. 1. This figure shows the possible causes of nausea based on time of the day and position when nausea develops, and suggested treatments.

anxiety? In our clinical experience, nausea seldom happens in only one of these circumstances, but rather it is related to 2–3 situations. These symptoms associated with the nausea may give some guidance on how to treat the nausea. For example, in a study in pediatrics, awakening from sleep with nausea was directly correlated with gastric retention (Wong et al., 2014).

4.2. Gastroparesis

Gastroparesis is characterized by delayed emptying of the stomach without a mechanical obstruction. Idiopathic gastroparesis is defined as gastroparesis without a known cause to explain the delayed emptying, including medications. It is the most common cause of gastroparesis (Soykan et al., 1998). Other causes of gastroparesis include diabetes, post-surgical, Parkinson's disease, multiple sclerosis, amyloidosis and medications (Zyluk, 1996). The symptoms of *idiopathic gastroparesis* include nausea, early satiety, vomiting and upper abdominal discomfort. Depending on the severity of the symptoms, weight loss and malnutrition may develop. These symptoms often overlap with functional dyspepsia. Usually, abdominal pain is more predominant in functional dyspepsia (Pasricha and Parkman, 2015). There is little correlation between the severity of the gastroparesis and the severity of the symptoms. The symptoms that are better correlated with the gastroparesis are the nausea, early satiety, vomiting and postprandial fullness (Pathikonda et al., 2012; Cassilly et al., 2008). When trying to understand the cause of nausea, sometimes is important to obtain a 4 h gastric emptying test with solid food to determine if gastroparesis is playing a role. Other studies available to assess for gastric emptying include wireless motility capsule, which is a capsule that gets swallowed and measures pH, pressure and temperature, and a breath test which uses a stable isotope (^{13}C-octanoate or ^{13}C-spirulina) which is absorbed in the small intestine, then metabolized to $^{13}CO_2$ and exhaled in breath (Lacy et al., 2018).

Treatment of gastroparesis depends on the severity. Dietary changes like small frequent meals, low fiber and low-fat diet may help. If symptoms are more severe, a liquid nutrient or blenderized diet may be indicated. If these measurements are not successful, a naso-jejunal tube or gastro-jejunal tube may be needed to improve hydration and nutritional status. Prokinetics such as metoclopramide, erythromycin or azithromicin and antiemetics such as ondansetron, promethazine, prochlorperazine may help. Metoclopramide works both on the D1 and D2 dopamine receptors and is the only Food and Drug Administration (FDA) approved medication for gastroparesis. Tricyclic antidepressants may help modulate the symptoms (Lacy et al., 2018). Erythromycin should be used with caution, since it prolongs QT interval. Furthermore, the response may decrease with time, requiring a “vacation” of the medication if it stops working. Metoclopramide has also severe potential side effects including depression, tardive dyskinesia which has an FDA black box warning. Except if otherwise indicated, metoclopramide should not be used for > 12 weeks (Lacy et al., 2018). Interestingly, since the relationship between gastroparesis and vomiting is not clear, a prokinetic may or may not help (Stapleton and Wo, 2009). In severe cases of gastroparesis refractory to medical medication, a gastric electrical modulator with or without pyloroplasty may be an option (Davis et al., 2017; McCallum et al., 2010). In diabetic gastroparesis, Relamorelin which is a selective prokinetic agonist of ghrelin has shown to accelerate gastric emptying and improve symptoms, but it is still in clinical trials and not yet approved by the FDA (Camilleri et al., 2017; Chedid and Camilleri, 2017).

4.3. Migraine

Migraine can be associated also with nausea and vomiting. Almost 60% of adults with migraine will report having nausea and vomiting (Gajria et al., 2017). Given the high overlap of POTS, OI and migraine, it is critical to include in the possible causes of nausea an association with migraines (Chelimsky et al., 2015). In our clinical experience, nausea often responds with the medical management of migraines. The nausea in migraine can be a premonitory symptom, and therefore is not related to trigeminal activation or pain. A PET scan study comparing subject with migraine with and without nausea, showed that the nausea group had activation of the rostral dorsal medulla and periaqueductal grey (PAG) which was not present in the subjects without nausea, suggesting involvement of the vagus in the development of migraine with nausea (Maniyar et al., 2014).

As described earlier in the chapter, nausea may also be due to an orthostatic challenge. The possible causes of this were discussed earlier in this chapter. As described earlier, nausea replicated during HUT (therefore secondary to an orthostatic challenge) often improves with volume expansion with fludrocortisone (Fortunato et al., 2011; Sullivan et al., 2005).

When treating nausea in the setting of subject with OI, depending on the presence of migraine, photo and phonophobia with the nausea, association of the nausea to headaches, etc., different treatment options should be considered. If the nausea is not related to orthostatic challenge and there is no clear delayed gastric emptying, we usually treat the nausea with cyproheptadine (monitor closely for increase weight), a tricyclic antidepressant or topiramate (Stapleton and Wo, 2009). Topiramate is an anticonvulsant. Some of the most common side effects of topiramate include weight loss, metabolic acidosis, kidney stones, cognitive slowing and glaucoma (Marmura, 2014). These medications have many potential side effects that need to be discussed with the

Table 1
Medications used in dyspepsia, mechanism of action and side effects.

Medication	Mechanism of action	Effects produced	Side effects
Histamine-type 2 receptor antagonists	? reducing gastroesophageal reflux and microscopic inflammation	Some improvement in epigastric pain and post-prandial fullness, but trials are poor (Lacy et al., 2012; Pinto-Sanchez et al., 2017)	Very seldom, and include headaches, dizziness, feeling tired mild gastrointestinal issues such as diarrhea, constipation and nausea (Vial et al., 1991)
Proton pump inhibitor	Suppress HCl secretion	Modest improvement in reflux symptoms and "ulcer-like" symptoms, but not in "dysmotility-like" symptoms (Lacy et al., 2012; Pinto-Sanchez et al., 2017)	Increased risk of *C. difficile* infection, pneumonia. Nutritional deficiencies, osteoporosis, headaches (Ksiadzyna et al., 2015)
Tricyclic antidepressant	Centrally mediated effect on antinociceptive pathways	May reduce nausea, but more studies are needed (Lacy et al., 2012)	Prolonged QTc, increased risk of suicide, mood changes, constipation, dry mouth
Acotiamide	Muscarinic and cholinesterase inhibitor In phase III trial for non-ulcer dyspepsia	Improvement in early satiety, abdominal bloating and post-prandial fullness (Lacy et al., 2012)	Diarrhea and headaches
STW 5-II	Contains extracts of bitter candy tuft, matricaria flower, peppermint leaves, caraway, licorice root and lemon balm. Works on many levels, decreasing inflammation, relaxing fundus, increases antral contraction, modulates acid secretion (Allescher and Abdel-Aziz, 2017)	Improvement of dyspepsia symptoms (Lacy et al., 2012)	Liver toxicity (Saez-Gonzalez et al., 2016)

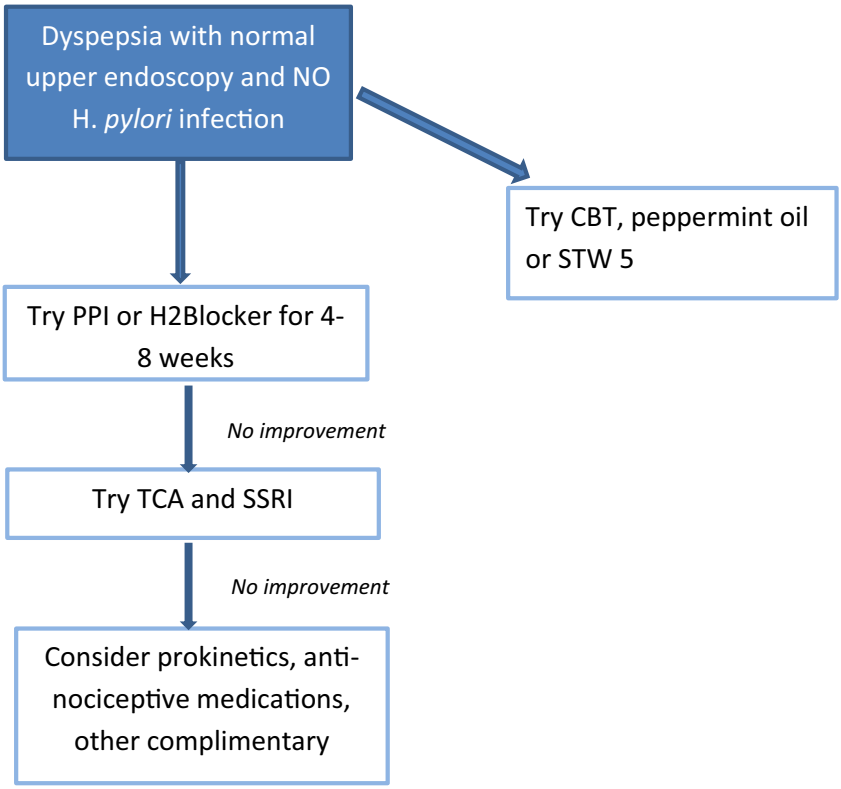

Fig. 2. Dyspepsia. In our institution we introduced peppermint oil, STW 5 and cognitive behavioral therapy (CBT) at any point in the managements.

patient (Marmura, 2014; He et al., 2017). Often we use a combination of medications.

4.4. Dyspepsia

Rome IV now includes 2 subgroups in dyspepsia, *postprandial distress syndrome* (*PDS*) and *epigastric pain syndrome* (*EPS*). These 2 sub-types of dyspepsia can overlap. PDS usually present with fullness after eating and early satiety but can also have epigastric pain/burning and nausea. Bloating and belching can also be present in both types of dyspepsia (Schmulson and Drossman, 2017).

Treatment of dyspepsia includes acid suppression, prokinetics like erythromycin, acotiamide (a muscarinic and cholinesterase inhibitor), tandospirone (5-HT1A agonist), buspirone (relaxes the gastric fundus), as well as some herbal products such as STW-5, and rikkunshito (Table 1). As a second line, tricyclic antidepressants (TCA) and serotonin reuptake inhibitors (SSRI) can be used. Low dose TCA are better tolerated than SSRI's and produce better results (Suzuki, 2017; Monkemuller and Malfertheiner, 2006). A consensus of which medication to use and in which order is not available. In general, after upper endoscopy has been done and an H pylori infection ruled out, most centers would start with antacid therapy with either a proton pump inhibitor or an H2 blocker. If the patient has delayed gastric emptying, a prokinetic could be tried. If these therapies fail, then TCA and SSRI

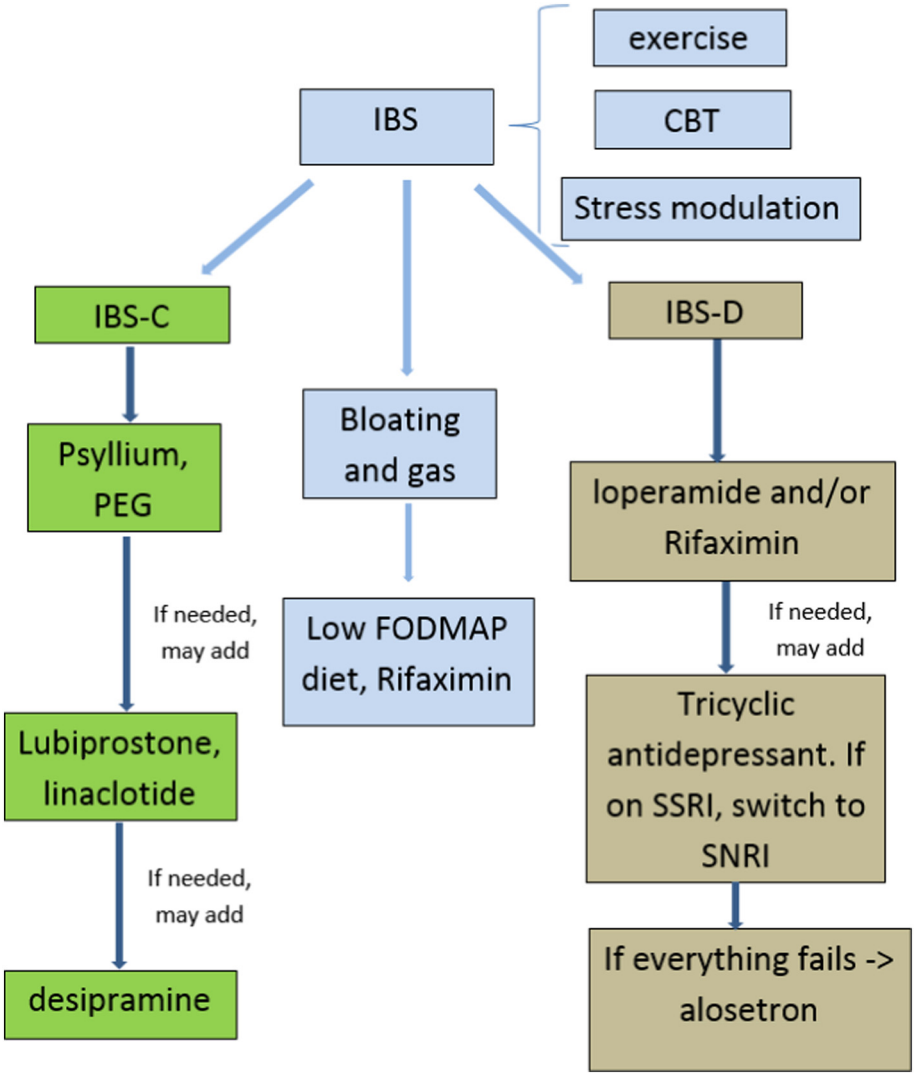

Fig. 3. Algorithm of proposed treatment of irritable bowel syndrome diarrhea predominant (IBS-D) and constipation predominant (IBS-C). The boxes in light blue may apply to IBS-C and IBS-D.

should be tried. Complimentary therapy can be tried as well as prokinetics without gastroparesis when the first 2 lines of therapy have failed (Yamawaki et al., 2017; Lacy et al., 2012). Fig. 2 summarizes a possible algorithm of treatment of dyspepsia.

4.5. Bloating and abdominal distention

These 2 terms, although similar, are different. Bloating is a sensation of abdominal pressure that may or may not be associated with visible distention of the abdomen (Malagelada et al., 2017). Many organic causes can produce bloating and distention. We will only focus here on functional bloating and distention. The mechanism of bloating is poorly understood. Several theories have been proposed, from small intestine bacterial overgrowth (SIBO), altered gas motility and abnormal gas handling, altered abdominal muscle reflexes, visceral hypersensitivity, carbohydrate malabsorption, and constipation. Based on these theories, the available treatment include antibiotics, like rifaximin, probiotics (although the results are inconsistent), prokinetics like levosulpiride and acotiamide have been used, again with conflictive results (Seo et al., 2013). Antispasmodic are also used, like peppermint oil, mebeverine and otilonium bromide among others (Seo et al., 2013). Dietary changes like low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet can be tried, as well as gas reducers (simethicone), or medications that treat constipation and increase fluid in the gut like lubiprostone and linaclotide. SSRI and TCA can be tried too (Seo et al., 2013).

4.6. Diarrhea and constipation associated with abdominal pain or discomfort

Altered bowel pattern has been reported in 70% of POTS patients (Wang et al., 2015). In contrast to the upper GI symptoms that often are replicated during the upright position, to the best of our knowledge there are no reports of diarrhea and constipation triggered by the upright position, therefore when discussing these symptoms, having POTS does not affect the management. In this chapter we will focus on the symptom of diarrhea and constipation that are usually part of irritable bowel syndrome.

Irritable bowel syndrome (*IBS*) is defined in the current Rome IV criteria.by a constellation of symptoms. IBS is a functional bowel disorder associated with recurrent abdominal pain for at least 1 day/week in the 3 months preceding diagnosis with and two or more of the following: a) pain related to defecation, b) pain associated with change in frequency of stool, c) pain associated with a change in form of stool. Rome IV described 4 types of IBS: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel

Table 2
Medications used in irritable bowel syndrome, mechanism of action and side effects (Wall et al., 2014).

	Mechanism of action	Effect produced	Side effects
Loperamide	Synthetic opioid inhibits peristalsis	Decreases stool frequency, improves stool consistency, does not reduce abdominal pain in IBS-C(Jailwala et al., 2000)	Constipation, not suggested in IBC-C(Hovdenak, 1987)
Tricyclic antidepressants	Centrally mediated effect on antinociceptive pathways	Decreases abdominal pain	Prolonged QTc, increased risk of suicide, mood changes, constipation, dry mouth
Bulking agents: psyllium, calcium polycarbophil, ispaghula	Bulking of stool	Increase stool frequency, quality and transit time, but improvement in abdominal pain	Insoluble fiber like wheat or corn bran increase bloating (Brandt et al., 2009)
Osmotic laxatives: PEG 3350 & lactulose	Increasing intraluminal water	Helps with constipation, but no effect in reducing abdominal pain and bloating	Gas (mainly lactulose)
Lubiprostone	Activates chloride channel in GI tract with increase fluid secretion	Decreases abdominal discomfort and pain, improves stool consistency, decreases straining and improves constipation	Nausea and diarrhea Contraindicated in pregnancy. Women should use contraception while on lubiprostone (Brandt et al., 2009)
Linaclotide	Agonist of guanylate cyclase, which leads to secretion of guanylin and uroguanylin into the lumen where they act as a second message to release fluids and electrolytes into the large bowel	Improves constipation, decreases abdominal symptoms (Yang et al., 2018)	Diarrhea (McCormack, 2014)
Rifaximin	Antibiotic with little or no systemic absorption	Not FDA approved in the US for IBS. Treats small bowel bacterial overgrowth Improves abdominal bloating and decrease IBS symptoms	In TARGET 1 and 2 studies, 2 weeks of Rifaximin did not produce any *Clostridium difficile* infection
Peppermint oil	Antispasmodic, blocking calcium channels	Decrease IBS symptoms	Gastroesophageal reflux, but limited data on side effects (Brandt et al., 2009)
Alosetron	5HT3 receptor antagonist	Decreases abdominal pain, urgency, diarrhea complaints and global IBS symptoms (Brandt et al., 2009)	Potential serious side effects including constipation and colon ischemia. Indicated only in females with severe IBS-D that have failed conventional therapy (used with restrictions by the FDA in the USA) (Brandt et al., 2009)

habits (IBS-M), and unclassified IBS (IBS-U) (Lacy et al., 2016).

The symptoms of diarrhea and abdominal discomfort although common in IBS, can also be present in other organic disorder. Therefore, it is important to recognize when more evaluation is indicated. Some of these red flags include fever, weight loss, blood in the stool (even occult), low albumin, elevated inflammatory markers, elevated calprotectin in the stool, family history of colon cancer or inflammatory bowel disease, history of antibiotic use, onset after age 50, failure to thrive (mainly in pediatrics), new onset, worsening of symptoms, etc. (Pimentel, 2018; Hulisz, 2004) A colonoscopy is indicated in the following situations: patients > 50 yr and in African Americans > 45 yrs., presence of any red flags, family history of colon cancer, and diarrhea that does not respond to initial management (Pimentel, 2018).

Like in many of the symptoms described in this chapter, hyperalgesia and visceral hypersensitivity are often the key factors in the pathogenesis of the symptoms of IBS, therefore treatment is aimed at pain modulation rather than treatment aimed at the end organ. The treatment should be stepwise depending on the severity of the symptoms (Fig. 3; Table 2). In general terms, the treatment should include increase exercise, stress modulation, and cognitive behavioral therapy. For IBS-C and IBS-D, if bloating and gas are a predominant or significant symptom, low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet and treatment with Rifaximin for presumed bacterial overgrowth should be considered (Pimentel, 2018).

For IBS-D, sometimes adding fiber to the diet or using bulking agents may increase the stool consistency. Loperamide, a synthetic opioid, acts on the intestinal muscles prolonging transit time and decreases peristalsis. There is little evidence that it helps in reducing the abdominal pain (Wall et al., 2014). A bile acid binder can also be added. Sometimes treatment of bacterial overgrowth with rifaximin may help the symptoms (Pimentel, 2018). Next step treatment includes a TCA, which produce constipation due to the anticholinergic effect. The dose is started low and slowly advanced over a few weeks. EKG should be followed for the risk of prolonged QTc. Furthermore, these medications have a black box warning regarding suicidal risk (Pimentel, 2018). If the patient is being treated with a selective serotonin reuptake inhibitor (SSRI) for psychiatric symptoms, consider switching to a serotonin norepinephrine reuptake inhibitor (SNRI) which may improve IBS symptoms, mainly in IBS-D (may produce constipation) (Brennan et al., 2009). SNRI like duloxetine can produce tachycardia. If significant, the heart rate can be lowered by adding propranolol (Stevens, 2008). Alosetron can be tried when everything else has failed and is only approved in the US with restrictions in the treatment of IBS-D in women. It reduces pain, stool frequency and rectal urgency. It is a highly selective 5-HT3 antagonist. The uncommon side effects include ischemic colitis and constipation (Lacy et al., 2016).

IBS-C: First line treatment include Psyllium, PEG or if needed, the newer chloride channel activators such as Lubiprostone (Lacy et al., 2016). Linaclotide is a guanylate cyclase-C agonist that has shown to improve constipation as well as abdominal symptoms (Yang et al., 2018). If a tricyclic antidepressant is needed, desipramine may be more useful, since it produces less constipation (Lin and Chang, 2017).

5. Conclusion

POTS and OI are frequently associated with gastrointestinal symptoms. From a therapeutic and diagnostic perspective, it is critical to determine if such symptoms are part of OI itself, because upright position replicates these symptoms and recumbence improves them, or are just comorbid conditions unrelated to upright position which could occur whether or not the patient has OI or POTS. The pathophysiology of the gastrointestinal symptoms produced by the orthostatic challenge is still unclear. Several theories can be postulated, including changes in perfusion, changes in vagal tone with consequent changes in motility,

or a central nervous process with central hypervigilance. Further work directly comparing changes in cardiac and gastric vagal modulations may shed light on these mechanisms.

Many gastrointestinal symptoms, such as nausea, bloating, constipation, early satiety can accompany POTS and OI, but they are not part of the POT *syndrome* or of the OI entity, just comorbid conditions. These other conditions therefore will not respond to the treatment of OI, but rather will need their own separate management.

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