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REVIEW ARTICLE

The Use of Non-Narcotic Pain Medication in Pediatric Gastroenterology

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Abstract The perception of pain in children is easily influenced by environmental factors and psychological comorbidities that are known to play an important role in its origin and response to therapy. Chronic abdominal pain is one of the most commonly treated conditions in modern pediatric gastroenterology and is the hallmark of 'functional' disorders that include irritable bowel syndrome, functional dyspepsia, and functional abdominal pain. The development of pharmacological therapies for these disorders in adults and children has been limited by the lack of understanding of the putative, pathophysiological mechanisms that underlie them. Peripheral and central pain-signaling mechanisms are known to be involved in chronic pain originating from the gastrointestinal tract, but few therapies have been developed to target specific pathways or enhance correction of the underlying pathophysiology. The responses to therapy have been variable, potentially reflecting the heterogeneity of the disorders for which they are used. Only a few small, randomized clinical trials have evaluated the benefit of pain medications for chronic abdominal pain in children and thus, the decision on the most appropriate treatment is often based on adult studies and empirical data. This review discusses the most common, non-narcotic pharmacological treatments for chronic abdominal pain in children and includes a thorough review of the literature to support or refute their use. Because of the dearth of pediatric studies, the focus is on pharmacological and alternative therapies where there is sufficient evidence of benefit in either adults or children with chronic abdominal pain.

Key Points

Currently, there are no FDA-approved drugs for the treatment of chronic abdominal pain in children

Although studies are lacking and drug development is limited, there is still a significant role for pharmacotherapy in children with chronic abdominal pain

Complementary and alternative therapies also provide a viable treatment option for children with less severe pain

1 Introduction

Psychological comorbidities such as anxiety and depression play an important role in the development and perception of pain [1]. The perception of pain is influenced by childhood emotions, physical and sexual abuse. Peripheral and central pain-signaling mechanisms are known to be involved in chronic pain arising from the gastrointestinal tract [2, 3]. Activation of primary sensory afferents through the inflammatory cascade can often lead to permanent changes in peripheral and/or central pain pathways through sensitization of nerve fibers or long-term potentiation [4–

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6]. Central and/or primary afferent sensitization can lead to permanent alterations in pain perception that have been shown to play a critical role in the development and maintenance of visceral hyperalgesia and chronic abdominal pain [7]. Pain pathways can initially be influenced by the presence of pathology such as inflammation or tissue damage that oftentimes persists despite the absence of identifiable pathology. The term 'functional abdominal pain' refers to pain that has no anatomical, histological or 'organic' etiology. This type of pain is the hallmark of functional bowel disorders that include irritable bowel syndrome (IBS), functional dyspepsia (FD), functional abdominal pain (FAP) and abdominal migraine [8]. These disorders are a heterogeneous group that can coexist with sleep disturbances, connective tissue and/or autonomic disorders and can negatively impact a child's functioning and quality of life [9–12]. No single factor can explain the origin of symptoms in patients with functional gastrointestinal disorders. A common feature among patients with functional gastrointestinal disorders is the heightened sensitivity to experimental pain, also known as visceral hyperalgesia [13]. A unifying theory of all functional gastrointestinal disorders is the alteration of the brain-gut axis. Interestingly, other chronic organic pediatric gastrointestinal diseases share similar symptoms as those seen in functional disorders. Inflammatory diseases can also alter the brain-gut axis and result in chronic abdominal pain despite resolution of the underlying inflammation. Inflammatory bowel disease, celiac disease, milk protein allergy and acute gastroenteritis (post-infectious enteritis) have been shown to predispose children to chronic abdominal pain that persists years after the organic disease has resolved or become quiescent [14–17]. The development of functional gastrointestinal disorders simultaneously or following an organic disease may lead to uncertainty for the care provider since it is not always clear when the pain results from the activation of the organic gastrointestinal disease or secondary alterations in chronic pain pathways. There have been no pediatric studies comparing outcomes between children presenting with post-inflammatory functional gastrointestinal disorders and children without a clinically evident inflammation preceding the onset of gastrointestinal symptoms. The current approach to the treatment of functional chronic abdominal pain that persists after the inflammatory component or initial insult has resolved is similar to that of functional pain without evidence of a preceding inflammatory disease. For the purpose of this review, we will refer to FAP in children as chronic abdominal pain. The treatment of chronic organic pain is beyond the scope of this review and will not be discussed.

Chronic abdominal pain in children often co-exists with somatic symptoms such as headaches, myalgias and chronic nausea [18] and, similar to that in adults, is often associated with psychological comorbidities such as anxiety, depression, and catastrophizing. A recent study showed that up to 38 % of children complain of abdominal pain at least once per week [19]. Only 2 % of these children sought medical care, suggesting that not all children with abdominal pain require medical treatment. However, severe, chronic abdominal pain often requires treatment as it can significantly impact social and school functioning [9]. Overall, chronic abdominal pain is one of the most common reasons for pediatric office visits and gastroenterology consultations [20]. While the cost in pediatrics is unknown, the annual direct cost of IBS in adults has been estimated at US$1.35 billion [21]. Care providers looking for a 'one size fits all' therapy often find it difficult and frustrating to manage this group of patients, since pharmacological therapies of proven efficacy are limited and treatment response may vary from patient to patient. In 2005, a technical report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) found little evidence to endorse the use of any drug in the treatment of chronic abdominal pain in children [22]. Fortunately, significant progress has been made in the past 15 years in understanding the pathophysiology of visceral hyperalgesia in animals and humans that will hopefully lead to newer and better treatment options in the future.

Currently, there are no FDA-approved drugs for the treatment of chronic abdominal pain in children and little evidence of efficacy for most commonly used medications. Responses have been variable, potentially reflecting the heterogeneity of the disorders for which they are used. Only a few small, randomized clinical trials have evaluated the effect of various pharmacological interventions in the treatment of chronic abdominal pain in children and thus, the decision on the most appropriate pharmacologic treatment to use is frequently based on adult studies and empirical data. Although studies are lacking and drug development is limited, there is still a significant role for pharmacotherapy in children with chronic abdominal pain. A major obstacle in the development of pharmacological therapies aimed at targeting specific pathways or correcting the underlying pathophysiology of chronic pain is the limited data on the putative, pathophysiological mechanisms that underlie this type of pain. The dearth of successful treatment options for chronic abdominal pain often results in patients opting for alternative methods without appropriate data to support their efficacy [23]. Treatments are considered as 'alternative' when used instead of conventional therapies and 'complementary' when used in addition to other treatments (i.e., conventional medical treatments). There appears to be a growing desire amongst patients and families for a more 'natural' approach to

treatment [24]. It has been suggested that approximately 35 % of patients with functional bowel disorders use complementary or alternative medicine [25, 26]. The use of these methods confronts the practitioner with a difficult problem. Despite the perceived lack of efficacy of some commonly used alternative approaches, the paucity of research to discredit some of these treatments and to confirm the superiority and safety of commonly used pharmacological treatments, interferes with the ability of the physicians to recommend the use of many commonly used pharmacological therapies. Some pharmacological agents being used or promoted to treat chronic abdominal pain are often no better or have minimal gain over placebo. In fact, one of the obstacles in evaluating the benefit of any pharmacological therapy for chronic abdominal pain in children and adults has been the high placebo response rates that can range from 20 to 50 % in some studies [27, 28]. Because commonly used agents such as antidepressants, antiepileptics, and antispasmodics are not devoid of side effects, the therapeutic gain over placebo becomes extremely important, particularly when other, equally effective therapies can be offered with potentially fewer side effects.

In this review article, we will focus on non-narcotic treatment options for children with chronic abdominal pain. We performed a detailed literature search to identify clinical trials examining the benefit of pharmacological therapy in children and adults with chronic abdominal pain. The search was done through PubMed and the Cochrane library using the following search terms: 'treatment' and/or 'children' along with 'recurrent abdominal pain', 'abdominal pain', 'irritable bowel syndrome', 'functional pain', 'dyspepsia', 'visceral hyperalgesia', 'visceral hypersensitivity', 'nociception', 'tricyclic antidepressant', 'selective serotonin reuptake inhibitor', 'serotonin–norepinephrine reuptake inhibitor', 'alpha 2 delta ligands', 'gabapentin', 'pregabalin', 'antispasmodic', 'cyproheptadine', 'rifaximin', 'linaclotide', 'lubiprostone', 'peppermint oil', 'STW 5', 'Iberogast', and 'melatonin'. In many instances, the focus will be on treatments for which only adult data exist; however, only those treatments that have been previously used in children will be discussed (Table 1). It is important to consider that while pharmacological treatment alone can be beneficial in the treatment of chronic abdominal pain, the clinician must spend time educating the family regarding the suspected mechanisms and how and why pharmacotherapy may work. In the more severe, disabled patients, it should be considered part of a therapeutic program that includes physical reconditioning, exercise, proper sleep, and in many cases, thought reprocessing. In this review, we will focus only on pharmacological therapies where there is sufficient evidence for benefit in chronic abdominal pain and will also discuss some anecdotal reports of medications being used with some success in children. Therefore, psychological therapies such as cognitive behavioral therapy, hypnosis, relaxation, meditation, or biofeedback will not be discussed despite the fact that these therapies have been shown to be as effective, and sometimes better, than pharmacological therapy. Families, nevertheless, should be educated on the potential modification of the 'pain behavior' and potential benefits of lifestyle modifications.

2 Treatments for Children with Chronic Abdominal Pain

2.1 Antidepressants

2.1.1 Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are frequently used for the treatment of chronic abdominal pain in children and adults. Amitriptyline is widely used for chronic pain conditions including migraine headaches, fibromyalgia, and neuropathic pain, and is considered to be effective independent of the presence of depression. The doses for patients with chronic pain are usually much lower than anti-depressive doses and while it is considered relatively safe, it is not without side effects. The anticholinergic and sedative effects are relatively immediate whereas the antidepressant effects can be delayed up to 3–6 weeks. The use of amitriptyline also takes advantage of the sleep-modifying effects that can, single-handedly, improve pain in children [29]. The absorption and metabolism of amitriptyline is highly variable among individuals and anecdotal experience suggested a prolonged period of up to several weeks to see benefits in pain. Recent unpublished results, however, suggest that those who respond to treatment will respond within the first week.

Several trials and meta-analyses have shown that TCAs have a beneficial effect in adult patients with IBS [30]. A meta-analysis of seven randomized, placebo-controlled clinical trials using various TCAs (amitriptyline, imipramine, desipramine, doxepin, trimipramine) showed a pooled relative risk for clinical improvement of almost two times in IBS patients receiving TCAs compared with placebo [31]. A recent meta-analysis of four large randomized, placebo-controlled clinical trials showed that patients receiving amitriptyline therapy for the treatment of IBS had a 4-fold improvement compared with those receiving placebo [32]. Data in children, however, are less clear. Two pediatric clinical trials resulted in apparently conflicting results. A randomized clinical trial on 33 adolescent females with IBS showed a beneficial effect of amitriptyline on quality of life at 4 and 8 weeks [33]. The study reported an exclusive and inconsistent improvement in

Table 1 Pharmacological treatment options for chronic abdominal pain

Drug	Location of action		Dosages	Common side effects
	Central	Peripheral		
Tricyclic antidepressants (TCAs)	+	+	**Amitriptyline** 0.1–1 mg/kg/day at bedtime	Constipation, dry mouth, dizziness, somnolence
Selective serotonin reuptake inhibitors (SSRIs)	+		**Citalopram** (≤11 years) 10–20 mg daily (≥12 years) 10–40 mg daily	Nausea, headache, somnolence, dry mouth
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	+		**Duloxetine** 30–60 mg daily (no pediatric data) **Venlafaxine** 12.5–25 mg 1–3× daily (no pediatric data)	Nausea, headache, somnolence, dry mouth
Alpha 2 delta ligands	+	+	**Gabapentin** 8–35 mg/kg/day divided 3× daily (max 3,600 mg/day) **Pregabalin** 75–225 mg 2× daily (no pediatric data)	Dizziness, somnolence, fatigue, ataxia
Antispasmodics		+	**Hyoscyamine** (2–12 years) 0.0625–0.125 mg every 6–8 h prn (max 0.75 mg/day) (>12 years) 0.125–0.25 mg every 6 h prn (max 1.5 mg/day) (no pediatric data) **Trimebutine** (≥12 years) 200 mg 3× daily (<12 years) 1 mg/kg 3× daily **Dicyclomine** 10–20 mg 3–4× daily (no pediatric data)	Dry mouth, dizziness, blurred vision
Cyproheptadine	+	+	**Cyproheptadine** 0.25–0.5 mg/kg/day divided 2–3× daily	Weight gain, somnolence, irritability
Rifaximin		+	**Rifaximin** 200–550 mg 3× daily	Peripheral edema, nausea, dizziness
Linaclotide		+	**Linaclotide** 145–290 μg daily (no pediatric data)	Diarrhea, abdominal pain, flatulence
Lubiprostone		+	**Lubiprostone** 8–24 μg 2× daily	Nausea, diarrhea, headache
Peppermint oil		+	**Peppermint oil** enteric-coated capsules (30–45 kg) 0.2 mL (187 mg or 1 capsule) 3× daily (>45 kg) 0.4 mL (374 mg or 2 capsules) 3× daily	Heartburn, headache, flushing
STW 5 (Iberogast)	+	+	**Iberogast** (6–12 years) 15 drops (0.75 mL) 3× daily before meals (>12 years) 20 drops (1 mL) 3× daily before meals	Abdominal cramps, diarrhea, nausea, dizziness
Melatonin	+	+	**Melatonin** 3–6 mg daily at bedtime	Somnolence, fatigue, hypothermia

right lower quadrant abdominal pain. Moreover, the improvement in localized pain was limited to 12.5 % and was only significantly better than the placebo arm due to the unusual nocebo effect (patients in placebo arm worsened) found in the group of children allocated to the placebo group. A larger, multicenter clinical trial conducted in 90 children diagnosed with chronic abdominal pain (FD, FAP and IBS) from six centers found that amitriptyline and placebo were equally effective in improving abdominal pain [27].The study found more than 50 % improvement in satisfactory relief of symptoms and satisfaction with treatment in both groups. Interestingly, patients that received amitriptyline had lower anxiety scores at the end of the 4-week trial. There was a large placebo effect that could explain the negative study. Although the conclusions of both pediatric amitriptyline studies seem contradictory, the samples, duration of treatment and pain outcomes differed. A comprehensive review of both studies by the Cochrane group found no evidence to recommend amitriptyline in the treatment of children with chronic abdominal pain [30]. Amitriptyline may be effective at a higher dose and only in a subset of children, an effect that may have not been noticed by the mixed sample in the studies. Despite the lack of definitive evidence of benefit, amitriptyline continues to be used in children with chronic abdominal pain. Interestingly, a retrospective chart review of 98 children who were prescribed TCAs for functional bowel disorders in a private practice setting found that 79 % of children responded to treatment [34].

Patients with IBS have lower abdominal pain thresholds, perceive higher pain intensity and have abnormal viscerosomatic referral patterns [35–39]. Physical and psychological stress induces greater changes in intestinal motility and visceral hypersensitivity in IBS patients compared with

healthy controls [40, 41]. The exact mechanism of action of amitriptyline in improving chronic abdominal pain remains unclear. TCAs are likely to affect multiple processes and have multisite actions. Amitriptyline has been suggested to inhibit currents and decrease expression of voltage-gated sodium channels in animals [42]. A predominant effect may be linked to the endogenous pain modulation system known as diffuse noxious inhibitory control (DNIC) or potentiation of endogenous opioids [43]. Other mechanisms related to the analgesic effect of amitriptyline include modulation and antagonism of the *N*-methyl-D-aspartate (NMDA) receptor [44]. Extensive studies have demonstrated that theses glutamate receptors play an important role in the development of chronic pain [45–49]. IBS patients treated with amitriptyline show reduction in visceral sensitivity to rectal balloon distention and reduced acute stress-induced visceral hypersensitivity [50, 51]. Because anxiety and higher depression scores are frequently found in patients with functional gastrointestinal disorders, treatment with TCAs may also have an effect on psychological comorbidities.

The use of amitriptyline has been associated with a modest QTc prolongation [52]. As a result, a screening electrocardiogram (ECG) is customary prior to initiating treatment with amitriptyline. However, the arrythmogenic effects of amitriptyline are dose dependent and the dose used in children with chronic abdominal pain is generally low (0.5–1 mg/kg/day). Long QT syndrome is rare in children (0.4 %) [53]. Even more controversial is the need for a follow-up ECG in children receiving amitriptyline. Currently, there are no clear guidelines on the need for ECG prior or after treatment in children receiving low doses of amitriptyline. The FDA's black box warning applied to antidepressants suggesting an increased risk of suicidal thoughts and suicidality in children and adolescents with psychiatric disorders has resulted in a decrease in the use of amitriptyline in children with major depressive disorder [54, 55]. However, the prevalence of major psychiatric conditions in children reporting chronic abdominal pain is low and there are currently no published reports of increased suicidal behavior in non-depressed children receiving low dose of amitriptyline for chronic abdominal pain.

2.1.2 Selective Serotonin Reuptake Inhibitors

Although generally considered as less effective drugs in the treatment of chronic abdominal pain, selective serotonin reuptake inhibitors (SSRIs) are sometimes used in the treatment of IBS. Two placebo-controlled trials and a meta-analysis of four studies in adult patients with IBS showed that citalopram was no better than placebo in reducing abdominal pain [30, 56, 57]. An uncontrolled open-label, variable-dose study assessed the effect of citalopram in a group of children with recurrent abdominal pain [58]. The study found a positive response in global outcomes in 84 % of children. The design of the study does not allow concluding on the possible benefit of citalopram in children and no placebo-controlled studies have been published on the use of citalopram in children with chronic abdominal pain. Several studies in adults with IBS have demonstrated conflicting results. A placebo-controlled study in adult patients with IBS demonstrated that citalopram significantly improves abdominal pain independent of the presence of anxiety or depression [59]. A more recent study, however, suggested that citalopram was not superior to placebo in treating non-depressed IBS patients [60]. The exact mechanisms of action of SSRI antidepressants in improving chronic abdominal pain symptoms are not completely understood. The central effects may be related to a decrease in somatization and reduced anxiety related to gut sensations. The mechanism may also involve peripheral effects through inhibition of serotonin transporter (SERT) that is expressed by enterocytes and nerves in the gastrointestinal tract. In healthy adult males, citalopram was shown to induce the occurrence of high amplitude propagating contractions and transiently increased phasic colonic contractility. Furthermore, citalopram increased colonic compliance and inhibited the postprandial increase in colonic tone after a meal [61]. The FDA has established recommendations and cautions against the use of citalopram in patients with underlying heart conditions because of the risk of QT prolongation. Citalopram is not recommended for use in patients receiving other drugs that also prolong the QT interval [62].

2.1.3 Serotonin–Norepinephrine Reuptake Inhibitors

There are no studies on the use of serotonin–norepinephrine reuptake inhibitors (SNRIs) in children with abdominal pain and there is very limited data on the use of duloxetine in adult patients with IBS. A small, open-label trial of duloxetine 60 mg daily, in 15 adult patients with IBS without concurrent major depressive disorder, showed improvement in IBS symptoms, functionality and quality of life [63]. Six participants discontinued duloxetine within 6 weeks for dose-limiting adverse events (predominantly constipation), which suggests that this drug may not be recommended in patients with constipation-predominant IBS. The drug is currently not approved for the treatment of IBS; however, it is approved for the treatment of other chronic pain disorders including diabetic peripheral neuropathic pain and fibromyalgia. Venlafaxine is a mixed-action antidepressant that inhibits serotonin and norepinephrine reuptake at variable doses. Venlafaxine was found to be effective for the management of neuropathic pain [64]

with an effect that is considered comparable to imipramine and with a better safety profile than TCAs [65]. No clinical trials have been published on the efficacy of venlafaxine in children or adults with chronic abdominal pain.

2.2 Alpha 2 Delta Ligands

Gabapentin and pregabalin are structurally related to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) but not functionally active at GABA or benzodiazepine receptors. Instead, both compounds bind to the α2δ subunits of voltage-gated calcium channels where they are likely to impart their analgesic effects [66]. Gabapentin has been used in the treatment of seizure disorders and most recently for chronic pain conditions including fibromyalgia, diabetic neuropathy, and neuralgia [67–69]. Similarly, pregabalin, a second-generation compound related to gabapentin, has also been used as an anti-epileptic drug, in addition to anxiety disorders and chronic pain conditions such as neuropathic pain and fibromyalgia [68, 70, 71]. The exact mechanism responsible for improving chronic pain is still poorly understood.

Animal studies suggest that α2δ subtype 2 receptors are distributed in CNS areas that regulate autonomic function and DNIC, including the periaqueductal gray and spinal cord [72]. This may in part help explain the antihyperalgesic effects of these drugs through a central mechanism [73]. Interestingly, these compounds also have been shown to alter the release of noradrenaline, serotonin, glutamate, substance P and calcitonin gene-related peptide (CGRP) in the CNS [74–77]. The increases in serotonin levels may partially explain its central antinociceptive effect and potentially the anxiolytic properties [78]. This is particularly important since anxiety disorders are common in patients with chronic abdominal pain and IBS [79]. Already, pregabalin has been shown to improve anxiety and gastrointestinal symptoms in patients with generalized anxiety disorder [80].

There are multiple reports in the literature regarding the antinociceptive effects of gabapentin and pregabalin in animal models of visceral pain and hyperalgesia including colitis models and mechanical distension of the colon [81–86]. However, the data in humans is much more limited. A single center, randomized, double-blind, placebo-controlled study evaluated the effects of oral gabapentin on rectal sensory and motor function in patients with diarrhea-predominant IBS [87]. In that study, gabapentin enhanced rectal compliance and attenuated rectal sensitivity symptoms in IBS patients and significantly increased threshold pressures for bloating, discomfort and pain compared with placebo. A randomized, double-blind, placebo-controlled study of pregabalin assessed rectal sensitivity using a barostat [88]. Pregabalin was shown to be significantly better than placebo in increasing sensory thresholds to mechanical distension in IBS patients with rectal hypersensitivity. Overall, the animal data demonstrating the visceral analgesic effects of gabapentin and pregabalin are convincing, but the limited studies in adults and absence of studies in children make it very difficult to promote the use of these compounds to treat chronic abdominal pain in children.

2.3 Antispasmodics

Colonic smooth muscle spasm has long been postulated to be responsible for FAP and IBS [89, 90]. However, the exact mechanism responsible for the efficacy of antispasmodics in alleviating abdominal pain is still unclear. Some studies suggest a reduced colon diameter and possibly accelerated small bowel transit [91]. One of the most commonly prescribed antispasmodics, hyoscyamine, has been used to treat episodic abdominal pain in adults and children. However, despite their widespread first-line use, there have been no clinical trials on antispasmodics in children with the exception of a study using trimebutine maleate [92]. The study showed improvement in global IBS scores in 95 % of children in the trimebutine maleate group compared with 20.5 % in the non-medicated group. There was also a significant improvement in headaches, back pain, and chronic fatigue in the trimebutine maleate group who received 3 mg/kg/day. The study was conducted in patients admitted to a pediatric gastroenterology service who were randomized to medication or no treatment for 3 weeks. The results have to be interpreted with caution, particularly since parents of children who did not receive treatment were asked to rate the global improvement of their child's symptoms after several weeks of no treatment and the study was not well controlled. Still, it supports adult studies that demonstrate superior efficacy of trimebutine over placebo in improving abdominal pain and flatus [93]. Trimebutine has complex effects on the gastrointestinal tract and animal studies suggest that it may modulate visceral hypersensitivity since it attenuates the response to mechanical distention of the colon [94]. The antinociceptive effects are likely mediated through (1) peripheral μ, κ, and δ opiate receptors, (2) a promotility effect through the release of motilin, and (3) modulation of the release of vasoactive intestinal peptide, gastrin, and glucagon [95]. Interestingly, a systemic review and meta-analysis suggested that trimebutine is not better than placebo in alleviating symptoms of IBS while other antispasmodics such as otilonium and hyoscine reduce the persistence of IBS symptoms [96]. The authors conclude that there was significant heterogeneity between study results and also evidence for publication bias in the studies that were examined. Further, a more recent comprehensive

review of studies on adult patients with abdominal pain and IBS showed a beneficial effect of some antispasmodic drugs [30]. The study showed a beneficial effect of dicyclomine, pinaverium bromide, and trimebutine in improving abdominal pain.

In a study of adult patients with IBS, the efficacy and safety profile of tiropamide and octylonium was recently compared. Both compounds are believed to reduce Ca^{2+} release into intestinal smooth muscle and exert a spasmolytic effect, and have been shown to be effective in improving IBS symptoms in adults [97]. The study concluded that tiropramide is as effective as octylonium in managing abdominal pain in patients with IBS. A different antispasmodic, mebeverine (135 mg three times daily), was recently compared with placebo in patients with IBS (age 16–60 years). Patients were also randomized to one of three websites providing cognitive behavioral therapy (CBT) as a web-based self-management tool. The primary outcomes measured were improvement in the IBS symptom severity scale and IBS Quality of Life Questionnaire (IBS-QOL) from baseline to 12 weeks [98]. In this study, there was no difference in the primary or secondary outcomes measured, suggesting that mebeverine is no better than placebo in improving symptoms of IBS. A recent systematic review also showed no statistically significant efficacy of mebeverine in global improvement of IBS, compared with placebo [99]. Overall, the heterogeneity of the groups being studied in all the antispasmodic trials along with the significant differences in study design have led to conflicting results, making it very difficult to interpret the overall efficacy of this class of drugs, particularly in children. However, the overall trend is positive for most antispasmodics in the treatment of abdominal pain and they appear to be well tolerated. Side effects can be significant, including dry mouth, dizziness, and blurred vision. In children, anecdotal evidence suggests that most antispasmodics should be used as adjuvant therapy for the treatment of chronic abdominal pain and bloating and only for episodic pain and not as daily treatment.

2.4 Dyspepsia and Chronic Abdominal Pain

2.4.1 Cyproheptadine

Cyproheptadine is an antagonist of serotonin, histamine H1, and muscarinic receptors. It has been used to treat allergic rhinitis and migraine headaches and anecdotally as an appetite stimulant in children [100, 101]. No studies in adult patients have evaluated the benefit of cyproheptadine for abdominal pain or dyspepsia. A single prospective trial has evaluated the benefit of cyproheptadine on chronic abdominal pain in children [102]. This small, double-blind, 2-week clinical trial conducted in 29 children and adolescents with FAP found a significant benefit of cyproheptadine over placebo. Children receiving cyproheptadine had a greater improvement in frequency and duration of abdominal pain compared with those on placebo. Children in the cyproheptadine group reported improved or much improved pain in 87 % of cases compared with 37.5 % of children in the placebo group. Another study retrospectively evaluated 80 children who had received cyproheptadine for dyspeptic symptoms defined as nausea, early satiety, abdominal pain, retching post-fundoplication, or vomiting [103]. Forty-four children in that study met Rome III criteria for FD and 41 % had a beneficial response to treatment. Further, 86 % of children who had dyspeptic symptoms after fundoplication showed improvement. The authors speculated that the beneficial effects of cyproheptadine in alleviating dyspeptic symptoms is mostly through improved gastric accommodation, due to its high affinity for blocking serotonin, 5-hydroxy tryptamine (5-HT2A and/or 5-HT2B) receptors in the gastric fundus or potentially by decreasing visceral hypersensitivity through its anti-serotonergic effects in the CNS. The study found no effect of dose or duration of therapy on the success of treatment. One in three children in the study reported side effects with the use of cyproheptadine, but side effects such as somnolence and weight gain were mild and self-limited. Somnolence was the most common side effect (16 %) and one fourth of the patients responded favorably to a 50 % dose reduction.

Cyproheptadine is usually given at a dose of 0.25 mg/kg/day, although higher doses are sometimes used. The drug has a high therapeutic window for severe side effects. A study evaluating accidental ingestion of cyproheptadine in children reported no life-threatening events with doses of 0.3–6.15 mg/kg; however, careful monitoring during cyproheptadine therapy is advised [104]. Overall, the drug appears safe and well tolerated in children and should be considered in the treatment of chronic abdominal pain with dyspeptic symptoms despite the fact that more studies are needed to confirm its superiority over placebo.

2.5 Antibacterials and Small Intestinal Bacterial Overgrowth

2.5.1 Rifaximin

The treatment of abdominal pain in children and adults has not always focused on the sensory pathways per se. Addressing other potential underlying mechanisms that cause abdominal pain is important. There is increasing evidence that small intestinal bacterial overgrowth (SIBO) may be a cause of chronic abdominal pain [105, 106]. This has led to the use of antimicrobial agents to alter the intestinal flora and to some extent alleviate the symptoms

of IBS and abdominal pain. Rifaximin has been of significant interest due to its very low systemic absorbance and localized effect on intestinal flora. Rifaximin is a semi-synthetic derivative of rifamycin that has Gram-positive, Gram-negative and anaerobic bacteria coverage in vitro and is currently FDA approved for traveler's diarrhea and hepatic encephalopathy. A study in children investigated the effects of rifaximin on gastrointestinal symptoms in children with SIBO and IBS [107]. Patients were classified into the three bowel subtypes including diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), and alternating bowel habit (IBS-A). Patients with SIBO, based on breath test, were treated with rifaximin 600 mg per day for 7 days and showed improvement in visual analog scale (VAS) scores for abdominal pain, bloating, and flatulence. This study had no control group and rifaximin, unfortunately, was not compared with placebo. A randomized, double-blind, placebo-controlled study in children with chronic abdominal pain evaluated the effect of a 10-day course of rifaximin 550 mg three times daily [108]. Subjects underwent a baseline breath test to evaluate for SIBO and completed symptom-based questionnaires. There was no difference in symptoms, including abdominal pain, between children who were treated with rifaximin and those treated with placebo. Interestingly, most children treated with rifaximin had persistently abnormal breath tests, suggesting inadequate treatment in this group. Several studies in adults have evaluated the benefit and safety of rifaximin in IBS patients with chronic abdominal pain; most have demonstrated favorable results [109–111].

Overall, the data seem to suggest that rifaximin has a small therapeutic gain over placebo in alleviating abdominal pain in patients with IBS (approximately 9–12 %) and this may be due to the differences in patients being treated and the heterogeneity of the disorders. In addition, recurrence of symptoms after initial therapy seems to be common in most trials, suggesting that most patients would require re-treatment. The drug is currently not approved for IBS mainly due to this problem and phase III trials are currently underway to investigate outcomes after a second round of treatment in patients with IBS. Although short-term treatment appears to be well tolerated in adults, multiple treatments with any antibacterial increases the concern for anti-microbial resistance and no studies have evaluated the safety and tolerability of rifaximin beyond 16 weeks of treatment.

2.6 Constipation-Predominant Abdominal Pain

2.6.1 Linaclotide

Linaclotide is a synthetic peptide that has high affinity for guanylate cyclase C (GC-C). Its effect is specific for the GC-C receptor in the intestinal epithelium and binding leads to activation of the cystic fibrosis transmembrane conductance regulator (CFTR). This results in secretion of chloride and bicarbonate ions and ultimately an increase in water in the intestinal lumen that accelerates colonic transit [112, 113]. It is no surprise that the most common adverse side effect in clinical trials has been diarrhea. The efficacy of oral linaclotide has been assessed in two randomized, double-blind, placebo-controlled trials in adult patients with IBS-C [114, 115]. In both studies, the proportion of responders for abdominal pain or degree-of-relief was higher in the linaclotide group at 12 and 26 weeks with a therapeutic gain of approximately 12–15 % over placebo for abdominal pain alone. Interestingly, animal studies suggest that linaclotide may also have antihyperalgesic properties by blocking intestinal nociceptor, but this has not been confirmed in human studies and it is possible that the improvement in abdominal pain in patients with IBS-C may be related to improvement in bowel movements alone [116]. Linaclotide has an overall favorable safety profile and does not appear to be associated with any relevant systemic side effects. This is likely related to the limited systemic absorption. To date, no studies have been carried out in children. It is important to consider that given linaclotide's mechanism of action, its use should be limited to those with constipation-predominant abdominal pain and not yet as an anti-hyperalgesic.

2.6.2 Lubiprostone

Lubiprostone is a compound that acts through CFTR and chloride channels (ClC-2) to increase chloride secretion and subsequently water across colonic epithelia. This mechanism is believed to be responsible for enhanced colonic transit and relief of constipation [117, 118]. The drug is approved in the US for the treatment of adults with idiopathic constipation and IBS-C. Two large trials in adults with IBS-C have demonstrated efficacy of lubiprostone over placebo in global relief of IBS symptoms [119]. However, while studies have demonstrated that lubiprostone can accelerate colonic transit, there are no data to support its role in the treatment of chronic abdominal pain. In fact, adult studies have already suggested that it has no effect on visceral sensitivity [120, 121]. Further, a recent, open-label, 4-week trial of lubiprostone in 124 children with constipation showed an increase in stool frequency, but no change in abdominal discomfort [122]. Lubiprostone in children and adults appears to be well tolerated, but the long-term safety in children is yet to be established. The most common gastrointestinal adverse events documented in studies have been nausea, diarrhea, bloating, sinusitis, and urinary tract infections. Overall, the current studies suggest that lubiprostone should be considered as a

therapy for constipation in children and not for the treatment of chronic abdominal pain.

2.7 Complementary and Alternative Therapies

2.7.1 Peppermint Oil

In general, patients and families seem to prefer a more 'natural' approach to treatment of chronic abdominal pain. This is particularly true if the symptoms are mild and not severe enough to interfere with a child's school or daily activities. In this regard, concentrated peppermint oil, obtained from the fresh leaves of the herb *Mentha paprika* L, is increasingly being used in the treatment of abdominal pain in children as a 'natural' or alternative product. The menthol component of peppermint oil acts as a calcium channel blocker that causes relaxation of intestinal smooth muscle [123, 124]. Kline et al. [125] evaluated the efficacy of peppermint oil in 42 children with IBS in a randomized, double-blinded controlled trial. Peppermint oil was administered in pH-dependent, enteric-coated capsules and showed a reduction in abdominal pain severity over placebo. However, these results need to be interpreted with caution since subjects were followed for only 2 weeks and the study included a relatively low number of patients. Peppermint oil has no significant effect in postprandial discomfort, fundic tone, accommodation, or nutrient tolerance in healthy adult volunteers [126]. The most common side effects seen with other antispasmodics have not been associated with peppermint oil and the most prevalent side effect in the pediatric trial was heartburn. The study showing benefit of peppermint oil in reducing abdominal pain in children is in accordance with adult studies in patients with IBS showing similar results [30, 96].

2.7.2 STW 5 (Iberogast®)

STW 5 is a mixture of nine herbal plant extracts that has received much attention as an alternative approach for the treatment of FD and IBS, particularly in Europe. The combination consists of liquid extracts from chamomile flowers, bitter candytuft, angelica root, caraway fruits, milk thistle, lemon balm leaves, greater celandine, licorice root, and peppermint leaves. This herbal preparation was originally used in Germany more than 30 years ago and several trials since have suggested that STW 5 is effective in alleviating global gastrointestinal symptoms. The exact mechanism in alleviating symptoms of FD and IBS is not known but studies suggest it may have anti-hyperalgesic properties, improve proximal gastric accommodation, and potentially have pro-secretory and anti-spasmodic properties [127, 128]. In vitro data also suggest STW 5 may bind 5-HT4, muscarinic M(3), and opioid receptors [129]. Perhaps the most rigorous study consisted of a randomized, double-blind, placebo-controlled study of STW 5 over a 4-week period in 208 adults patients with IBS [130]. In that study, STW 5 significantly improved quality of life and reduced abdominal pain in IBS patients compared with placebo. A separate study compared SWT 5 with placebo in alleviating dyspeptic symptoms [131]. Adults with FD were evaluated using a standard Gastrointestinal Symptoms (GIS) score comprising several symptoms including epigastric pain, cramps, fullness, early satiety, nausea, vomiting, and heartburn. STW 5 was superior to placebo in improving GIS scores after 4 and 8 weeks of treatment. However, because of the trial design, the specific symptoms that improved with treatment were not defined. Several other studies have also shown superiority of this treatment over placebo [132]. To date, there have been no well controlled studies in children evaluating the benefit of this treatment, but the tolerability in adults appears to be very good and no serious adverse events have been reported. Anecdotal evidence suggests that SWT 5 is likely to improve dyspeptic symptoms in children and less likely to improve severe, chronic abdominal pain.

2.7.3 Melatonin

Melatonin, (*N*-acetyl-5-methoxytryptamine) a derivative of serotonin, is a neurohormone that has been implicated in the control of the wake–sleep cycle [133, 134]. While it is produced in the pineal gland, a large source of melatonin is actually derived from the gastrointestinal tract [135]. Recently, evidence has been mounting in humans and animals supporting the role of melatonin in pain modulation [4, 136–138]. While melatonin appears to play an important role in sleep, interactions with other systems including the serotonergic, dopaminergic, adrenergic or opioidergic pathways have been proposed as potential mechanisms that mediate its analgesic properties [139, 140]. Adult studies have documented the benefit of melatonin in improving pain in patients with FD, fibromyalgia, and migraine headaches independent of its effects on sleep [141–144]. In a placebo-controlled trial, nightly melatonin at a dose of 3 mg over 4 weeks was shown to be significantly better than placebo and improved abdominal pain and symptoms of IBS adult patients [145]. Several studies have suggested that receptors for melatonin (MT1 and MT2) are expressed throughout the nervous system including the thalamus, hypothalamus, anterior pituitary, and in the dorsal horn of the spinal cord where they are believed to be involved in nociceptive transmission [146, 147]. To date, the precise mechanisms through which melatonin improves pain is not well understood. Multiple animal models of acute, inflammatory, and neuropathic pain have also demonstrated the antinociceptive effect of

melatonin [136, 148–151]. A proposed mechanism for melatonin analgesia involves the release of endogenous β-endorphin. Studies suggest that exogenously administered melatonin in rats increases somatic pain thresholds and the release of endogenous opioids from the periaqueductal gray area, the same midbrain region known to influence the autonomic nervous system and descending pain modulation [140, 152]. Unpublished results suggest that melatonin is effective in improving chronic abdominal pain in approximately 50 % of children; however, more data are needed to confirm these results. Melatonin is likely to be effective in less severe patients with minimal co-morbidities and has the added benefit of having a low side-effect profile.

3 Conclusion

Chronic abdominal pain continues to be one of the most common reasons for pediatric gastroenterology referrals and has been shown to negatively impact quality of life [9]. While there are currently no FDA-approved drugs for the treatment of chronic abdominal pain in children, small, randomized clinical trials in children and larger trials in adults suggest that pharmacological therapy may play an important role in treatment of these disorders. In this review, we included medications that are most commonly used in clinical practice for the treatment of chronic abdominal pain in children. The studies that were reviewed included both adult and pediatric trials, since only a few methodologically sound studies have investigated pharmacological treatment in children. The types of medications found to be efficacious varied widely and the study populations were markedly different, making it very difficult to suggest superiority of one treatment over another. In most cases, the underlying mechanisms for each therapy are not fully understood and are very different from one another. This rather diverse group of therapies most likely reflects the heterogeneity of functional bowel disorders.

In the clinical setting, the decision on the most appropriate pharmacologic treatment is usually based on an attempt to alleviate the most debilitating symptom. However, not all children with chronic abdominal pain require pharmacological treatment since the pain can oftentimes be mild, episodic, and not interfere with school or activities. In cases of mild pain, the clinician must take advantage of the high placebo response rate and also the lower side-effect profiles of some alternative therapies. In many instances, a thorough explanation of the underlying etiology of the pain and reassurance is enough to alleviate anxiety and symptoms in children. This requires establishing a good doctor–patient relationship and success usually depends on the severity of the symptoms and associated comorbidities. While non-pharmacological therapies were not included in this review, it is important to remember that, as with any chronic pain disorder, the treatment may require physical reconditioning, exercise, and thought reprocessing. This is a critical part of treatment in patients with more severe symptoms or those who desire a non-pharmacological approach. Therefore, psychological therapies such as cognitive behavioral therapy, hypnosis, relaxation, or biofeedback should be considered as potential treatment options in all children who present with chronic abdominal pain.

Conflict of interest Drs. Adrian Miranda and Miguel Saps have abided by all ethical standards. Dr. Miranda is a consultant for QOL Medical and has no conflicts of interest. Dr. Saps has no conflicts of interest. No sources of funding were used to support the writing of this manuscript.

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