Emerging potential therapies for chronic abdominal visceral pain: an overview

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ABSTRACT

Despite advancements in pain medicine, management of chronic abdominal visceral discomfort remains a substantial concern for both patients and physicians. Standard pharmacological treatment fails to produce meaningful therapeutic outcomes. As a result, researchers are working on identifying additional modulable targets. Among others, specific receptors (serotonin, α2 adrenergic, cholecystokinin), as well as transient receptor potential vanilloid-1 channel, calcitonin gene-related peptide, mitogen-activated protein kinase and hypothalamic-pituitary-adrenal axis have been proposed as specific targets. Identification of genetic polymorphisms also plays a significant role. In this narrative review, which follows the SANRA criteria, we aimed to present the latest developments of the past five years, in visceral analgesia, without focusing on established pain management modalities. Cannabinoid receptor 2 agonists, high-dose inhaled salbutamol, μ-opioid receptors agonist in acidified microenvironment, 5-HT 4 receptor-antagonist, pomegranate mesocarp, guanylate cyclase-C agonists, assembled system of molecules of vegetal origin, monoclonal antibodies against calcitonin gene-related peptide receptors, palmitoylethanolamide, as well as polydatin micro-RNA based treatments have a possible role in the management of abdominal visceral pain. However, more research is needed because the majority of the findings are based on animal models of visceral pain or preliminary human investigations.

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Introduction

Chronic visceral pain is an unresolved neurobiological, medical, and socioeconomic challenge.[1] One in five adults suffers from visceral pain, while abdominal complaints constitute a prevalent symptom also in adolescents and children.[2]

Chronic visceral pain is classified as primary, where a definite cause cannot be identified. It is secondary, where an underlying disease such as persistent inflammation, vascular mechanisms, or mechanical factors represent the cause of pain.[1] Current treatment options often fail to provide adequate pain relief, while patients typically suffer from multiple concomitant physical and psychological symptoms.[2] A review published a few years ago introduced the idea of managing functional visceral pain with an initial focus on dietary measures including fiber supplementation, low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet (FODMAPs).[3] Additionally, they suggested a multimodal pharmacological approach with a variety of agents: simple medication such as peppermint oil, secretagogues (lubiprostone, linaclotide), 5-HT3 receptor antagonists (alosetron, ondansetron, ramosetron), antispasmodics, antidepressants and antiepileptics (gabapentin and pregabalin) or non-absorbable antibiotics (rifaximin). They also recommended strong opioid agonists (μ-opioid receptor (OR) and κ-OR agonist), or newer drugs such as δ-OR antagonist (eluxadoline), histamine H1 receptor antagonist (ebastine), and neurokinin-2 receptor antagonist (ibodutant).[3] As expected, side effects such as somnolence or gastrointestinal tract symptoms can affect the use of many of those drugs. Combinations of medications, to lower the dose of each agent, might be helpful, to mitigate the side effects.[4] When a clear cause of chronic pain is identified, such as chronic pancreatitis, more specific agents can be used, such as pancreatic enzymes and antioxidants.[5] In addition to pharmaceutical treatments, endoscopy,[5] sympathetic blocks,[6] and other neuromodulatory methods[7,8] were

used to treat visceral pain. Psychological support and behavioral interventions have been reported to have a very positive outcome as well, in some of the cases.[9]

The aim of this review is to explore the most recent available data on multimodal pharmacological analgesic approach for the treatment of abdominal visceral pain. Hence, interventional, and psychological approaches, as well as the traditional pharmacological therapy, are not going to be discussed.

Methods

This narrative review follows the Scale for the Assessment of Narrative Review Articles (SANRA) criteria.[10] In January 2024, PubMed/Medline, Scopus, and Cochrane databases were employed to identify relevant articles, using a combination of the following search terms**:** "abdominal visceral pain", "analgesia", "new approach", "therapy", "treatment", "medication" in various combinations, e.g., "analgesia for (abdominal) visceral pain", "visceral pain and treatment", "abdominal pain and therapy", "medication for abdominal pain". The primary search was supplemented with a secondary search using the bibliographies of the articles retrieved. Only full-length original articles were accepted, and the search was limited to English-language publications. The research was focused on medications that are used as a new/ non-conventional approach for the management of abdominal visceral pain. To better achieve the goal, only therapeutic approaches published in the last ten years were included. All retrieved articles were reviewed by title, abstract and the article itself, when necessary. The inclusion criteria were as follows: i) articles referred to abdominal visceral pain; ii) suggesting a novel treatment approach or medication therapy that would target the underlying mechanism; iii) published within the last ten years; iv) having at least the abstract in English. Articles that were not referring to the pharmacological treatment of abdominal visceral pain or were referring to already established treatments were excluded.

This narrative review article is based on previously conducted studies and does not contain any study with human participants or animals performed by any of the authors, without a previous Ethics Committee approval. Hence, it did not need any approval by Ethics Committees.

Results

The search provided a total of 1,098 articles for inclusion. The details of the screening are represented in Figure 1. First, it was interesting to notice how many therapeutic proposals the scientific literature is proposing for this challenging pain condition. Due to the restrictive inclusion criteria only 29 publications were included in this narrative review. The rest of the identified studies were referring to already established treatments or interventional approaches.

Pathophysiology of chronic abdominal visceral pain

In general, the pathophysiology of abdominal visceral pain includes inflammation, vascular causes, and/or mechanical etiology.[11] The basis of the pain mechanism focuses on the fact that, after an initial inflammatory process of the gastrointestinal tract, a signal is transmitted through various receptors and ion channels to the central nervous system. In some cases, the process undergoes pathological changes and results in enhanced nociceptive signaling, wind up, reduced descending inhibition and central sensitization.[12] Visceral pain does not follow specific dermatomal pathways and is also characterized by viscero-somatic and viscero-visceral convergence.[13] Among various mechanisms, serotonin polymorphisms also play a significant role in chronic visceral pain, as they influence pain inhibition.[14,15] Genetic polymorphisms that involve anti-inflammatory and proinflammatory interleukins, $\alpha 2$ adrenergic receptors, and cholecystokinin (CCK) receptors also might play a role.[14] The transient receptor potential vanilloid-1 (TRPV-1), as well as its regulator phosphoinositide-binding protein 'Pirt', have recently been identified as another important factor for visceral pain.[16] The latter was proven by downregulation of this protein expression in the dorsal root ganglion (DRG) after application of electroacupuncture.[16] Hypothalamic-pituitary-adrenal (HPA) axis has also a role in the responses of splanchnic organs stimulation and affects the corticotropin-releasing hormone (CRH), hence the visceral pain threshold and the relevant stress.[17] Other important molecules that play a role in pain propagation and chronicity are the calcitonin gene-related peptide (GCRP),[11] as well as the mitogen-activated protein kinase (MAPK) signaling pathway.[18]

Differential diagnosis of abdominal visceral pain

Visceral pain is a complex entity and the mentioned viscero-somatic and viscero-visceral convergence further complicate the clinical picture.[13] Abdominal pain has a particularly lengthy list of possible causes, including abdominal visceral and extra abdominal causes, as well as referred pain.[19] The list of causes of abdominal pain/ abdominal visceral pain is further extended with conditions such as centrally mediated abdominal pain syndrome (CAPS),[20] and abdominal migraine in children.[21] Although excluding red flags (e.g., loss of weight, bleeding, fever, *etc*.) is crucial, it is important to highlight that a pathophysiological cause is not always identified, and this condition shall be treated as chronic primary visceral pain.[22]

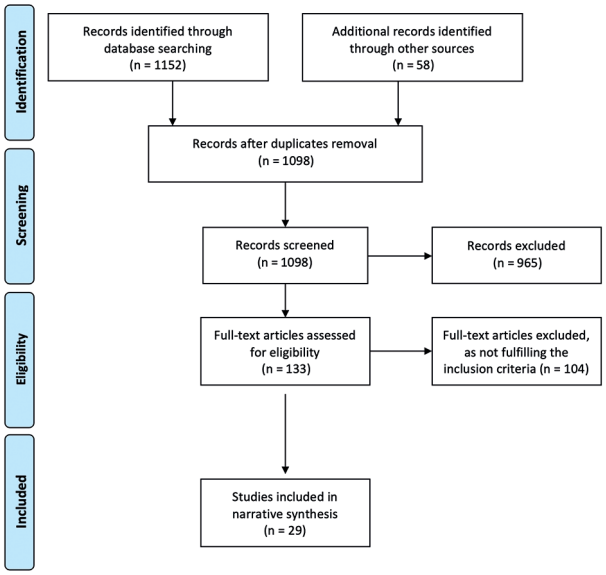

Figure 1. PRISMA diagram reporting the different stages of articles' selection.

The Rome IV criteria for disorders of gut-brain interaction (former functional gastrointestinal disorders) focuses on multicultural factors, age-gender-women's health, intestinal microenvironment, biopsychosocial factors, centrally mediated disorders, and newly recognized disorders (e.g., opioid-induced gastrointestinal hyperalgesia, opioid-induced constipation, cannabinoid hyperemesis, reflux hypersensitivity and centrally mediated abdominal pain syndrome). This evidence-based criteria serve as a useful research and clinical tool for the physician.[23]

Recent developments, possible targets, cutting edge research

This review identified interesting and completely new perspectives in the pharmacological treatment of patients with chronic abdominal pain. These are summarized in Table 1. Each of them is discussed below, aiming to provide the clinical interpretation of the published data.

Cannabinoid receptor 2 agonists

Two studies have identified the cannabinoid receptor 2 (CB2 receptor) as a target for the treatment against abdominal visceral pain.[24,25] LY3038404 HCl, a potent CB2 receptor agonist, with tissue protective and analgesic properties as well as lack of effects on higher visceral functions was studied on rats. The rats were fed with an alcohol/high fat diet to develop visceral pain-like behaviors leading to a chronic pancreatitis pain model.[24] Additionally, olorinab (APD371), a peripherally acting, highly selective, full agonist of the cannabinoid receptor 2, was found to reduce colitis-induced acute and chronic visceral hypersensitivity in animals.[25]

In a Phase 2a clinical trial studying patients with chronic abdominal pain associated with Crohn's disease, olorinab (25 mg and 100 mg), despite showing improvement in pain scores resulted in frequent (67-75%) and some serious treatment emergent adverse events (acute interstitial pneumonitis and interstitial lung disease) with the highest dose.[26]

In a placebo-controlled, randomized clinical trial (RCT) in patients with irritable bowel syndrome (CAPTIVATE Trial), olorinab 50 mg failed to reach the primary endpoint (change in patient-reported average abdominal pain score (AAPS) from baseline to week 12, but it was well-tolerated and improved weekly AAPS compared with placebo.[27] However, in a prespecified analysis of patients with moderate to severe pain at baseline, the 50 mg dose yielded clinically and statistically meaningful pain improvements over placebo (p=0.01).[27]

High-dose inhaled salbutamol

Data from a retrospective study suggest a potential efficacy of high-dose inhaled salbutamol, a short-acting β2 adrenergic receptor agonist usually used to treat bronchospasm, for the treatment of abdominal pain due to IgE-mediated food allergy.[25] The authors suggested that the mechanism of action is relaxation of visceral smooth muscle *via* β-adrenergic stimulation. However, they stress the importance of a RCT study to further support the data.[28]

μ-opioid receptor (MOR) agonist in acidified microenvironments

In a preclinical inflammatory bowel disease model in mice, a fentanyl analogue, (±)-N-(3-fluoro-1 phenethylpiperidine-4-yl)-N-phenyl propionamide (NFEPP), was investigated for its effectiveness on the treatment of visceral pain.[29] It was found that NFEPP inhibited colitis pain without the opioid side effects typically caused by fentanyl, such as respiratory depression, constipation, and hyperactivity.[29] Also, this opioid only acted in acidified microenvironments (inflamed colon), unlike fentanyl that acted in both colitis and healthy control mice. The mechanism of action of NFEPP was speculated to be the inhibition of the excitability of DRG neurons and the suppression of mechanical sensitivity of colonic afferent fibers in acidified pH conditions. At cellular level this is translated as inhibition of cAMP formation, recruitment of β-arrestins and μ-opioid receptor endocytosis.[29] The experimental results are exciting, but there are no human data available.

5-HT$_4$ receptor-antagonist

A selective 5-hydroxitriptamin (5-HT$_4$) antagonist, GR113808, led to negative modulation of visceral nociceptive transmission in animal models, mediated by 5-HT$_4$-dependent

Table 1. Summary of existing literature on new proposed pharmacological therapies for patients affected by chronic abdominal pain.

Possible future therapies for chronic abdominal pain
Cannabinoid receptor 2 agonists
High-dose inhaled salbutamol
MOR agonist in acidified microenvironments
5-HT4 receptor-antagonist
Pomegranate mesocarp Pomegranate decoction (300 mg/kg), polysaccharides (300 mg/kg), and ellagitannins (45 mg/kg)
Guanylate cyclase-C agonists - Plecanatide and dolcanatide
Assembled system of molecules of vegetal origin
Monoclonal antibodies against calcitonin gene-related (CGRP) peptide or receptors
Palmitoylethanolamide and polydatin
Micro-RNA based treatments
Microglia-derived TNF-α
Peptidomimetic G protein-biased MOR agonist and neuropeptide FF receptor antagonist (KGFF09)
Venoms and toxins

mechanisms through the caudal ventrolateral medulla (CVLM). The CVLM is the first site for processing the ascending visceral nociceptive signals *via* spinal pathways and an important component of the endogenous supraspinal pain modulatory system.[30] Specific receptor antagonists as CVLM might help in mitigation of unwanted side effects such as visceral pain and functional gastrointestinal disorders symptoms.

Pomegranate mesocarp

The pomegranate decoction, and its polysaccharide and ellagitannin components were evaluated for their effectiveness on preventing the development of colitis-induced abdominal pain.[31] After colitis induction by 2,4-dinitrobenzenesulfonic acid (DNBS) in rats, the pomegranate decoction (300 mg/kg), polysaccharides (300 mg/kg), and ellagitannins (45 mg/kg) were orally administered for 2 weeks. The results of the study showed that all three preparations reduced the overall amount of mast cells, the number of degranulated mast cells, and the density of collagen fibers in the mucosal stroma.[31] Ellagitannins seemed to be responsible for most of the beneficial effects of pomegranate on colitis, whereas the polysaccharides support and enhance its effect, rendering pomegranate mesocarp a useful complementary approach to conventional therapies against abdominal visceral pain.[31] Control animals were almost insensitive to the stimuli, an indication that the increase in visceromotor sensitivity in other experimental groups was not caused by the method procedures.[31] It is worth mentioning that *Punica granatum* (Pomegranate) has been used in a variety of medical systems for the treatment of a wide range of diseases and illnesses for the prevention and treatment of diseases related to respiratory and digestive systems in humans.[32]

Guanylate cyclase-C agonists – plecanatide, dolcanatide, linaclotide

Pre-clinical studies showed potent anti-nociceptive activity of these 2 substances through activation of guanylate cyclase-C signaling in rat visceral hypersensitivity models.[33,34] This signaling pathway would be a possible target for treating pain caused by functional constipation disorders and inflammatory gastrointestinal conditions. Considering the high prevalence of this health condition, if the data are confirmed in humans, the clinical results would be important in many chronic visceral pain patients.

Linaclotide has been shown to inhibit colonic nociceptors and reduce peripheral drive from the colon, resulting in reduced numbers of activated dorsal horn neurons within the spinal cord and reduced pain responses to noxious colorectal distension. In human phase III clinical studies in patients with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation, linaclotide significantly improved abdominal pain, discomfort and bloating. Additionally, in preclinical studies linaclotide has been found to be beneficial for bladder dysfunction and endometriosis-associated pain.[35] In real world study conducted in the United Kingdom, linaclotide significantly improved IBS symptoms severity score at 12 and 52 weeks.[36] This treatment has also excellent patient satisfaction (79.3% in week 4 and 100% in week 12). One in 10 patients may develop diarrhoea.[37]

Assembled system of molecules of vegetal origin

An innovative therapeutic addition to pain management in visceral pain due to bowel diseases are the natural substances *Boswellia serrata* resins, *Aloe vera* polysaccharides, *Matricaria chamomilla* and *Melissa officinalis* polyphenols. These molecules, already used as officinalis remedies, were found to protect the intestinal mucosa and to promote its healing from lesions at histological level.[38] They protect from the development of intestinal damage and reduce the onset of visceral hypersensitivity in a rat model of 2,4-dinitrobenzenesulfonic acid (DNBS)-induced colitis.[38] These data represent a possible scientific explanation of the efficacy of officinalis substances used for many years.

Monoclonal antibodies against calcitonin gene-related peptide or receptors

Calcitonin gene-related peptide has been found to serve as a primary afferent neurotransmitter by communicating with second-order neurons in the posterior grey column of the spinal cord. Regarding visceral pain, β-CGRP was found to predominate in nerves of the enteric system, rendering it a possible target against antinociception. Although the data from clinical trials regarding safety and tolerability of anti-CGRP monoclonal antibodies are promising, data for long term blocking of CGRP are limited,[11] thus remaining to be explored by RCTs with lengthy follow-up.

Palmitoylethanolamide and polydatin

Palmitoylethanolamide (PEA) has been used in many chronic pain syndromes,[39-43] including fibromyalgia.[39] The dietary supplement PEA/polydatin in IBS patients with abdominal pain was suggested as a promising natural approach for pain management.[42] In a multicenter placebo controlled RCT, this substance has already been largely investigated,[42] and its clinical use is well supported.[40] Hence, it could serve as an integral part of a multimodal pharmacological approach to chronic visceral pain, especially thinking of its safety profile. It is worth mentioning that one of the most important aspects in the PEA pharmacology is the difficulty in the absorption of the oral formulation, especially in inflamed intestine. A novel branded formulation, EquiPEA® (extract of *Equisetum arvense L.)*, seems very promising.[43]

miRNA based treatments

miRNAs are short RNA molecules that, although they do not code for protein production, are capable of post-translational regulation of expression of several target mRNAs.[44] Some miRNAs have been shown to target serotonin reuptake transporter, such as miRNA-24, which is upregulated in IBS mouse models.[44] MiRNA-199 expression correlates with visceral pain through translational upregulation of transient receptor potential vanilloid type 1 in patients with IBS-D.[45] Upregulation of miR-19b, on rat colonic epithelial cells in a lipopolysaccharide-induced colitis model has effectively been targeted by galacto-oligosaccharides.[46] MiR-200a[47] and MiRNA-29a[48] have also been implicated to have an important relationship with visceral pain modulation. miRNAs regulation might play a significant role in visceral hyperalgesia.[44]

Microglia-derived TNF-α

Microglia-derived TNF-α is presenting as a novel potential regimen for patients with IBS suffering with visceral pain. The main finding of a recent study was that it suppresses the activity of the GABAergic neurons in the anterior ventral bed nucleus of the stria terminalis (alBNST).[49] The researchers created a rodent model of neonatal colorectal distension, causing visceral hyper-

sensitivity to mechanical luminal distension, which showed that a microglia-driven disinhibitory mechanism has an essential role in visceral hypersensitivity.[49]

Peptidomimetic G protein-biased MOR agonist and neuropeptide FF receptor antagonist (KGFF09)

The design of a bifunctional ligand MOR agonist (activator)/neuropeptide FF receptor antagonist (blocker) showed great potential as an antinociceptive agent in a mouse model of visceral pain.[50] A significant benefit of this new multifunctional formulation was the reduced unwanted side effects compared to the conventional opioid analgesics (e.g., rewarding effects, sedation, and locomotor difficulties, respiratory depression, analgesic tolerance, opioid-induced hyperalgesia and physical dependence).[50]

Venoms and toxins

Tarantula venom - voltage-gated sodium channel NaV1.7 inhibitor

Tsp1a, a novel selective hNaV1.7 inhibitor, isolated from tarantula venom has a greater than 100-fold selectivity over hNaV1.3-hNaV1.6, 45-fold selectivity over hNaV1.1, and 24-fold selectivity over hNaV1.2.[51] Tsp1a is a gating modifier that suppresses NaV1.7 function by causing a hyperpolarizing change in the voltage-dependent nature of channel inactivation and delaying recovery from rapid inactivation. NMR investigations indicated that Tsp1a has a conventional knottin fold and, like many knottin peptides, is very stable in human blood. Surprisingly, intracolonic injection of Tsp1a totally restored chronic visceral hypersensitivity in an irritable bowel syndrome mice model.[51] Tsp1a's ability to diminish visceral hypersensitivity in an irritable bowel syndrome model implies that pharmacological suppression of hNaV1.7 at peripheral sensory nerve terminals might be a feasible method for inducing analgesia in individuals suffering from chronic visceral pain.[51]

Scorpion toxin – BotAF

A new potent scorpion neuropeptide BotAF has shown to be effective in treating acute and inflammatory visceral pain in animals, through a spinal or peripheral anti-nociceptive mechanism.[52] This new agent does not produce any toxicity or motor impairment, even at high doses, and outperforms traditional analgesics under similar conditions. Additionally, it reduces lumbar spinal cord c-fos/c-jun mRNA upregulation in visceral pain models in a dose-dependent manner.[52]

Discussion

This narrative review provides the clinician with a perspective of the most updated current evidence and future perspective regarding pharmacological agents against visceral pain and hypersensitivity. Human replicability of those therapies in well-designed RCTs would provide more scientific data for the clinical applicability, and aid in the treatment of this complex pathophysiological condition. Focusing on visceral pain receptors and neurotransmission many more treatments can be identified as possible beneficial medication.[53] Considering the safety profiles, many of these therapies may be used as add-on therapy, providing a good basis for a multimodal approach to a difficult pain syndrome. Further systematic reviews and metanalysis as well as placebo controlled RCTs utilizing different dosing regimens would be necessary to further evaluate the safety and efficacy of most of these medications.

This study has some limitations. Most of the presented results were obtained in animal studies, without any exploration on humans. Additionally, we included studies with at least the abstract in English language, freezing out possible important data published in other languages. A further limitation was the omission of studies involving the use of microbiota- directed therapies. This topic is extensively studied by our group and will be fully presented in a future publication.

Conclusions

Abdominal visceral pain is a challenging health condition, with complex and multifactorial pathophysiological mechanisms. A detailed identification of the pathophysiology that is involved along with a personalized approach that would lead to precision pain medicine is the ultimate target. A multimodal approach would be appropriate. However, the current existing options based on paracetamol, non-steroidal anti-inflammatory medications, and opioids, as well as adjuvants like antidepressants, anticonvulsants, and antispasmodics, are not sufficient to cover all the different pain conditions. Future promising treatments such as cannabinoid receptor 2 agonists, high-dose inhaled salbutamol, μ-opioid receptor agonist in acidified microenvironments, 5-HT_4 receptor-antagonist, pomegranate mesocarp, guanylate cyclase-C agonists, molecules of vegetal origin, monoclonal antibodies against CGRP or receptors, PEA, micro-RNA based treatments, Microglia-derived TNF-α, KGFF09 and venoms and toxins would serve as a valuable addition to the pharmacological armamentarium of the clinicians. Treatments that have already been used in humans and show some benefits are most probably closer to become established treatments. Further exploration of the above-mentioned molecules in human trials would be the next important step.

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